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Version History

SAP Version	Date	Rationale
1.0	30 Sep 2024	Original version
2.0	30 Jun 2025	• Added the actual enrollment • Added prognostic factors and subgroup analyses related to LG NMIBC and tumor characteristics pre-biopsy vs post-biopsy • Added subgroup analyses of US vs Non-US • Removed Bayesian analysis of CRR • Added DOR and DCR analysis in Per-Protocol analysis set • Added sections of pathological evaluation by visit, and SoC procedures for residual disease or progression at 3-month visit • Added PRO summaries and associated charts of disposition, completion rates, and tabulation of categorical responses
3.0	23 Feb 2026	• [redacted], added FDA analysis set to be used for the primary efficacy analysis and changed the ITT analysis set to be used for sensitivity analyses of CRR, DOR, and DCR. • Updated analysis visit windows to align with updated protocol V4.0 • [redacted], added concordance analysis between central and local lab review of biopsy samples, analyses of TEAEs and PCS labs by subgroups, summary of potential adverse reactions, analyses of [redacted] AESIs.

ABBREVIATIONS

ADaM	Analysis Data Model
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical (classification)
BMI	body mass index
CI	confidence interval
CDISC	Clinical Data Interchange Standards Consortium
CR	complete response
CRR	complete response rate
CTCAE	Common Terminology Criteria for Adverse Events
DBL	Database lock
DBP	diastolic blood pressure
DCR	durable complete response
DOR	duration of response
eCRF	electronic case report form
EOR	evaluation of response
EORTC	European Organisation for Research and Treatment of Cancer
EOS	end of study
FDA	Food and Drug Administration
ICH	International Council for Harmonisation
IR	intermediate risk
ITT	intent-to-treat
LFT	liver function test
LG	low grade
LLN	lower limit of the normal range
LOCB	last observation carried backward

LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MMC	Mitomycin C
NCR	non-complete response
NPT	non-protocol therapy
NMIBC	non-muscle invasive bladder cancer
PCS	potentially clinically significant
PP	per protocol
PRO	patient reported outcome
PT	preferred term
QoL	quality of life
QLQ-C30	30-item quality of life questionnaire for cancer patients
RD	recurrence disease
RS	raw score
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System
SBP	systolic blood pressure
SI	international system of units
SoA	schedule of activities
SoC	standard of care
SOC	system organ class
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TIP	trial integrity plan
TLFs	tables, listings, figures
TSQM	treatment satisfaction questionnaire for medication
TURBT	transurethral resection of bladder tumors
UCMH	urothelial carcinoma related medical history
ULN	upper limit of the normal range

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to define all prespecified analyses of study BL013 (UTOPIA), a phase 3, single-arm, multicenter study to evaluate the efficacy and safety of UGN-103 for the treatment of patients with recurrent low grade (LG) nonmuscle invasive bladder cancer (NMIBC) at intermediate risk (IR) of recurrence.

This SAP is based on the following study documents:

- Protocol Amendment 3, Version 4.0 dated 06 August 2025
- Case report form (CRF), Version 5.0 dated 12 June 2025

2. STUDY OBJECTIVES AND ENDPOINTS

Table 1 lists the study objectives and corresponding endpoints of the study.

Table 1: Study Objectives and Endpoints

Objective	Endpoint
Primary	
• To evaluate the tumor ablative effect of UGN-103, a novel formulation of UGN-102, in patients with LG NMIBC	• CRR, defined as the proportion of patients who achieved CR at the 3-month Visit (3 months after the first instillation of UGN-103) as determined by cystoscopy, for cause biopsy, and urine cytology
Secondary	
• To evaluate the durability of response with respect to DOR and DCR rate at scheduled disease assessment time points	• DOR in patients who achieved CR at the 3-month Visit, defined as the time from the date of evidence of CR at the 3-month Visit to the earliest date of recurrence or progression as determined using the date of cystoscopy, for cause biopsy, or cytology, or death due to any cause, whichever occurred first • DCR rate at scheduled disease assessment time points, defined as the proportion of patients who achieved CR at the 3-month Visit and maintained CR (ie, no detectable disease) up to that particular follow-up disease assessment

• To evaluate the safety and tolerability of UGN-103 in patients with LG NMIBC	• Safety and tolerability will be evaluated through the reporting of AEs, including SAEs and AESIs, and through standard clinical and laboratory tests (eg, hematology and chemistry, urinalysis, physical examination, and vital signs)
• To assess the PK profile of mitomycin in plasma in a subgroup of patients treated with UGN-103	• Concentration data and PK parameters (C_{max}, t_{max}, and AUC)
Exploratory	
• To assess the effect of UGN-103 on PRO measures including disease related quality of life and treatment satisfaction	• Changes from baseline in patient scores on the QLQ-C30 and TSQM questionnaires
• To identify mechanisms of sensitivity and/or resistance to UGN-103	• DNA, RNA and/or protein biomarkers in tumor tissue
• To evaluate preliminary responses following SoC treatment in patients who have an NCR at the 3-month Visit	• Number (%) of response outcomes evaluated at the first disease assessment visit after SoC

AE=adverse event; AESI=adverse event of special interest; AUC=area under then concentration-time curve; C_{max}=maximum plasma concentration; CR=complete response; CRR=complete response rate; DCR=durable complete response; DNA=deoxyribonucleic acid; DOR=duration of response; LG=low grade; NCR=non-complete response; NMIBC=non-muscle invasive bladder cancer; PK=pharmacokinetic(s); PRO=patient-reported outcome; QLQ-C30=Quality of Life Questionnaire for Cancer Patients; RNA=ribonucleic acid; SAE=serious adverse event; SoC=standard of care; t_{max}=time to maximum plasma concentration; TSQM=Treatment Satisfaction Questionnaire for Medication

3. STUDY DESIGN

This Phase 3, single-arm, multicenter study will evaluate the efficacy and safety of UGN-103, a novel formulation of UGN-102, instilled in the bladder of patients with LG-IR-NMIBC via urinary catheter.

Patients who provide informed consent will undergo a Screening Visit to determine eligibility. The Screening Period is up to 35 days for all patients. Screening procedures are to provide evidence of LG-IR-NMIBC and no evidence of high grade (HG) disease, and every effort will be made to minimize the time interval between diagnosis and treatment.

Eligible patients will be treated with UGN-103 once weekly for 6 weeks (a total of 6 doses).

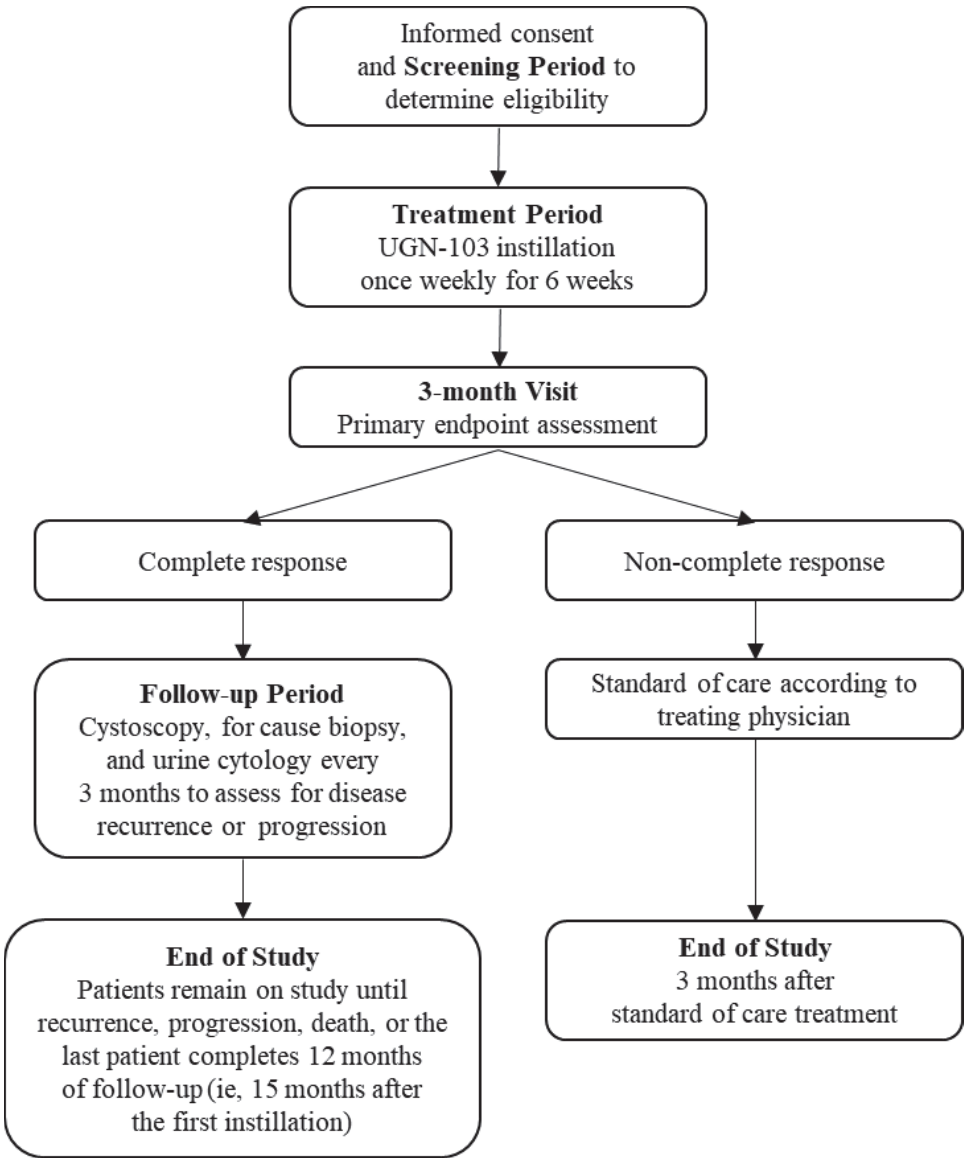
Efficacy will be assessed by the complete response rate (CRR) at the 3-month Visit (approximately 3 months after the first instillation). Response will be determined based on visual observation (white light cystoscopy), histopathology of any remaining or new lesions by central pathology lab (if applicable), and interpretation of urine cytology by central pathology lab. Any lesions or suspect tissue must be biopsied to evaluate for persistence or recurrence of disease.

Patients who have a complete response (CR) at the 3-month Visit, defined as having no detectable disease (NDD) in the bladder, will enter the Follow-up Period of the study. During the Follow-up Period, patients will return to the clinic every 3 months for evaluation of response. Patients will remain on study until disease recurrence, disease progression, death, or the last patient completes 12 months of follow-up (ie, 15 months after the first instillation), whichever occurs first.

Patients who have a non-complete response (NCR) at the 3-month Visit will undergo investigator designated standard of care (SoC) and subsequently have a separate End of Study (EOS) Visit performed 3 months after SOC treatment.

The study design is depicted in Figure 1 below. Schedules of activities from Screening to EOS are available in Protocol Section 1.3.

Figure 1: Study Schema



3.1. Statistical Hypothesis

No formal hypotheses will be tested for the confirmation of efficacy. The estimations shown in Section 3.2 are only for the justification of the sample size of this study.

3.2. Sample Size Determination

The primary endpoint of this study is CRR at the 3-month Visit.

Approximately 87 patients were to be enrolled. The sample size calculation was based on the level of precision of the estimated CRR. For an observed CRR of 60.9%, the 95% exact

CI is (49.8%, 71.2%) for 87 patients. Assuming the true CRR of UGN-103 is 60%, the power to demonstrate that the lower bound of the 95% CI is greater than 45%, which is considered as the minimum clinical benefit of this population, is 79.2% using a binomial exact test.

The actual enrollment reached 99 patients to account for patients erroneously enrolled despite not meeting all the eligibility criteria and to meet the protocol requirement of at least 9 patients with PK data. Any erroneously enrolled patients will be considered for exclusion from the Per-Protocol analysis set (Section 10.2).

Table 2 shows the 95% CI for a range of possible response rates based on 87 patients, and Table 3 shows the power under different assumptions of true 3-month CRR.

Table 2 Sample Size Sensitivity

Sample Size	Number of Responders (Observed 3-month CRR)	95% Exact 2-sided CI
87	50 (57.5%)	(46.4, 68.0)
	53 (60.9%)	(49.8, 71.2)
	57 (65.5%)	(54.6, 75.4)

CI = confidence interval; CRR = complete response rate.

Table 3 Statistical Power Scenarios

Sample Size	True 3-month CRR	Probability That the Lower Bound of a 2-sided 95% Exact CI Will Exclude 0.45
87	0.65	0.963
	0.64	0.944
	0.63	0.918
	0.62	0.885
	0.61	0.842
	0.60	0.792
	0.59	0.733
	0.58	0.666
	0.57	0.595
	0.56	0.521
	0.55	0.446

CI = confidence interval; CRR = complete response rate.

3.3. Randomization and Blinding

Not applicable.

4. PLANNED ANALYSES

4.1. Interim Analyses

No formal interim analyses are planned in the Protocol.

4.2. Timing of Analyses

Any changes to this plan will be described in the Trial Integrity Plan (TIP).

3-Month Data Freeze

The analysis of the primary endpoint will be performed after all patients have completed

the 3-month Visit for their primary disease evaluation or discontinued from the study.

The safety profile of UGN-103 will be also evaluated at the 3-month data freeze date through the reporting of adverse events (AEs), including serious adverse events (SAEs) and adverse events of special interest (AESIs).

Relevant electronic case report form (eCRF) pages, e.g., Informed Consent, Inclusion/Exclusion Criteria, Enrollment, Demographics, Evaluation of Response, Cystoscopy, Histopathology and Urine Cytology up to the 3-month Visit, and available Standard of Care for Disease Recurrence or Progression up to the 3-month Visit will be frozen prior to this analysis. No formal database lock (DBL) will be conducted for this analysis.

UroGen Statistics&Programming (S&P) team will be restricted from accessing patient-level and aggregate-level efficacy data prior to the 3-month data freeze date, and all other UroGen personnel will be restricted from accessing aggregate-level efficacy data prior to 3-month data freeze date. Further details regarding the data restrictions will be described in the TIP.

Final DBL

A formal DBL will be conducted after all patients have completed the study, withdrawn consent, been lost to follow-up, died during the study, or when the study is closed by the sponsor.

The final analysis will be performed using the formally locked database.

UroGen S&P team will remain restricted from accessing patient-level and aggregate-level efficacy data collected after the 3-month data freeze date and until approximately 2 months prior to the formal DBL. All other UroGen personnel will be restricted from accessing aggregate-level efficacy data after the 3-month data freeze date and until approximately 2 months prior to the formal DBL. UroGen S&P team and selected UroGen personnel from other functions will gain access to efficacy data approximately 2 months prior to the final DBL.

5. ANALYSIS POPULATIONS

For the purposes of analysis, the following analysis sets are defined:

Table 4: Analysis Set

Analysis Set	Description
Intent-to-Treat (ITT) Analysis Set (Safety Analysis Set)	The ITT analysis set (safety analysis set), hereafter referred to as ITT analysis set, will consist of all patients who received any dose of UGN-103 and will serve as the primary population for safety analyses. Sensitivity analyses of the efficacy endpoints will be performed using the Safety analysis set.
Per Protocol (PP) Analysis Set	The per protocol (PP) analysis set will include the subset of the patients in the ITT analysis set without major protocol deviations that would confound efficacy evaluation. Protocol deviations or

	conditions leading to exclusion from the PP analysis set will be determined before database freeze and database lock. Sensitivity analyses of the primary endpoint will be performed for PP analysis set.
FDA analysis set	The FDA analysis set includes patients in the PP analysis set who had at least 1 prior TURBT to treat LG NMIBC. The FDA analysis set will serve as the primary population for efficacy analyses.
PK analysis set	The PK analysis set includes patients in the safety analysis set who provide consent for PK samples and have at least 1 plasma sample for evaluation of PK properties of mitomycin.
CR at 3-month Disease Assessment Analysis Set (3-month$_{CR}$)	The CR at 3-month disease assessment (3-month$_{CR}$) analysis set will consist of all patients from the ITT analysis set who achieved CR at the 3-month Visit. Sensitivity analyses of the secondary endpoints DOR and DCR rate at specific time points will be performed using this analysis set.
CR at 3-month Disease Assessment Per Protocol Analysis Set (3-month CR Per Protocol Analysis Set)	The CR at 3-month disease assessment per protocol (3-month CR Per Protocol) analysis set will consist of all patients from the PP analysis set who achieved CR at the 3-month Visit. Sensitivity analyses of the secondary endpoints DOR and DCR rate at specific time points will be performed using this analysis set.
CR at 3-month Disease Assessment FDA Analysis Set (3-month CR FDA Analysis Set)	The CR at 3-month disease assessment FDA (3-month CR FDA) analysis set will consist of all patients from the FDA analysis set who achieved CR at the 3-month Visit. The secondary endpoints DOR and DCR rate at specific time points will be analyzed using this analysis set.
Imputed CR at 3-month Disease Assessment Analysis Set (3-month Imputed CR)	The imputed CR at 3-month disease assessment (3-month Imputed CR) analysis set will consist of all patients from the ITT analysis set who had either observed CR or imputed CR at the 3-month disease assessment based on the imputed algorithm in Section 11.1.1 and will be used for sensitivity analyses of the secondary endpoints of DOR and DCR rates at specific time points.
NCR at 3-month Disease Assessment Analysis Set (3-month$_{NCR}$)	The NCR at 3-month disease assessment (3-month$_{NCR}$) analysis set will consist of all patients from the ITT analysis set who had NCR at the 3-month visit. The preliminary response of these patients following the SoC treatment will be analyzed using this analysis set.

6. TREATMENT COMPARISONS

Not applicable.

7. CHANGES TO THE PLANNED ANALYSES

[redacted], the efficacy analyses of CRR, DOR, and DCR will be conducted using the FDA analysis set. Corresponding sensitivity analyses will be conducted using the ITT analysis set.

8. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Data will be listed and summarized according to Clinical Data Interchange Standards Consortium (CDISC) standards and International Council for Harmonisation (ICH) E9 Guideline. SAS software Version 9.4 or higher 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 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.

8.1. Multicenter Studies

It is anticipated that patient accrual will be spread thinly across centers and summaries of data by center would be unlikely to be informative; therefore, data from all participating centers will be pooled prior to analysis.

A summary of the number of patients by country and by site will be provided.

8.2. Other Strata and Covariates

Not applicable.

8.3. Multiple Comparisons and Multiplicity

Not applicable.

9. 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 will 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.

9.1. Premature Withdrawal and Missing Data

A patient will be considered to have completed the study if the patient completes all follow-up visits in accordance with the Schedule of Activities (SoA) (Protocol Section 1.3) as planned. A patient with CR at the 3-month Visit will be considered as a completer if the patient has a recurrence or progression during the follow-up period, dies during the study, or is still in follow-up when EOS is declared. A patient with non-CR at the 3-month Visit will be considered a completer if the patient receives SoC and has a separate subsequent EOS Visit performed.

A patient will be considered to have withdrawn from the study if the patient has not recurred, progressed, or died and is lost to follow-up, has withdrawn consent, or is no longer being followed at the Investigator's discretion.

No time-to-event data will be interpreted at the time of the analysis of the primary endpoint. For endpoints which determine the percentage of CRs, indeterminate or missing responses will be handled according to the rules specified in the corresponding sections (11.1.1 and 11.2.2.1).

Missing data occurs when any requested data are 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 will be displayed as such.

There will be no imputation for missing data other than what is described in Appendix 1.

All relevant data will be summarized and/or listed. Summaries of the number of patients who have discontinued study treatment, as well as details on those in follow-up will be provided.

9.2. Derived and Transformed Data

9.2.1. Reference Date

There are two reference dates:

- The reference date for age is the date of Informed Consent.
- The safety/efficacy reference date (study day 1) is the date of first instillation of UGN-103 and will be used to calculate study day for safety/efficacy measures.

9.2.2. Study Day

The study day for safety and efficacy measures are the same. 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.

9.2.3. Calculation of Durations

Durations (e.g., duration of adverse event, time to recurrence between prior NMIBC episodes, etc.) will be calculated as stop date minus start date plus one.

When reporting time to event durations (DOR) or any other duration in months, the duration in days will be divided by 30.4375; by 7 to report in weeks; by 365.25 to report in years. These algorithms for time to event return decimal numbers and ignore the actual numbers of days in the months or years between start date and stop date. The "year" used in these algorithms is 365.25 days long, and the "month" is one twelfth of that year.

9.2.4. Imputation of Partial Dates

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

Imputed dates will not be displayed in listings. However, where necessary, partial dates will be imputed for the purpose of sorting data in listings only. In addition, partial dates may be imputed for 'slotting' data for specific analysis purposes.

Details on imputing partial dates for specific datasets are outlined in Appendix 1.

9.2.5. Baseline Definition

In general, baseline will be defined as the most recent non-missing value prior to the first instillation of UGN-103, i.e., prior to Day 1.

9.2.6. Change from Baseline

Change from baseline is calculated as:

- For records occurring after baseline: visit value – baseline value.

Percent change from baseline is calculated as:

- For records occurring after baseline: change from baseline / baseline value * 100.

If either the baseline or visit value is missing, the change from baseline and/or percent change from baseline is set to missing as well.

9.2.7. Analysis Visit Window

A windowing convention will be used to determine the analysis value for a given study visit only for the following visit-based assessments:

- Patient Reported Outcome (PRO)
- Urological exam
- Clinical chemistry, hematology, and urinalysis
- Vital signs

The window for the visits during the treatment period will be constructed in such a way that the upper limit of the interval falls halfway between the two actual visits analysis days (the lower limit of the first post-Day 1 visit will be Day 2). The window for the visits during

the follow-up period will be constructed in such a way that the upper limit of the interval falls halfway between the two planned visits analysis days.

If an odd number of days exists between two consecutive visits, then the upper limit will be taken as the midpoint value minus 1 day.

Table 5: Analysis windows

Analysis Visit	Target Day	Analysis Window Lower Limit (Analysis Day) [a,b]	Analysis Window Upper Limit (Analysis Day) [a,b]
Baseline	< 1	N/A	< 1
Day 1	1	1	1
Week 2	W2DY	2	(W2DY + W3DY)/2 - 1
Week 3	W3DY	(W2DY + W3DY)/2	(W3DY + W4DY)/2 - 1
Week 4	W4DY	(W3DY + W4DY)/2	(W4DY + W5DY)/2 - 1
Week 5	W5DY	(W4DY + W5DY)/2	(W5DY + W6DY)/2 - 1
Week 6	W6DY	(W5DY + W6DY)/2	(W6DY + M3DY)/2 - 1
Month 3	M3DY	(W6DY + M3DY)/2	M3DY + 44
Month 6	M3DY + 90	M3DY + 45	M3DY + 134
Month 9	M3DY + 180	M3DY + 135	M3DY + 224
Month 12	M3DY + 270	M3DY + 225	M3DY + 314
Month 15	M3DY + 360	M3DY + 315	M3DY + 404
Month 18	M3DY + 450	M3DY + 405	M3DY + 494
Month 21	M3DY + 540	M3DY + 495	M3DY + 584
Month 24	M3DY + 630	M3DY + 585	N/A

M3DY = Month 3 Study Day based on the earliest of cystoscopy and cytology assessment at 3-month Visit; WxDY = Week x Study Day based on analysis day of the x-th instillation.
a. Upper and lower limits are rounded up to the next integer in case of decimals.
b. If patient discontinues treatment at the x-th instillation, then the upper limit of the analysis window of the x-th visit is (WxDY + M3DY)/2 – 1, and the lower limit of the Month 3 analysis window is (WxDY + M3DY)/2.

9.2.8. Multiple Assessments

Endpoints will be reported according to the nominal visit date on which they were reported. Analysis windows will be applied during dataset creation for the summaries of clinical hematology, chemistry, urinalysis, vital signs, urological examination, and the PRO assessments. Both scheduled and unscheduled data will be included in the analysis windows and the summary sections labelled as worst-case.

One or more results for a particular variable may be obtained in the same visit window. In such an event, the result with the date closest to the expected visit date will be used in the analysis. If two observations are equidistant from the expected visit date, the later observation will be used in the analysis.

If multiple assessments are reported on the same date for the same scheduled planned time, then the worst-case result will be analyzed, except for laboratory data reported from both

central and local laboratories. If laboratory data is reported from both central and local laboratories with the same date, then the central laboratory data will be analyzed to provide consistency with measurements from other patients.

Data from all assessments (scheduled and unscheduled), including multiple assessments, will be included in the listings.

10. PATIENT DISPOSITION, DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

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

10.1. Disposition of Patients

A summary of the number of patients who signed informed consent and met all eligibility criteria, or did not meet all eligibility criteria, and reasons, will be provided.

A summary of the number of patients in each of the analysis sets described in Section 5 will be provided. In addition, the number of patients by country and site will be summarized using the ITT analysis set.

A summary of treatment with UGN-103 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 summary of patient status regarding 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, discontinued or are ongoing in the study, and primary reasons for study completion/discontinuation. Reasons for study completion or withdrawal will be presented in the order they are displayed in the eCRF.

A patient will be considered as completing the study based on the following criteria.

- 3-month CR patients who have a disease recurrence or progression during the Follow-up Period, or who are still in follow-up when EOS is declared
- 3-month NCR patients who complete the EOS visit 3 months after the SoC treatment

A combined listing of treatment and study discontinuation will be generated.

10.2. Protocol Deviations

All protocol deviations will be summarized and 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 ITT population. The details of protocol deviations will be included in the Protocol Deviation Management Plan.

Patients with major protocol deviations that would confound efficacy evaluation will be excluded from the PP analysis set. All protocol deviations or conditions leading to

exclusion from the PP analysis set will be finalized prior to the data freeze and database lock. Sensitivity analyses of the primary endpoint CRR, and secondary endpoints of DOR, DCR will be performed using data from the PP analysis set.

10.3. Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized and listed. Age (years), height (cm), weight (kg) and BMI (kg/m^2) will be summarized using the mean, standard deviation, minimum, median (quartiles), and maximum as appropriate. In addition, age will also be categorized and summarized by < 65, ≥ 65 to < 75, ≥ 75 to < 85 and ≥ 85; < 65 and ≥ 65; < 75 and ≥ 75. BMI will also be categorized and summarized by < 30 and ≥ 30. Sex, race, ethnicity, renal impairment, hepatic impairment, diabetes mellitus history will be summarized using the count and percentage.

Baseline renal impairment (based on eGFR) categories are defined as normal: $\geq$ 90 mL/min; mild: $\geq$60 to <90 mL/min; moderate: $\geq$30 to <60 mL/min; and severe: <30 mL/min. Baseline hepatic impairment (baseline liver enzyme elevation) is defined as baseline AST (aspartate aminotransferase) or ALT (alanine transaminase) value > ULN (upper limit of normal). Diabetes mellitus history is defined as a medical history event where the high level term (HLT) is 'Diabetes mellitus (incl subtypes)'.

The following baseline bladder cancer prognostic factors will be provided by count and percentage:

- Treatment course (instillations): (6, < 6)
- Longest tumor diameter pre-biopsy, defined as the longest diameter among all measurable lesions (cm): ($\leq$ 3, > 3)
- Tumor burden pre-biopsy, defined as the sum of the longest diameters of the measurable lesions (cm): ($\leq$ 3, > 3)
- Tumor count pre-biopsy (single, multiple)
- Longest tumor diameter post-biopsy (cm): ($\leq$ 3, > 3)
- Tumor burden post-biopsy (cm): ($\leq$ 3, > 3)
- Tumor count post-biopsy (single, multiple)
- Disease history
    - Previous NMIBC episodes (Yes, No)
    - Previous NMIBC episodes within 1 year of current diagnosis (Yes, No)
    - Number of previous NMIBC episodes (0, 1, 2, > 2)
    - Previous LG NMIBC episodes (Yes, No)
    - Previous LG NMIBC episodes within 1 year of current diagnosis (Yes, No)
    - Number of previous LG NMIBC episodes (0, 1, 2, > 2)
- Number of prior TURBT to treat NMIBC (0, 1, 2, > 2)
- Number of prior TURBT to treat LG NMIBC (0, 1, 2, > 2)
- Smoking history (smoker, non-smoker)

Smoking has been recognized as the strongest established risk factor for bladder cancer. Smoking related data will be collected in the eCRF in detail and will be summarized by:

- Category for substance use (Cigarettes, Cigar, Pipe, Other, and any combination)

- Baseline Status (Current vs Former)
- Duration (< 10, 10 - 20, 21 - 30, > 30 years)
- For cigarettes only: number of cigarettes per day (< 5, 5 – 15, 16 – 25, > 25)

A summary of prior NMIBC along with its standard of care (TURBT) will be provided. Number of prior NMIBC episodes, time to recurrence of baseline NMIBC episode, number of prior TURBT procedures, and time since last TURBT will be summarized using the mean, standard deviation, minimum, median (quartiles), and maximum as appropriate. In addition, the count and percentage will be provided for number of prior TURBT groups (0, 1, 2, ≥ 3) and time since last TURBT procedure at the time of first instillation of UGN-103 (≤ 365 days, >365 days). A listing of prior NMIBC diagnoses and TURBT procedures will also be generated.

10.4. General Medical History, Prior and Concurrent Urothelial Carcinoma Related Medical Conditions

Reported terms of general medical history, prior and concurrent urothelial carcinoma medical conditions will be coded to a system organ class and preferred term (PT) using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA) Version 27.0 or later. Number and percent of patients reporting any general medical history, prior or concurrent urothelial carcinoma medical conditions will be provided by system organ class and PT for the ITT analysis set. A patient with multiple terms will be counted once per system organ class and PT. For computing percentages, the denominator will be the number of patients in the ITT analysis Set. The summary table will be sorted by descending order of frequency of system organ class (then alphabetically for ties), then by descending order of frequency of PT within each system organ class (then alphabetically for ties). A patient data listing of medical history will be provided.

The UCMH status at baseline will be summarized as:

- Time in months between the date of initial diagnosis and the first instillation of UGN-103
- Number of prior UCMH episodes
- Visual appearance of the lesions at baseline (pre-biopsy)
- Longest tumor diameter (cm) at baseline (pre-biopsy)
- Tumor burden (cm) at baseline (pre-biopsy)
- Visual appearance of the lesions at baseline (post-biopsy)
- Longest tumor diameter (cm) at baseline (post-biopsy)
- Tumor burden (cm) at baseline (post-biopsy)
- Staging of prior UCMH episodes (Noninvasive papillary carcinoma (Ta), Tumor invades lamina propria (T1), Tumor invades muscular propria (T2), Tumor invades perivesical tissue/fat (T3), Tumor invades prostate, uterus, vagina, pelvic wall or abdominal wall (T4), Other
- Grade of the prior UCMH episodes (Papillary urothelial carcinoma - low grade, Papillary urothelial neoplasm of low malignant potential, Urothelial carcinoma in situ, Papillary urothelial carcinoma - high grade, Other)
- Prior UCMH episode treated (Yes, No)

- Treatment given for prior episodes of UC (TURBT, Fulguration, BCG, MMC, Other).

10.5. Prior and Concomitant Medications

All medications will be coded using the World Health Organization Drug Dictionary, September 2020 version or later. The Anatomical Therapeutic Chemical (ATC) Level 2, Level 3 and preferred name will be used to list and summarize the medication data. Analysis of prior and concomitant medications use will be performed in the following manner:

- Prior medications: Any UC related medications that were started and stopped prior to the first instillation of UGN-103. The number and percentage of patients reporting the use of prior medications by ATC Level 2, ATC Level 3 and preferred names will be summarized for the ITT analysis set. For computing percentages, the denominator will be the number of patients in the ITT analysis set.

- Concomitant medications: Any medications that are ongoing or any new medication administered following the first instillation of UGN-103. The number and percentage of patients reporting the use of concomitant medications by ATC Level 2, ATC Level 3 and preferred names will be summarized for the ITT analysis set. For computing percentages, the denominator will be the number of patients in the ITT analysis set.

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

10.6. Prior and Concomitant Surgical Procedures

Prior surgical procedures are UC related surgical procedures that are done prior to the first instillation of UGN-103.

Concomitant surgical procedures are surgical procedures performed following the first instillation of UGN-103 through end of study.

All surgical procedures will be coded to a system organ class and PT using the most recent version of the MedDRA dictionary (version 27.0 or later). Prior and concomitant surgical procedures will be summarized by SOC and PT in a similar manner to that described for medical history in Section 10.4.

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

10.7. Study Follow-up

Duration of follow-up (months) in the ITT, PP, and FDA analysis sets is defined as

(last contact date or death date – date of first instillation of UGN-103 + 1) / 30.4375

Duration of follow-up (months) in the 3-Month CR, 3-Month Imputed CR, 3-Month CR PP, and 3-Month CR FDA analysis sets is defined as

(last contact date or death date – 3-Month date + 1) / 30.4375

Duration of follow-up will be summarized using descriptive statistics.

Additionally, the number and percentage of patients who underwent disease assessments will be summarized by Visit.

11. EFFICACY ANALYSES

Efficacy analyses of CRR, DOR, and DCR will be based on the FDA population as defined in Section 5 or a subset of the FDA population as described for each analysis. All analyses will be presented for the single UGN-103 group.

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

11.1. Primary Efficacy Analyses

11.1.1. CRR at 3-Month Visit

The CRR is defined as the proportion of patients in the FDA population who achieved CR at the 3-month Visit (3 months after the first instillation of UGN-103) as determined by cystoscopy, for-cause biopsy, and urine cytology. If response cannot be evaluated for a patient at the 3-month Visit, the patient will be considered as an NCR for the purpose of the analysis and will be included in the denominator of the CRR. Patient response will be evaluated by the investigator according to the evaluation of response (EOR) outlined in the Protocol Appendix 1 and will be recorded on the 3-Month EOR eCRF page.

CRR will be presented along with the exact 95% CIs. The exact two-sided 95% CI for the CRR will be derived using the Clopper-Pearson method (Clopper and Pearson, 1934). In addition, reasons for NCR comprised of 'Residual Disease,' 'Progression', 'Indeterminate', and 'Missing' will be tabulated using the number and percentages of patients.

A sensitivity analysis will be performed in the ITT analysis set where the response at the 3-month Visit will be imputed for the following cases:

- If a patient received SoC or Non-Protocol Therapy (NPT) prior to the 3-month assessment, then the 3-month assessment will be imputed as 'NCR'.
- If the 3-month response is missing or 'Indeterminate', and a patient received SoC or NPT prior to the next disease assessment then the 3-month response will be imputed as 'NCR'.
- If the 3-month response is missing or 'Indeterminate', and a patient has not had any further disease assessment visits then the 3-month response will be imputed as 'NCR'.
- If the 3-month response is missing or 'Indeterminate', and the next disease assessment is 'NCR' or 'Recurrence' then the 3-month response will be imputed as 'NCR'.

- If the 3-month response is missing or 'Indeterminate', and a patient did not receive SoC prior to the next disease assessment and the next disease assessment is 'CR' then the 3-month response will be imputed as 'CR'.

If response cannot be imputed for a patient at the 3-month Visit (e.g., due to death or lost to follow-up or no follow-up visits beyond the 3-month Visit), the patient will be considered as NCR for the purpose of the analysis and will be included in the denominator of the CRR. The date of disease assessment associated with CR/NCR will be determined using the date of cystoscopy, for-cause biopsy, or cytology, whichever occurs first.

Sensitivity analyses will be performed using data from ITT, and PP analysis sets.

11.1.1.1. Subgroup Analysis

Subgroup analyses will be performed on each level of the following factors using the FDA, and ITT populations and corresponding summary tables will be produced. The summaries will also be displayed by forest plots. Additional exploratory subgroup analyses may be performed.

Subgroups will include (but not limited to):

- Baseline age group (years): (< 65, ≥ 65, < 75, and ≥ 75)
- Sex: (Male, Female)
- Region: (US, Non-US)
- BMI category (kg/m^2): (< 30, ≥ 30)
- Treatment course (instillations): (6, < 6)
- Longest tumor diameter pre-biopsy (cm): (≤ 3, > 3)
- Tumor burden pre-biopsy (cm): (≤ 3, > 3)
- Tumor count pre-biopsy: (Single, Multiple)
- Longest tumor diameter post-biopsy (cm): (≤ 3, > 3)
- Tumor burden post-biopsy (cm): (≤ 3, > 3)
- Tumor count post-biopsy: (Single, Multiple)
- Previous LG NMIBC episodes (Yes, No)
- Frequent recurrence, defined as having > 1 previous NMIBC episodes per year (Yes, No)
- Early recurrence, defined as having previous LG NMIBC episodes within 1 year of current diagnosis (Yes, No)
- Early or Frequent recurrence (Yes, No)
- Number of previous LG NMIBC episodes (≤ 1, > 1, ≤ 2, and > 2)
- Prior TURBT to treat LG NMIBC (Yes, No)
- Number of prior TURBT to treat LG NMIBC (≤ 1, > 1, ≤ 2, and > 2)
- Smoking History (Smoker, Non-smoker)

11.2. Secondary Efficacy Analyses

11.2.1. DOR in Patients Who Achieved CR at the 3-month Visit

The secondary endpoint is DOR in patients who achieved CR at the 3-month Visit in the FDA analysis set, defined as the time from the 1st documented CR to the earliest date of recurrence or progression as determined using the date of cystoscopy, for cause biopsy, or cytology, or death due to any cause, whichever occurred first.

The DOR in months is calculated as (first event date / censored date – date of 1st documented CR + 1) / 30.4375.

The distribution of DOR will be estimated using the Kaplan-Meier method. Median times of DOR, first and third quartiles along with 95% CI (Brookmeyer and Crowley, 1982) will be estimated. The median follow-up time along with 95% CI will be estimated using the inverse Kaplan-Meier method. A figure and listing of DOR time will also be provided. This analysis will be based on the 3-month$_{CR}$ analysis set.

A supplementary table showing the details of the number at risk, number of events, and number censored with the event time will also be displayed.

Patients without any adequate disease assessments during the follow-up will be censored at the date of first documented CR at the 3-Month disease assessment. An adequate assessment is defined as an assessment where the visit level response is not missing, and not Indeterminate.

If a patient has not had an event (recurrence or progression or death), DOR will be censored at the date of the last adequate disease assessment. DOR will be censored if no DOR event is observed or the date when a new anti-cancer therapy or another investigational treatment for cancer is started, whichever occurs earlier. The censoring date will be the date of last adequate disease assessment before either of these two dates.

During the Follow-up Period, patients will return to the clinic every 3 months. Patients will remain on study until disease recurrence, disease progression, death, or the last patient completes 12 months of follow-up (i.e., 15 months after the first instillation), whichever occurs first.

A patient will be considered to have an extended lost to follow-up if they missed two or more consecutive adequate assessments. Patients who recurred or progressed or died after an extended lost to follow-up will be censored at their date of last adequate assessment prior to recurrence or progression or death, even if subsequent information is available regarding recurrence or progression or death. For example, a patient will be considered having an extended lost to follow-up during the Follow-up Period if the patient does not have an adequate assessment for 210 days (6 months + 4 weeks = 6*30.4375+28) and then had a recurrence (or progression or death).

If a recurrence or progression or death is observed after a single missing or Indeterminate disease assessment, the actual date of recurrence or progression or death will be used as the event date.

Example (protocol defined schedule of follow-up disease assessments is every 3 months ± 2 week): A patient had the disease assessments at 3 months (CR) - 6 months (CR) – 9

months (missing) – 12 months (missing) - Recurrence. Then the DOR status of this patient will be censored, and the censoring date will be the date of 6-month visit.

Non-Protocol Therapy (NPT) are prohibited concomitant anti-cancer medications or surgical procedures as outlined in Section 6.5 of the Protocol. These medications will be identified via clinical review of the Concomitant Medications and Surgery datasets. If a patient received multiple NPTs, the earliest date will be considered as the start date of NPT. These dates will be used to define event or censoring dates for DOR.

For patients who receive an NPT the following rules will apply:

- If the start date of the NPT is partial (i.e., either missing the day but has the month and year available or missing both day and month), the imputation rules described in Appendix 1 will be applied. No imputation will be made for completely missing dates.
- If the NPT is started prior to documented disease recurrence or progression, then DOR will be censored at the date of the last adequate assessment that is no later than the date of initiation of NPT (i.e., if an assessment occurs on the same day as the start of NPT, the assessment will be used - as it will be assumed the assessment occurred prior to the start of NPT). The date of response at the last adequate assessment will be used as the censoring date.
- If a patient does not have any post-baseline adequate assessment, DOR will be censored at the date of the 3-Month disease assessment.
- If a patient has neither recurrence or progression nor died nor started NPT, then DOR will be censored at the date of the last adequate assessment.

A summary of the assignments for progression and censoring dates for DOR are specified in the following table.

Table 7: Assignments for Event and Censoring Dates for DOR analysis

Scenario	Date of Event or Censoring	Outcome
No adequate assessments during follow-up [a]	Date of 1st documented CR at the 3-Month disease assessment	Censored
Received NPT after 3-Month disease assessment prior to documented recurrence or progression	Date of last 'adequate' assessment [a,b] on or prior to starting NPT [c]	Censored
No recurrence or progression or death	Date of last 'adequate' assessment [a,b]	Censored
No recurrence or progression and the last response evaluation is 'indeterminate'	Date of last 'adequate' assessment [a,b]	Censored

Recurrence or progression or death after 2 or more missed visits	Date of last 'adequate' assessment [a,b] prior to missed assessments	Censored
Disease recurrence or progression documented at or between scheduled visits	Date of first recurrence or progression [b]	Event
Death prior to documented disease recurrence or progression	Date of death	Event

a. An adequate assessment is defined as an assessment where the visit level response is not missing and not indeterminate.
b. The earliest of (i) Date of cystoscopy, or (ii) Date of biopsy, or (iii) Date of cytology.
c. If recurrence/progression and NPT occur on the same day assume the recurrence/progression was documented first.

Sensitivity analyses will be performed based on the 3-month Imputed CR, 3-month CR, and the 3-month CR Per Protocol analysis sets.

Sensitivity analyses may be performed ignoring extended lost to follow-up. That is, patients who recurred or progressed or died after an extended lost to follow-up (i.e., after missing two or more consecutive visits), are considered as events. Additional sensitivity analyses may also be performed ignoring NPT. That is, patients who recurred or progressed or died after receiving NPT are considered as events.

11.2.1.1. Subgroup Analysis

Subgroup analyses will be performed on each level of the subgroups defined in Section 11.1.1.1 and a corresponding summary table will be produced using the 3-month CR FDA, and the 3-month imputed CR analysis sets. The summaries will also be displayed by forest plots.

11.2.2. DCR

DCR rate at scheduled disease assessment timepoints is defined as the proportion of patients in the FDA analysis set who had CR at the 3-Month disease assessment and maintained CR up to that particular follow-up disease assessment. This endpoint will be summarized only for CR patients at the 3-Month visit. Patient response will be evaluated by the investigator according to the guidance on EOR in Protocol Appendix 1 and will be recorded on the follow-up EOR eCRF page.

The EOR will be based on central laboratory results. When central laboratory results are unavailable local laboratory results will be used. When results from both central and local laboratories are available, central laboratory results will supersede the local laboratory results.

Three types of analyses will be performed to estimate the visit level DCR rate. Patients who have an indeterminate response or missed a visit during follow-up will have the response imputed according to the rules specified in Section 11.2.2.1 prior to conducting the analyses.

If a patient receives SoC or any other NPT during the follow-up period, the response status at all subsequent follow-up visits after the SoC (or NPT) start date will be considered as non-DCR for these analyses.

Analysis 1

DCR rate will be presented with nominal 95% exact CI (Clopper-Pearson) at each scheduled timepoint (e.g., 6, 9, 12 months etc.). The denominator to calculate the proportion will include all patients who were CR at 3-month visit.

Number and percentage of patients who have indeterminate response that is not imputed (i.e. not confirmed by subsequent visits) and those who have recurrence of LG disease, or progression, will also be presented at each scheduled timepoint.

This analysis represents the worst-case scenario where all patients are assumed as not CR for all timepoints beyond their last disease evaluation, including those patients who are still ongoing in the study and have not reached those timepoints, and any patients who completed/discontinued the study and would have not reached those timepoints had they not completed/discontinued the study.

Analysis 2

The above analysis will be repeated using as denominator the number of patients who were CR at 3-month visit and reached the follow-up visit or would have reached the follow-up visit at the time of the data read-out had they not recurred, progressed, died, or discontinued the study.

This analysis represents a scenario where all patients who completed/discontinued the study are assumed as not CR for all time points that they would have reached had they not discontinued/completed the study. Any patients ongoing in the study are excluded from timepoints that they have not reached and any patients who have completed/discontinued the study are excluded from timepoints that they would have not reached had they not discontinued/completed the study.

Illustrating cases of patients who had CR at 3-month visit and would be excluded from the denominator of Analysis 2 for computing proportion of patients who maintained CR at 6, 9, 12, and 15 months are provided below.

Table 8: Examples of Exclusion from Time Points for Analysis 2

Cases	Exclusion from time points			
	6-Month	9-Month	12-Month	15-Month
Patient A: ongoing, CR up to 12-Month visit, and has not reached 15-Month visit	No	No	No	Yes
Patient B: ongoing, CR up to 9-Month visit, indeterminate response at 12-Month visit and has not reached 15-Month visit	No	No	No	Yes

Patient C: completed study due to recurrence/progression at 9-Month visit, would have reached up to 12-Month visit had they not recurred/progressed	No	No	No	Yes
Patient D: completed study due to death prior to 9-month visit and would have reached up to 15-Month visit had they not died	No	No	No	No
Patient E: CR up to 6-Month visit, discontinued study prior to 9-Month visit, would have reached up to 12-Month visit had they not discontinued	No	No	No	Yes
Patient F: CR up to 6-Month visit, indeterminate response at 9-Month visit, discontinued study prior to 12-Month visit, would have reached up to 12-Month visit had they not discontinued	No	No	No	Yes

Analysis 3

The above analysis will be repeated using as denominator the number of patients who were CR at 3-month visit and reached the follow-up visit with conclusive disease evaluation (i.e., either CR or recurrence or progression) or would have reached the follow-up visit at the time of the data read-out had they not recurred, progressed, or died.

This analysis makes no assumptions on the response status of patients who do not have a conclusive disease evaluation. Any patients ongoing in the study are excluded from timepoints that they have either not reached or have not had a conclusive disease evaluation (i.e. not confirmed by subsequent visits). Any patients who had CR at their last conclusive disease evaluation prior to completing/discontinuing the study are excluded from subsequent timepoints.

Illustrating cases of patients who were CR at 3-month visit and would be excluded from the denominator of Analysis 3 for computing proportion of patients who maintained CR at 6, 9, 12, 15, and 18 months are provided below. Highlighted in red are the cases where Analysis 2 and Analysis 3 differ.

Table 9: Examples of Exclusion from Time Points for Analysis 3

Cases	Exclusion from time points			
	6-Month	9-Month	12-Month	15-Month
Patient A: ongoing, CR up to 12-Month visit, and has not reached 15-Month visit	No	No	No	Yes

Patient B: ongoing, CR up to 9-Month visit, indeterminate response at 12-Month visit and has not reached 15-Month visit	No	No	Yes	Yes
Patient C: completed study due to recurrence/progression at 9-Month visit, would have reached up to 12-Month visit had they not recurred/progressed	No	No	No	Yes
Patient D: completed study due to death prior to 9-month visit and would have reached up to 15-Month visit had they not died	No	No	No	No
Patient E: CR up to 6-Month visit, discontinued study prior to 9-Month visit, would have reached up to 12-Month visit had they not discontinued	No	Yes	Yes	Yes
Patient F: CR up to 6-Month visit, indeterminate response at 9-Month visit, discontinued study prior to 12-Month visit, would have reached up to 12-Month visit had they not discontinued	No	Yes	Yes	Yes

Sensitivity analyses may be performed based on the 3-month Imputed CR analysis set and on the 3-month CR analysis set.

11.2.2.1. Imputation of Missing Visit Level Response

The following rules will be used to impute missing or indeterminate visit level responses:

1. If any recorded response is CR, then all previous missing or indeterminate scheduled visits responses will be considered CR (Patient A in Table 10), using the method last observation carried backward (LOCB).
2. If any recorded response is recurrence disease (RD), then all previous missing or indeterminate scheduled visits responses will be considered RD (Patient B; Patient C in Table 10), using the method last observation carried backward (LOCB); unless there is a previous CR response from an unscheduled visit closer in time (days) to the scheduled visit in which case the visit response will be CR (Patient D), using the method last observation carried forward (LOCF). In the case of ties, the scheduled visit response will be RD (Patient E in Table 10).
3. Otherwise, responses will not be carried forward to scheduled visits that have not occurred (Patient C; Patient E in Table 10)

Table 10: Imputation of Missing Visit Level Response

Visit	Target Day/ Study Day	Visit Window	Patient A	Patient B	Patient C	Patient D	Patient E
3-Month	90 (± 1 week)	83-97	CR	CR	CR	CR	CR
6-Month	180 (± 2 week)	166-194	U/CR	U/ RD	U/RD	CR	CR
Unscheduled	190						CR
Unscheduled	220					CR	
9-Month	270 (± 2 week)	256-284	CR	RD	RD	CR	RD
Unscheduled	300				RD		
Unscheduled	350						RD
12-Month	360 (± 2 week)	346-374				RD	
…….							

RD = Recurrence disease; U = Unknown/Indeterminate; Red indicates imputed response.

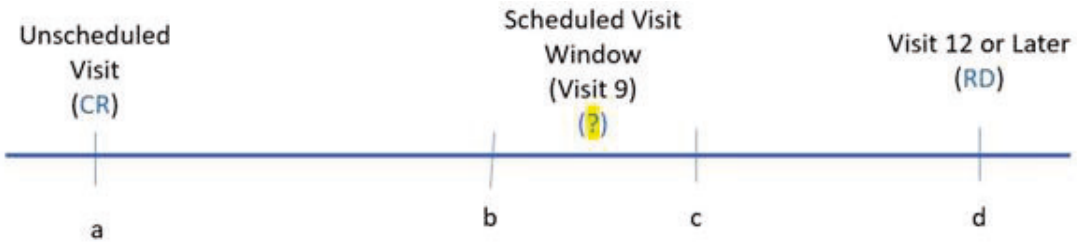
To further explain 'closer in time (days) to the scheduled visit,' the following variables are defined:

a = Study day of the CR unscheduled visit

b = Lower limit of next scheduled visit (days)

c = Upper limit of the next scheduled visit (days)

d = Study day of the following RD visit



If (b-a) < (d-c) then the response at the scheduled visit will be CR; otherwise, RD.

For example, Patient D has a CR response on Study Day 220, 36 days before the beginning of the 9-Month Visit window. This patient also has a RD response on study day 346 (say), 62 days (346-284) after the end of the 9-Month Visit window. Since the CR response is closer to the 9-Month Visit, the response will be CR.

A patient listing will be generated to display visit level responses as recorded in the eCRF along with derived responses (indicating the method of derivation, LOCF or LOCB). Evaluation based on local laboratory results will be flagged.

If the 3-month EOR is 'Indeterminate', it will be imputed using the rules defined in Section 11.1.1.

11.3. Exploratory Efficacy Analyses

11.3.1. Preliminary Responses Following SoC Treatment in 3-month NCR Patients

Preliminary responses (approximately 3 months) following SoC treatment in 3-month NCR patients are defined as the response outcomes evaluated at the EOS visit 3 months after SoC. The number (%) of CR and NCR responders (as defined in EOS Evaluation of Response eCRF) will be summarized using descriptive statistics and the 95% exact CI of CRR will be calculated. A listing will also be provided. This analysis will be based on the 3-Month NCR analysis set.

11.3.2. Pathological Evaluation by Visit

The pathological evaluation of cystoscopy/histopathology and urine cytology will be summarized at baseline, each planned visit, and for periods between planned visits where any unscheduled evaluations will be grouped together. The following will be provided by counts and percentage: number of lesions, visual appearance of the lesions, staging, primary diagnosis, and urine cytology result.

A summary of lab review source (central, local) for determination of disease at enrollment and during study will be generated.

Summaries of concordance between central and local lab review of biopsy samples collected at screening and during the study (Month 3 or follow-up) will be provided.

11.3.3. SoC Procedures for Residual Disease or Progression at 3-Month Visit

The SoC procedures done for residual disease or progression at the 3-month Visit will be summarized using counts and percentages. A listing will also be provided. This analysis will be performed on the 3-Month NCR analysis set.

12. PATIENT REPORTED OUTCOME (PRO) ANALYSES

The ITT analysis set will be used for analyzing PRO data unless specified differently. The PRO will be assessed using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire for Cancer Patients (QLQ-C30) and Treatment Satisfaction Questionnaire for Medication (TSQM) questionnaires provided in Protocol Appendix 2 and Appendix 3, respectively. These questionnaires will be completed by patients following the SoA (Protocol Section 1.3). The baseline is defined as the last PRO assessment prior to the first instillation.

12.1. Quality of Life Questionnaire for Cancer Patients (QLQ-C30)

The EORTC QLQ-C30 assesses a variety of side effects that are common during cancer treatment, including fatigue, pain, nausea and vomiting, dyspnea, insomnia, appetite loss, constipation and diarrhea, mood, cognition, physical functioning, role functioning (daily activities), and a global health status scale. The recall period for the items is the past week.

The EORTC QLQ-C30 is composed of both multi-item scales and single-item measures. These include 5 functional scales, 3 symptom scales, a global health status / quality of life (QoL) scale, and 6 single items as detailed in the table below. No item occurs in more than one scale.

Table 11: EORTC QLQ-C30 Domain

Functional Scales (15 Questions)	**Symptom Scales (7 Questions)**	**Symptom Single Items (6 Questions)**	**Global QoL (2 Questions)**
Physical [redacted]	Fatigue [redacted]	Constipation [redacted]	Global QoL [redacted]
Role [redacted]	Pain [redacted]	Diarrhea [redacted]	
Cognitive [redacted]	Nausea/Vomiting [redacted]	Insomnia [redacted]	
Emotional [redacted]		Dyspnea [redacted]	
Social [redacted]		Appetite loss [redacted]	
		Financial difficulties [redacted]	

All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. Thus, a high score for a functional scale represents a high/healthy level of functioning; a high score for the global health status/QoL represents a high QoL, but a high score for a symptom scale/item represents a high level of symptomatology/problems.

Patients will be asked to complete the questionnaire as completely and accurately as possible. Missing data will be handled as recommended in the EORTC scoring manual:

[redacted]

[redacted]

A summary table and associated bar charts of patient disposition and completion rates will be provided for the functional/symptom scales, the global QoL, and the single items at baseline, each planned visit, and worst-case post-baseline (includes both scheduled and unscheduled assessments).

Summary statistics of the observed values will be provided for the functional/symptom scales, the global QoL, and the single items at baseline, each planned visit, and worst-case post-baseline (includes both scheduled and unscheduled assessments). The change from baseline will also be summarized with summary statistics at each of the above-mentioned timepoints. In addition, figures showing mean values of observed and change from baseline will be provided for the functional/symptom scales, the global QoL, and the symptom single item. A listing of the above-mentioned score values will be produced for each patient.

A summary table and associated bar charts of categorical responses and change from baseline in categorical responses will be provided for each single item at baseline, each planned visit, and worst-case post-baseline (includes both scheduled and unscheduled assessments).

12.2. Treatment Satisfaction Questionnaire for Medication (TSQM)

The TSQM is a general measure of patient satisfaction with medication consisting of 14 questions for 4 domains: effectiveness, side effects, convenience, and global satisfaction.

Table 12: TSQM Domain

Domain	Item	Response Categories, n
Effectiveness	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]

Side effects	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
Convenience	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
Global satisfaction	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]

Each domain score will be computed by summing the individual TSQM items in each domain and then transforming the composite score into a value ranging from 0 to 100, with higher scores indicating higher patient satisfaction with medication. [redacted]

[redacted]

A summary table and associated bar charts of patient disposition and completion rates will be provided for the 4 domains at each planned visit, and worst-case post-baseline (includes both scheduled and unscheduled assessments).

Summary statistics of the observed values will be provided for 4 domain scores at each planned visit and worst-case post-baseline (includes both scheduled and unscheduled assessments). The change from Week 6 will also be summarized with summary statistics at each of the above-mentioned timepoints. In addition, figures showing the mean of observed scores and change from Week 6 over time for each domain will be provided. A listing of the 4 domain scores and each item will be produced for each patient.

A summary table and associated bar charts of categorical responses and change from baseline in categorical responses will be provided for each single item at baseline, each planned visit, and worst-case post-baseline (includes both scheduled and unscheduled assessments).

13. SAFETY ANALYSES

All safety analyses will be based on the safety analysis set. All tables and listings will display the analysis population as ‘Safety Analysis Set’.

13.1. Extent of Exposure of UGN-103

Treatment exposure of UGN-103 will be categorized as follows:

- 1 instillation of UGN-103
- 2 instillations of UGN-103
- 3 instillations of UGN-103
- 4 instillations of UGN-103
- 5 instillations of UGN-103
- 6 instillations of UGN-103

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-103 dose (mg) instilled at week 1 through week 6 will be presented.

A data listing of treatment exposure will be presented.

13.2. Adverse Events

AEs will be coded according to the latest version of MedDRA. AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

All AEs (including local and systemic reactions not meeting the criteria for SAEs) and SAEs will be collected from the signing of the ICF until the 6-month Visit. After the 6-month Visit, all SAEs (regardless of causality) and non-serious AEs assessed as related to study treatment or study procedures will be collected at all visits until the EOS Visit.

A treatment-emergent adverse event (TEAE) is defined as an AE that occurs or worsens on or after the day of the first instillation of UGN-103; or a pre-treatment AE that worsens during the study.

TEAE incidence will be presented as the number and percentage of patients with a specific TEAE. Percentages will be calculated as the number of patients with TEAE divided by the number of patients in the treatment group, except for sex-specific PTs where percentages will be calculated using only males or only females in the denominator.

An overall summary with number and percentage of patients with all AEs, TEAEs, different TEAE categories, including Grade $\geq$ 3, treatment-related, procedure-related, serious, serious related to treatment or procedure, leading to treatment discontinuation, treatment interruption, study discontinuation, fatal, and AESIs will be provided.

Separate summaries will be provided for study treatment-related TEAEs and study procedure-related TEAEs. A study treatment-related AE is defined as an AE for which the investigator classifies the relationship to study treatment (UGN-103) as “Related”. A study procedure-related AE is defined as an AE for which the investigator classifies the relationship to study procedure (e.g., cystoscopy, biopsy, MRI, pyelogram, CT urogram, catheter insertion, cytology) as “Related’. A worst-case scenario approach will be taken to handle missing relatedness data, i.e., the summary table will include events with the relationship to study treatment as ‘Yes’ if missing. The same approach for missing data will be applied to study procedure-related SAEs.

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 and for each 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 PT will be summarized under the maximum CTCAE grade recorded for the event.

In AE summaries, the primary system organ class will be presented by descending order of frequency (alphabetically for ties), then PTs will be sorted by descending order of frequency within each system organ class (alphabetically for ties).

The overall observation period will be divided into three mutually exclusive time periods:

1. Pre-treatment period: from day of patient’s informed consent to the day before administration of first treatment
2. Up to 3-months: from day of first treatment administration to 3-month visit
3. Post 3-months: after the 3-month visit until the end of the study.

Some key TEAE tables will be summarized by the following time periods: overall (anytime during the study from the treatment start date), up to 3-month and post 3-month. This will help to distinguish the AE profile of UGN-103 from SoC procedures as patients who are NCR at the 3-Month visit will undergo SoC. The calculation of percentages for the post 3-months period will be based on the number of patients who completed/discontinued or are ongoing in the study after the 3-month visit.

The overall summary of AEs, and the summary of all TEAEs by PT will also be generated using the following subgroups (but not limited to):

- Age (years): < 65, ≥ 65
- Sex: Male, Female
- Region: US, Non-US
- BMI (kg/m2): < 30, ≥ 30
- Renal Impairment: Normal, Mild, Moderate, Severe
- Hepatic Impairment: Yes, No
- Diabetes Mellitus History: Yes, No

A listing of all AEs will be presented.

13.3. 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).

All serious TEAEs will be tabulated based on the number and percentage of subjects who experienced the event. Separate summaries will also be provided for study treatment-related serious TEAEs and procedure-related serious TEAEs. The summary tables will be displayed in descending order of incidence by system organ class (SOC) and PT.

A study treatment-related SAE is defined as an SAE for which the investigator classifies the relationship to study treatment (UGN-103) as “Related”. A study procedure-related SAE is defined as an SAE for which the investigator classifies the relationship to study procedure (e.g., cystoscopy, biopsy, MRI, pyelogram, CT urogram, catheter insertion, cytology) as “Related’. A worst-case scenario approach will be taken to handle missing data, i.e., the summary table will include events with the relationship to study treatment as ‘Yes’ if missing. The same approach for missing data will be applied to study procedure-related SAEs.

A separate listing for SAEs will be generated.

13.4. Adverse Events Leading to Discontinuation of Study Treatment and/or Withdrawal from the Study

The following categories of TEAEs will be summarized separately in descending order of incidence by system organ class and PT and separate supportive listings will be generated with patient level details for those patients:

- TEAEs Leading to Treatment Discontinuation
- TEAEs Leading to Treatment Interruption
- TEAEs Leading to Study Discontinuation

13.5. Adverse Events of Special Interest

An AESI is an AE of potential scientific and medical concern specific to UGN-103. AESIs will be identified through manual clinical/safety review of all AEs by system organ class and PT prior to the database lock.

[redacted]

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 and related to study procedure, 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. In addition, the onset and duration of the first occurrences for each type of events will be summarized if data permits. These summaries will be provided for each type of AESI separately.

[redacted]

AESIs will be flagged in the general AE listing.

13.6. Clinical Laboratory Evaluations

Samples for hematology, serum chemistry and urinalysis will be collected at Screening and subsequent visits following the Protocol SoA (Section 1.3). Samples will be tested at the central laboratory. Additional tests may be part of a clinical site's local laboratory's standard panel and therefore reported along with these specified tests. Data from all sources (central and local laboratories) will be combined, and the reference ranges of the central laboratory will be used for analyses. When results from both central and local laboratories are available, central laboratory results will supersede the local laboratory results.

Hematology and serum chemistry results will be standardized to both conventional units and SI units and will be stored in the datasets. Summaries of laboratory parameters will include hematology and serum chemistry using SI units. Baseline will be defined as the latest non-missing assessment prior to the first instillation of UGN-103, i.e., prior to Day 1. Changes in hematology and serum chemistry variables between baseline and each subsequent assessment will be calculated. For values recorded with a leading greater than or less than ('>,' '<') symbol, the reported numeric value will be used for analysis and the value with the symbol will be included in the listings, unless otherwise specified. For example, a value of <0.01 will be analyzed as 0.01 and listed as <0.01.

The summary of observed values of the laboratory 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 lab values.

Summaries of worst-case grade increase from baseline grade will be provided for all the lab tests that are gradable by CTCAE version 5.0 (Appendix 2). These summaries will display the number and percentage of patients with a maximum post baseline grade increasing from their baseline grade. Any increase in grade from baseline will be summarized along with any increase to a maximum grade of 3 and any increase to a maximum grade of 4. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

For lab tests that are not gradable by CTCAE version 5.0, summaries of worst-case changes from baseline with respect to normal range will be generated. Decreases to low, changes to normal or no changes from baseline, and increases to high will be summarized at each planned time. If a patient has a decrease to low and an increase to high during the same time interval, then the patient is counted in both the "Decrease to Low" categories and the "Increase to High" categories.

Listing of patients with laboratory values outside the laboratory normal ranges will be generated. Complete listings of hematology and chemistry laboratory values will be generated. Scatter plots of baseline vs worst post-baseline values for ALT, AST, and TBL will also be generated.

No summary table of urinalysis will be produced. Urinalysis laboratory values with change from baseline will be listed.

13.6.1. 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 the following table.

The summary will be repeated for (but not limited to) the subgroups defined in Section 13.2.

Table 13: PCS Laboratory Criteria

Laboratory Parameter	SI Unit	Lower Limit	Upper Limit
Chemistry			
Creatinine	umol/L		>194
Sodium	mmol/L	≤130	>150
Potassium	mmol/L	<3.0	>5.5
Total bilirubin	umol/L		>1.5 × ULN
ALT	U/L		>3 × ULN
AST	U/L		>3 × ULN
GGT	U/L		>2.5 × ULN
Hematology			
Hemoglobin	g/L	<0.8 × LLN and >20% decrease from baseline	>1.3 × ULN and >30% increase from baseline
Leukocytes	$\times 10^9$/L	≤ 2.8	≥ 16.0
Lymphocytes	$\times 10^9$/L	<0.5	>20
Neutrophils	$\times 10^9$/L	<1.0	
Platelets	$\times 10^9$/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

13.6.2. 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 the following table.

Table 14: Liver Function Tests Criteria

Parameter	Criterion
ALT	>3×ULN; >5×ULN; >10×ULN
AST	>3×ULN; >5×ULN; >10×ULN
ALP	>2xULN
TBL	>2xULN
ALT and TBL	ALT >3×ULN and TBL >2×ULN
AST and TBL	AST >3×ULN and TBL >2×ULN
ALP and TBL	ALP >2xULN and TBL >2xULN
Hy's Law met	ALT or AST >3×ULN and TBL >2×ULN and ALP <2×ULN

ALP = alkaline phosphatase; 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.

13.7. 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 Protocol SoA (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.

13.7.1. 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 the following table.

Table 15: 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

13.8. General Physical Examination

General physical examinations as described in Section 8.2.1 of the Protocol will be performed at the screening visit only. Abnormal results (clinically significant or not clinically significant) will be listed by the body system.

13.9. Urology-Oriented Examination

Urology-oriented examinations as described in Section 8.2.1 of the Protocol, will be performed at screening and subsequent visits following the Protocol SoA (Section 1.3).

Abnormal results (clinically significant or not clinically significant) will be summarized for each body system by planned visits, and worst-case post-baseline (includes both scheduled and unscheduled assessments) as time points.

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

14. PHARMACOKINETIC ANALYSES

Patients at select sites will be asked to participate in blood sample collection for PK analysis. A subgroup of 9-12 patients who provide informed consent will have blood samples collected pre-dose and 0.5 (± 5 min), 1, 2, 3, 4, 5, and 6 hours (± 15 min at all time points) after the first instillation of UGN-103. Concentration data will be listed for each patient, summarized using descriptive statistics, and will be plotted over time since the 1st instillation in the normal and the log scale.

The following PK parameters will be listed for each patient and summarized using descriptive statistics:

- C_{max} – Observed maximum plasma concentration
- t_{max} – Time to reach maximum plasma concentration
- AUC_{0-6} – Area under the concentration-time curve from time zero to 6 hours post-instillation on Day 1, calculated using the linear trapezoidal rule

The PK parameters obtained, specifically the C_{max}, will be compared to the mitomycin plasma concentration known to be associated with myelosuppression (400 ng/mL). No samples will be used for non-study related purposes.

15. PHARMACODYNAMIC AND BIOMARKER ANALYSES

Pharmacodynamic parameters are not evaluated in this study.

Tumor tissue from an archival biopsy obtained within 12 months before screening (if available) and remaining tumor tissue from on study visits may be used for correlative studies to understand mechanisms of sensitivity and/or resistance to UGN-103. Biomarker analyses may be performed using these samples and are out of scope of this SAP.

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.

Clopper CJ and Pearson ES (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrical*, 26, 404-413.

18. APPENDICES

Appendix 1 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 16: 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 17: Imputation Rules of Prior or Concomitant Medication (CM) Start and End Dates

Dataset	Date	Missing Element	Rule
CM	Start Date	day, month,	• No Imputation for completely missing dates

		and year	
		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 if year is missing
		day, month	• Min (Last visit date, 31DECYYYY, Date of Death) • If imputed CM end date < CM start date (complete or imputed), then imputed CM end date should be set to CM start date.
		day	• Min (Last visit date, last day of the month, death day) • If imputed CM end date < CM start date (complete or imputed), then imputed CM end date should be set to CM start date.

Table 18: 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 of start date of the current urothelial carcinoma diagnosis, then set MH start date = start date of the last prior urothelial carcinoma episode. • 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 if year is missing
		day, month	• Min (Start date of the current urothelial carcinoma diagnosis, Last visit date, 31DECYYYY, Date of Death) • If imputed MH end date < MH start date (complete or imputed), then imputed MH end date should be set to MH start date.
		day	• Min (Start date of the current urothelial carcinoma diagnosis, Last visit date, last day of the month, death day) • If imputed MH end date < MH start date (complete or imputed), then imputed MH end date should be set to MH start date.

Table 19: 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 2 Laboratory CTCAE Grade Version 5.0 Criteria

Table 20: Laboratory CTCAE Grade Version 5.0 Criteria

Lab Parameter	SI Unit	CTCAE Grade v5.0				
		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin decreased (Anemia)	g/L	≥LLN	100 – <LLN	80 – <100	< 80	
Hemoglobin increased	g/L	≤ULN	>ULN – 20 + ULN	>20 + ULN – 40 + ULN	>40 + ULN	
Albumin (Hypoalbuminemia)	g/L	≥LLN	30 - <LLN	20 - <30	<20	
Alkaline phosphatase increased	IU/L	≤ULN	BASE Normal [a]: >ULN – 2.5 × ULN BASE Abnormal: 2 × BASE – 2.5 × BASE	BASE Normal [a]: >2.5 × ULN – 5.0 × ULN BASE Abnormal: >2.5 × BASE – 5 × BASE	BASE Normal [a]: >5.0 × ULN – 20.0 × ULN BASE Abnormal: >5 × BASE – 20 × BASE	BASE Normal [a]: >20.0 × ULN BASE Abnormal: >20 × BASE
Alanine aminotransferase increased	U/L	≤ULN	BASE Normal [a]: >ULN – 3 × ULN BASE Abnormal: 1.5 × BASE – 3 × BASE	BASE Normal [a]: >3 × ULN – 5 × ULN BASE Abnormal: >3 × BASE – 5 × BASE	BASE Normal [a]: >5 × ULN – 20 × ULN BASE Abnormal: >5 × BASE – 20 × BASE	BASE Normal [a]: >20 × ULN BASE Abnormal: >20 × BASE
Aspartate aminotransferase increased	U/L	≤ULN	BASE Normal [a]: >ULN – 3 × ULN BASE Abnormal: 1.5 × BASE – 3 × BASE	BASE Normal [a]: >3 × ULN – 5 × ULN BASE Abnormal: >3 × BASE – 5 × BASE	BASE Normal [a]: >5 × ULN – 20 × ULN BASE Abnormal: >5 × BASE – 20 × BASE	BASE Normal [a]: >20 × ULN BASE Abnormal: >20 × BASE
Blood bilirubin increased	umol/L	≤ULN	BASE Normal [a]: >ULN – 1.5 × ULN BASE Abnormal: >BASE – 1.5 × BASE	BASE Normal [a]: >1.5 × ULN – 3 × ULN BASE Abnormal: >1.5 × BASE – 3 × BASE	BASE Normal [a]: >3 × ULN – 10 × ULN BASE Abnormal: >3 × BASE – 10 × BASE	BASE Normal [a]: >10 × ULN BASE Abnormal: >10 × BASE
Creatinine increased	umol/L	≤ULN	>ULN – 1.5 × ULN	>1.5 × ULN – 3 × ULN or >1.5 × BASE – 3 × BASE	>3 × ULN – 6 × ULN or >3 × BASE	>6 × ULN
Gamma-glutamyl transferase increased	U/L	≤ULN	BASE Normal [a]: >ULN – 2.5 × ULN BASE Abnormal: 2 × BASE – 2.5 × BASE	BASE Normal [a]: >2.5 × ULN – 5 × ULN BASE Abnormal: >2.5 × BASE – 5 × BASE	BASE Normal [a]: >5 × ULN – 20 × ULN BASE Abnormal: >5 × BASE – 20 × BASE	BASE Normal [a]: > 20 × ULN BASE Abnormal: >20 × BASE
Eosinophils increased (Eosinophilia)	$\times 10^9$/L	≤ULN	BASE Normal [a]: >ULN BASE Abnormal: >ULN and >BASE			
Lymphocyte count decreased	$\times 10^9$/L	≥LLN	0.8 – < LLN	0.5 – <0.8	0.2 – <0.5	<0.2
Lymphocyte count increased	$\times 10^9$/L	≤4		>4 - 20	>20	

Neutrophil count decreased	$\times 10^9$/L	≥LLN	1.5 – <LLN	1.0 – <1.5	0.5 – <1.0	<0.5
Platelet count decreased	$\times 10^9$/L	≥LLN	75 – <LLN	50 – <75	25 – <50	<25
White blood cell decreased	$\times 10^9$/L	≥LLN	3.0 – <LLN	2.0 – <3.0	1.0 – <2.0	<1.0
White blood cell increased (Leukocytosis)	$\times 10^9$/L	≤100			>100	
Hyperkalemia (Potassium increased)	mmol/L	≤ULN	>ULN – 5.5	>5.5 – 6.0	>6.0 – 7.0	>7.0
Hypokalemia (Potassium decreased)	mmol/L	≥LLN		3.0 – <LLN	2.5 – <3.0	<2.5
Hypernatremia (Sodium increased)	mmol/L	≤ULN	>ULN – 150	>150 – 155	>155 – 160	>160
Hyponatremia (Sodium decreased)	mmol/L	≥LLN	130 – <LLN	125 – <130	120 – <125	<120
Notes: BASE = baseline; LLN = lower limit of normal; ULN = upper limit of normal a. Also apply for baseline values, or when BASE is missing.						