# STATISTICAL ANALYSIS PLAN

**VERSION: 1.0**

**DATE: 19January 2024**

**STUDY DRUG:**

**Lurbinectedin**

**Protocol/STUDY Number:**

*JZP712-201 Protocol Amendment 2 (14-Oct-2022)*

**STUDY TITLE:**

*EMERGE-201: A phase 2, multicenter, open-label study of lurbinectedin efficacy and safety in participants with advanced or metastatic solid tumors*

**SPONSOR:**

*Jazz Pharmaceuticals*

*3170 Porter Dr, Palo Alto, CA 94304*

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

# Signature Page

This document has been prepared by:

DocuSigned by:
[redacted]
DEAD014948F54E9...

31 January 2024

Signature | Date

Study Biostatistician,
Biometrics
Jazz Pharmaceuticals, Inc.

This document has been reviewed and approved by:

DocuSigned by:
[redacted]
D908FED4ED294BD...

31 January 2024

Signature | Date

Senior Director, Biostatistics
Biometrics
Jazz Pharmaceuticals, Inc.

DocuSigned by:
[redacted]
01C1EDC751374B9...

05 February 2024

Signature | Date

Medical Monitor
Director, Clinical Development
Jazz Pharmaceuticals, Inc.

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# 1. LIST OF ABBREVIATIONS

**Table 1: List of Abbreviations**

| Abbreviation | Term |
|---|---|
| AE | Adverse Event |
| AAGP | Alpha-1 Acid Glycoprotein |
| ALT | Alanine Aminotransferase |
| AP | Alkaline Phosphatase |
| AST | Aspartate Aminotransferase |
| ATC | Anatomical Therapeutic Chemical |
| BOR | Best Overall Response |
| BLLQ | Below the Lower Limit of Quantification |
| BPP | Bayesian Posterior Probability |
| BSA | Body Surface Area |
| CI | Confidence Interval |
| CR | Complete Response |
| CrCl | Creatinine Clearance |
| CPK | creatinine phosphokinase |
| CRF | Case Report Form |
| CSR | Clinical Study Report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CV | coefficient of variation |
| DCR | Disease Control Rate |
| DOR | Duration of Response |
| ECG | Electrocardiogram |
| ECHO | Echocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| EOS | end-of-study |
| EOT | end of treatment |
| eCRF | electronic case report form |
| GGT | Gamma-glutamyl transferase |
| HBcAb | hepatitis B core antibody |
| HBsAg | hepatitis B surface antigen |

| | |
|---|---|
| HER-2 | Human Epidermal Growth Factor receptor 2 |
| HIV | human immunodeficiency virus |
| HRD | homologous recombination deficient |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| IRT | Interactive Response Technology |
| K-M | Kaplan-Meier |
| PD-NEC | poorly differentiated neuroendocrine carcinoma |
| LDH | lactate dehydrogenase |
| LLOQ | Lower Limit of Quantification |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NCI | National Cancer Institute |
| [redacted] | [redacted] |
| ORR | Overall Response Rate |
| OS | Overall Survival |
| PD | Progressive Disease |
| PFS | Progression-free Survival |
| [redacted] | [redacted] |
| PR | Partial Response |
| PT | Preferred Term |
| PTT | partial thromboplastin time |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| Q3W | every 3 weeks |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SAS | Statistical Analysis Software |
| SD | Stable Disease |
| SOC | System Organ Class |
| SD | Standard Deviation |
| TEAE | Treatment Emergent Adverse Event |
| TTP | Time to Progression |
| TTR | Time to Response |
| UC | urothelial cancer |

| | |
|---|---|
| ULN | Upper Limit of Normal |
| UTD | Unable to determine |
| WHO | World Health Organization |

# 2. MODIFICATION HISTORY

Version History for SAP:

| Version | Date | Description |
|---|---|---|
| Original | | |
| | | |

# 3. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe in detail the statistical methodology and planned analyses to be conducted for Study *JZP712-201* for inclusion in the clinical study report (CSR). The current version of the SAP is based on Protocol Amendment 2 dated 14-Oct-2022. Any additional analyses or deviation from the analyses outlined in this plan will be documented with rationale in the final CSR. Mock tables, listings, and figure shells will be provided in a separate supporting document.

This SAP complies with the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline Topic E9, Statistical Principles for Clinical Trials.

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

# 4. STUDY OBJECTIVES AND ENDPOINTS

## 4.1. Study Objectives

### 4.1.1. Primary Objective

- To evaluate the antitumor activity of lurbinectedin in the selected advanced solid tumors.

### 4.1.2. Secondary Objectives

- To evaluate the overall safety profile of lurbinectedin in the selected advanced solid tumors.
- To assess other antitumor efficacy parameters of lurbinectedin in the selected advanced solid tumors.

[redacted]

- [redacted]
- [redacted]

## 4.2. Study Endpoints

### 4.2.1. Primary Endpoint

- Investigator-assessed objective response rate (ORR) according to RECIST v1.1.

### 4.2.2. Secondary Endpoints

- Adverse events (AEs) and serious adverse events (SAEs) as graded by NCI CTCAE v.5.0.
- Investigator-assessed duration of response (DOR) according to RECIST v1.1.

[redacted]

- [redacted]
- [redacted]

# 5. STUDY DESIGN

## 5.1. Summary of Study Design

This is an open-label, multicenter, phase 2 study of lurbinectedin monotherapy in participants with advanced (metastatic and/or unresectable) solid tumors.

The study population comprises participants in 3 cohorts with advanced (metastatic and/or unresectable) urothelial cancer (UC), advanced (metastatic and/or unresectable) poorly differentiated neuroendocrine carcinoma (PD-NEC), or homologous recombination deficient (HRD)-positive tumor agnostic malignancies.

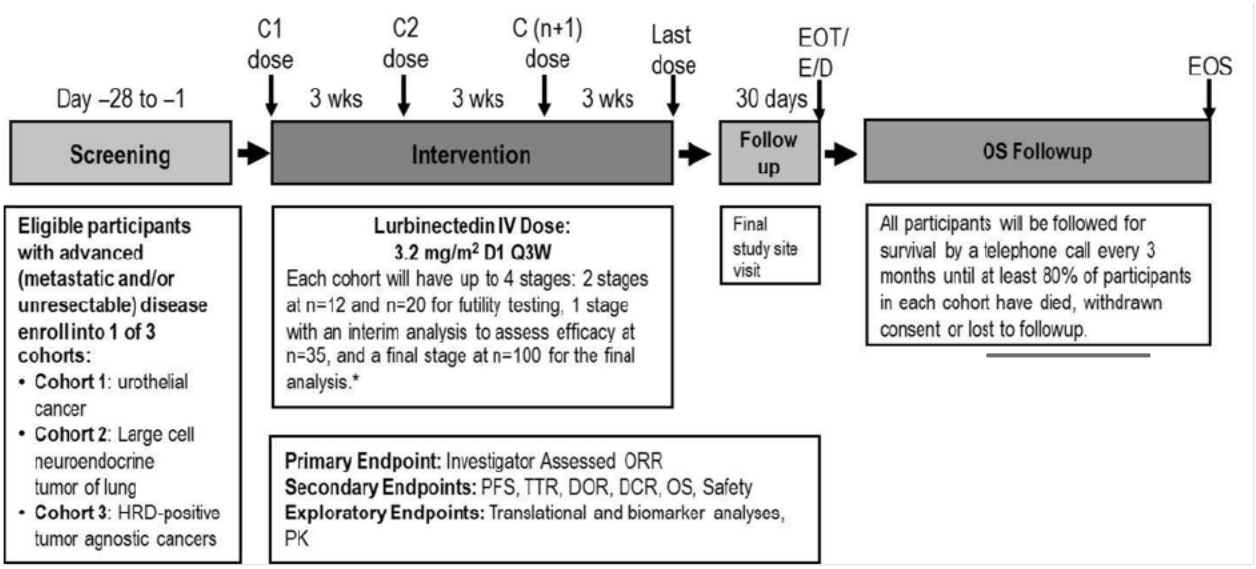
This is a signal-seeking study of lurbinectedin 3.2 mg/m$^2$ monotherapy Q3W. Review of the safety and efficacy data will be performed on an ongoing basis by the sponsor. The sponsor may decide to close a cohort or cohorts due to safety concerns, lack of efficacy or any other reasons. A cohort or cohorts may be expanded at the sponsor's discretion to greater than 20 participants if an efficacy signal is observed without any safety concerns.

Beginning on Cycle 1 Day 1, participants still on study treatment will undergo tumor assessments per RECIST v1.1 every 6 weeks (± 7 days) through Week 36, regardless of treatment dose delays. After Week 36, tumor assessments will be required every 12 weeks (± 14 days). Participants will undergo tumor assessments until radiographic disease progression, withdrawal of consent, lost to follow-up, study termination by the sponsor, or death, EOT visit, or study termination, whichever occurs first. After the EOT visit, all participants will be followed for survival by a telephone call every 3 months until at least 80% of participants in each cohort have died or withdraw consent or are lost to follow-up. If a cohort closes due to futility, the OS follow-up for that cohort will end.

The projected study duration for each participant will be approximately 17 months including: Screening Period (28 days), Intervention Period (9 months), Safety Follow-up Period (30 days), and OS Follow-up Period (6 months).

An overview of the study design is illustrated in Figure 1 and details regarding study assessments are in Appendix 1.

**Figure 1: Study Schematic**




Abbreviations: C = cycle; D = day; E/D = early discontinuation; EOS = end of study; HRD = homologous recombination deficient; OS = overall survival; Q3W= every 3 weeks; wks = weeks.

## 5.2. Study Treatment

Participants will receive lurbinectedin 3.2 mg/m$^2$ IV on Day 1 of Q3W cycle. Lurbinectedin (JZP712) also known as PM01183 is a lyophilized powder for concentrate for solution for infusion. All participants will receive standard antiemetic prophylaxis before each treatment infusion.

For any treatment delay due to treatment-related AEs lasting more than 1 week, a dose reduction should be implemented upon recovery. Participants may continue the study treatment at a reduced dose if they present any of the following:

- Grade ≥ 3 treatment-related nonhematological toxicity. Exceptions are Grade ≥ 3 nausea and/or vomiting not optimally treated, Grade 3 asthenia lasting ≤ 3 days, Grade 3 diarrhea lasting ≤ 2 days or not optimally treated, Grade 3 transient ALT/AST elevations that are rapidly reversible and not leading to subsequent delays, and nonclinically relevant biochemical abnormalities
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia concomitantly with Grade ≥ 3 bleeding
- Grade 4 neutropenia, any grade febrile neutropenia or neutropenia associated with infection/sepsis
    - Note: Participants with Grade 4 neutropenia may continue with secondary G-CSF prophylaxis instead of dose reduction. However, if the episode is repeated despite secondary G-CSF prophylaxis, then the dose must be reduced.
- Frequent or prolonged (> 1 week) dose delays due to treatment-related AEs
- Unacceptable toxicity in the judgement of the investigator.

Participants who experience Grade 3/4 hypersensitivity reactions will be discontinued from study intervention.

Dose reduction levels are shown in Table 2. Up to 2 dose reductions are allowed per participant.

**Table 2: Lurbinectedin Dose Reduction Levels**

| Dose Reduction | Lurbinectedin Dose ($mg/m^2$) |
|---|---|
| 1 (starting dose) | 3.2 |
| -1 | 2.6 |
| -2 | 2.0 |

Participants who continue to experience treatment-related toxicity and/or frequent dose delays after permitted dose reductions should be discontinued from the study. However, they can continue receiving the study intervention if objective clinical benefit is adequately documented by the Investigator, and upon agreement with the Sponsor. Once the dose has been reduced for an individual participant, it will not be re-escalated under any circumstance.

Study intervention will continue until confirmed disease progression, withdrawal of participant consent, participant lost to follow-up, unacceptable toxicity, or the study or individual cohort is terminated by the sponsor, whichever comes first.

## 5.3. Power and Sample Size Considerations

This is a nonrandomized multi-cohort signal finding study designed to assess the antitumor activity of lurbinectedin in terms of the ORR according to the RECIST v1.1 in three different advanced (metastatic and/or unresectable) solid tumors cohorts.

This study includes up to a total of 60 participants in the initial assessment of efficacy in which each tumor cohort includes up to 20 participants. If there is evidence of efficacy in a cohort, enrollment beyond 20 participants in the individual cohort may be considered.

Each cohort will have up to 4 stages of enrollment: stage 1 at n = 12 and stage 2 at n = 20 for futility testing; if a cohort is expanded beyond 20 participants, the study may enroll into stage 3 with an interim analysis to assess efficacy at n = 35, and a final stage 4 at n = 100 for the final analysis.

If there are ≥ 4 responses (a target of 20% ORR) out of 20 participants in a cohort, the lower bound of 70% confidence interval (CI) of ORR (10.5% to 33.4%) will exclude a 10% ORR (Table 3) and the cohort may continue. This will provide approximately 85% confidence that the true ORR is > 10%, where a 10% or lower response rate is not clinically meaningful.

**Table 3: Two-sided, Exact CI of ORR Under Varying Scenarios for n = 20**

| Sample Size | No of Responders | Observed ORR (%) | 70% CI of ORR (%) | 80% CI of ORR (%) | 90% CI of ORR (%) | 95% CI of ORR (%) |
|---|---|---|---|---|---|---|
| 20 | 4 | 20 | (10.5, 33.4) | (9.0, 36.1) | (7.1, 40.1) | (5.7, 43.7) |
| | 5 | 25 | (14.4, 38.8) | (12.7, 41.5) | (10.4, 45.6) | (8.7, 49.1) |
| | 6 | 30 | (18.5, 44.0) | (16.6, 46.7) | (14.0, 50.8) | (11.9, 54.3) |
| | 7 | 35 | (22.8, 49.1) | (20.7, 51.8) | (17.7, 55.8) | (15.4, 59.2) |
| | 8 | 40 | (27.2, 54.1) | (24.9, 56.7) | (21.7, 60.6) | (19.1, 63.9) |

Abbreviations: ORR: Objective response rate; CI: Confidence interval.

If there are ≥ 8 responses (22.9% ORR) out of 35 participants in a cohort, the lower bound of 95% CI of ORR (10.4% to 40.1%) will exclude a 10% ORR (Table 4) and the cohort may continue enrollment up to a total of 100 participants.

If there are ≥ 20 responses (20% ORR) out of 100 participants in a cohort, the lower bound of 95% CI of ORR (12.7% to 29.2%) will exclude a 10% ORR (Table 4).

**Table 4: Two-sided, Exact CI of ORR Under Varying Scenarios for n = 35 and n=100**

| Sample Size | No of Responders | Observed ORR (%) | 95% CI of ORR (%) |
|---|---|---|---|
| 35 | 7 | 20.0 | (8.4, 36.9) |
| | 8 | 22.9 | (10.4, 40.1) |
| | 9 | 25.7 | (12.5, 43.3) |
| 100 | 18 | 18.0 | (11.0, 26.9) |
| | 19 | 19.0 | (11.8, 28.1) |
| | 20 | 20.0 | (12.7, 29.2) |

Abbreviations: ORR: Objective response rate; CI: Confidence interval.

## 5.4. Randomization and Blinding

Not applicable. This is a nonrandomized multi-cohort, open-label signal finding study.

## 5.5. Interim Analysis

Review of the safety and efficacy data will be performed by the sponsor on an ongoing basis in this study.

Assessment of the observed responses will be performed after enrollment of approximately 12 and 20 efficacy-evaluable participants for treatment benefit. If no confirmed response per RECIST v1.1 is observed in approximately the first 12 evaluable participants of a cohort with at least two post-baseline evaluable tumor assessments, the recruitment of participants in that cohort will be stopped. If there are ≤ 3 confirmed responses in the first 20 evaluable participants of a cohort, the recruitment of participants in the cohort will be stopped. There will be no pause in enrollment during the interim analysis of the first 12 evaluable participants of a cohort, and the futility boundary will be adjusted based on the actual number of participants at each stage.

Interim futility monitoring will be implemented through the Bayesian Posterior Probability (BPP) approach with the prior distribution for ORR assumed to be Beta (0.5, 0.5). Table 5 has the operating characteristics for futility of stopping at 12 and 20 participants.

If no response is observed in the first 12 participants of a cohort, there is an 89% posterior probability that the actual response rate is no more than 10%. If there are ≤ 3 responses in the first 20 participants of a cohort, there is a 70% posterior probability that the actual response rate is no more than 20%.

**Table 5: Posterior Probability for Interim Futility Monitoring**

| No Participants | Futility Stopping | Prob (θ≤10%\|r, n) | Prob (θ≤15%\|r, n) | Prob (θ≤20%\|r, n) |
|---|---|---|---|---|
| 12 | 0 | 89% | 95% | 98% |
| 20 | 1 | 76% | 91% | 97% |
| 20 | 2 | 46% | 72% | 87% |
| 20 | 3 | 21% | 47% | 70% |

θ = True response rate; r = the observed responses; n = the number of participants

# 6. ANALYSIS SETS

For purposes of analysis, the following populations are defined:

| Analysis Set | Description |
|---|---|
| Enrolled | All participants who sign the informed consent form (ICF). |
| Safety | All participants who took at least one dose of study treatment. This is the primary set for safety analyses. |
| Efficacy evaluable | Participants in Safety analysis set with measurable disease at baseline and one of the following: (a) at least one post-baseline evaluable tumor assessment, (b) clinical progressions, or (c) death. |
| [redacted] | [redacted] |
| [redacted] | [redacted] |

# 7. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

The statistical principles applied in the design and planned analyses of this study are consistent with International Conference on Harmonization (ICH) E9 guidelines (ICH 1998). Section 5.5 describes the planned interim assessment of the observed response and decision process following the interim assessment. The primary analysis is planned to take place when the last enrolled participant in a cohort has had 6 months of treatment and follow-up. The primary analysis described in this SAP may be performed separately for each cohort based on enrollment.

## 7.1. General Methods

The efficacy analyses will be performed using the Efficacy evaluable analysis set, separately for each cohort. The safety analyses will be performed using the Safety analysis set by cohort and across cohorts. By-participant listings will be generated by cohort and across cohorts.

Unless otherwise specified, continuous data will be summarized using descriptive statistics comprising of the number of participants with data to be summarized (n), mean, standard deviation (SD), median, minimum (min) and maximum (max). Categorical variables will be tabulated by the frequency and proportion of participants falling into each category.

All summaries, statistical analyses, data listings and figures will be completed using version 9.4 of the Statistical Analysis System (SAS Institute, North Carolina, USA) unless otherwise noted. All figures will be generated with high resolution in black and white. Each summary, figure or data listing will include the data cutoff date in addition to the production date.

## 7.2. Baseline, Post Baseline, and Study Day Definitions

### 7.2.1. Baseline

Baseline evaluations are defined as evaluations with a date on or prior to the date of the first dose of study treatment. If there are multiple valid observations in the Screening Period, then the latest non-missing observation on or before the first dose of study treatment will be used as the baseline for analyses.

### 7.2.2. Post-Baseline

Post baseline evaluations are defined as evaluations taken after the date of the first dose of study treatment.

The post-baseline period is further characterized into:

- A treatment period, which is the time period from the date of the first dose to the date of the last dose of study treatment
- A 30-day safety follow-up period after the last dose of study treatment
- An OS follow-up period, which is the period following the 30-day safety follow-up period after the last dose of study treatment until participants die or withdraw consent or are lost to follow-up or the cohort closes. If a participant is to permanently discontinue study intervention before disease progression, the participant will be followed for survival by telephone visits every 3 months until at least 80% of participants in each cohort have died, withdrawn consent, or are lost to follow-up.

### 7.2.3. Study Day

The day of receiving the first dose of study treatment is defined as Study Day 1 or Day 1. All other study days will be computed relative to Day 1. Day 0 will not be used. The day before receiving the first dose of study treatment is Day -1 and the day after receiving the first dose of study treatment is Day 2. The following computation rules will be used:

- For events on or after Day 1, study day for a particular event or visit will be calculated as: Date $_{event}$ – Date $_{Day\ 1}$ + 1.
- For events before Day 1, study day for a particular event will be calculated as: Date $_{event}$ – Date $_{Day\ 1}$.

### 7.2.4. Visit Windows

Analysis Visit windowing in general will not be applied. In the case of a retest (same visit number assigned), the latest available test results as provided in the data transfer for that visit/time point will be used for by-visit summaries.

A 30-day safety follow-up period after the last dose of study treatment will be considered for assessing treatment-emergent adverse events (TEAEs).

All scheduled and unscheduled visits will be included in by-participant listings.

## 7.3. Derived Variable Definitions

### 7.3.1. Treatment -Emergent Adverse Events

Treatment-emergent adverse events are defined as AEs with an onset date on or after the date of the first dose of study treatment. An AE is a TEAE if it occurs up to 30 days after the last dose of study intervention. TEAEs can be pre-treatment AEs that worsen in CTCAE grade after the start of study treatment.

### 7.3.2. Creatinine Clearance (CrCL)

The creatinine clearance will be calculated using Cockcroft-Gault formula (1976), defined as:

$$CrCL(ml/min) = \frac{\left(140\ - age\ (in\ years)\right) \times weight\ (in\ kg)}{72\ \times serum\ creatinine\ (in\ \ mg/dL)}$$

for males and

$$CrCL(ml/min) = \frac{\left(140\ - age\ (in\ years)\right) \times weight\ (in\ kg)}{72\ \times serum\ creatinine\ (in\ \ mg/dL)} \times 0.85$$

for females. Baseline weight will be used.

## 7.4. Handling of Missing and Partial Data

### 7.4.1. Missing Data

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 participant listing displays. Note that if any non-date missing data is imputed, the imputed data will only be used in summaries and will not be included in any listing. Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and will not be displayed as missing.

Imputed dates will not be used to derive study day or duration. Imputed dates will be displayed in listings and identified as imputed.

### 7.4.2. Imputation of Non-date Missing Data

Data used for evaluating efficacy and safety endpoints may be missing for technical reasons (e.g., unreadable scan, participant missed appointment).

The primary efficacy analysis for ORR will be performed on the Efficacy-evaluable analysis set.

For participants without any post baseline disease assessment, the response will be imputed as non-responder for sensitivity analyses of ORR in the Safety analysis set.

AEs and SAEs with missing relationship to study treatment will be considered related to study treatment for the purpose of analyses.

AEs and SAEs with missing severity (CTCAE grade) will be considered missing for the purpose of analyses.

### 7.4.3. Incomplete and Missing AE Start Date

The following imputation rules will be followed, when the AE start date is incomplete (e.g., only *year* is present, but *month* and *day* are missing) or completely missing:

- If *year* is missing (including the situation where the start date is completely missing), set the date to the first dose date.
- If *year* is present, and *month* and *day* are missing, or *year* and *day* are present, and *month* is missing,
    - if *year* = year of first dose, set the date to the first dose date,
    - if *year* < year of first dose, set *month* and *day* to December 31$^{st}$.
    - if *year* > year of first dose, set *month* and *day* to January 1$^{st}$.
- If *year* and *month* are present, and *day* is missing,
    - if *year* = year of first dose, and
        - if *month* = month of first dose, set *day* to day of first dose;
        - if *month* < month of first dose, set *day* to the last day of *month*;
        - if *month* > month of first dose, set *day* to the first day of *month*;
    - if *year* < year of first dose, set *day* to the last day of *month*;
    - if *year* > year of first dose, set *day* to the first day of *month*.
- For all other cases that are not covered above, set the date to the first dose date.

Imputed dates for AEs with partial dates will be used to identify treatment emergent AEs and for sorting in data listings. They will not be used to calculate duration of AEs. If an AE start or end date is completely missing, then the duration of the AE will be set to missing and the AE will be considered treatment emergent.

### 7.4.4. Incomplete and Missing Prior and Concomitant Medication Start Date

The following imputation rules will be followed, when the prior and concomitant medication start date is incomplete (e.g., only *year* is present, but *month* and *day* are missing) or completely missing:

- If *year* is missing (including the situation where the start date is completely missing), do not impute, and the start date will be treated as missing in the analysis. Medications with missing start date will be considered concomitant for the purpose of summary tables.

- If *year* is present, and *month* and *day* are missing, set *month* and *day* to January 1st.
- If *year* and *month* are present, and *day* is missing, set *day* to the first day of *month*.
- If *year* and *day* are present, and *month* is missing, set *month* to January.

### 7.4.5. Incomplete and Missing Prior and Concomitant Medication End Date

The following imputation rules will be followed, when the prior and concomitant medication end date is incomplete (e.g., only *year* is present, but *month* and *day* are missing) or completely missing:

- If it is indicated that the medication is ongoing (i.e., "Yes" is checked for the question "Ongoing?" in the CRF), do not impute, since there should not be an end date for this medication.
- If *year* is missing (including the situation where the end date is completely missing), do not impute, and the end date will be treated as missing in the analysis.
- If *year* is present, and *month* and *day* are missing, set *month* and *day* to December 31st.
- If *year* and *month* are present, and *day* is missing, set *day* to the last day of *month*.
- If *year* and *day* are present, and *month* is missing, set *month* to December.

## 7.5. Hypotheses Testing

This nonrandomized multi-cohort signal finding study will use estimation rather than hypothesis testing to characterize the ORR for each cohort.

## 7.6. Level of Significance & Multiplicity Adjustment

Not applicable.

## 7.7. Subgroups and Subgroup Analyses

No subgroups and subgroup analyses are planned. However, the influence of baseline and demographic characteristics on the treatment effect may be explored via exploratory subgroup analyses if the number of subjects in the subgroup category is >= 5.

## 7.8. Changes to Planned Analyses

None.

# 8. STUDY POPULATION SUMMARIES

## 8.1. Enrollment

All participants who signed informed consent will be accounted in this study (Enrolled analysis set).

The number of participants screened, number of screen failures and reasons for screen failure (did not meet eligibility criteria, withdrew consent, adverse event, investigator discretion, lost to follow-up, study enrollment closed, other) will be summarized overall and by assigned cohort (as per IRT) and details will be included in a data listing using Enrolled analysis set.

The number and percentage of participants included in each analysis set (Safety, Efficacy Evaluable, [redacted] and reason(s) for exclusion from each analysis set will be summarized by assigned cohort: UC, PD-NEC, HRD-positive tumor agnostic malignancies. Percentages for Safety analysis set will be based on number of enrolled participants in each cohort. Percentages for Efficacy Evaluable [redacted] analysis sets will be based on number of participants in each assigned cohort in Safety analysis set.

## 8.2. Disposition

Participant disposition will be summarized (number and percentage) overall and by assigned cohort for Enrolled analysis set. Participant disposition data, including study treatment completion, study treatment discontinuation, study completion, study withdrawal, primary reason for study treatment discontinuation, and primary reason for study withdrawal as provided on the CRF, will be listed by participant for Enrolled analysis set. Study treatment completion and study completion status will be assessed based on corresponding CRF pages. The number and percentage of participants followed-up for survival status will be summarized by assigned cohort and listed for Safety analysis set.

If a participant completes the study per protocol, the last on-study date is the last visit date for this participant; if a participant terminates the study early, the date entered in the early termination folder in eCRF is the last on-study date for this participant.

## 8.3. Protocol Deviations

Protocol deviations will be categorized as important and non-important. Important protocol deviations will be summarized descriptively for participants with at least one important protocol deviation by cohort. The summary will include the following subtypes:

- Inclusion criteria not met
- Exclusion criteria not met
- Expired/compromised IP administered
- Subject dose not modified per protocol
- Incorrect dose of study treatment
- Failure to take action in response to apparent toxicity and failure to appropriately monitor the patient with toxicity
- Missed pregnancy test
- Failure to complete any efficacy assessments (e.g., imaging evaluations) at any timepoint

- Failure to obtain initial informed consent, or obtaining informed consent after initiation of study procedures
- Use of an invalid/outdated consent form
- Prohibited medication taken or prohibited treatment given
- Falsification of source documentation
- Significant PI or staff misconduct or fraud
- Breach of confidentiality of participant/data privacy
- IRB approval lapse
- Non-compliance with protocol withdrawal criteria
- Significant, repeated protocol non-compliance that significantly impacts participant safety and/or the integrity of the study conduct or study data

Every subtype will be kept in the summary even if it has 0 participants. A participant with more than one important protocol deviation will be counted only once in the total number of participants with at least one important protocol deviations. A by-participant listing of all protocol deviations will be provided with deviation subtype, description, and a flag for important protocol deviation.

## 8.4. Demographic and Baseline Characteristics

Demographic data and other baseline characteristics will be summarized using descriptive statistics overall (across all cohorts) and by assigned cohort for the Safety analysis set and Efficacy evaluable analysis set. The denominator for percentages will be the number of participants in each cohort with non-missing data available for the variable of interest. All demographic data and other baseline characteristics will be included in by-participant data listings using Safety analysis set.

The following demographic and baseline disease characteristics will be included in the summaries mentioned above:

- Age (years) at informed consent (as continuous variable)
- Age group at informed consent: <65 years, ≥ 65 years
- Sex at birth (male, female)
- Childbearing potential (female participants only) (yes/no)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple, Other, or Not Reported)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, or Not Reported)
- Weight at baseline (kg)
- Height at baseline (cm)
- Body surface area (BSA) ($m^2$)

- Alcohol use
- Tobacco use
- Baseline creatinine clearance (CrCL)
- Baseline ECOG performance status (0, 1)

Baseline results for biochemistry, hematology, coagulation laboratory tests, urinalysis, vital signs, and ECG test results will be reported in the corresponding summary tables and listings for each safety endpoint.

## 8.5. Disease Characteristics

Oncology history will be summarized descriptively by cohort using the Safety analysis set and for Efficacy evaluable analysis set for the following:

- Initial disease diagnosis (histopathologic diagnosis)
- Time (months) since initial disease diagnosis (histopathologic diagnosis) to first dose date
- Stage at diagnosis (0, 1, 2, 3, 4)
- Cancer stage at enrollment (TNM staging) (0, 1, 2, 3, 4)
- Histopathology (urothelial cancer, large cell neuroendocrine tumor of lung, HRD positive endometrial, HRD positive biliary tract, HRD positive breast TNBC, HRD positive HR+HER2-, HRD positive pancreas, HRD positive gastric/esophageal solid tumor, other)
- Mutation type (germline, somatic, unknown) for HRD-positive tumor agnostic malignancies cohort only

Time since initial disease diagnosis (months) = (first dose date – date of initial disease diagnosis + 1)/30.4375. Partial dates for initial disease diagnosis will not be imputed, and time since initial diagnosis will be set to missing.

Planned summaries for prior oncology treatments including prior anti-cancer mediation, prior anti-cancer radiotherapy, prior anti-cancer procedure or surgery are described in Section 8.7.

All disease characteristics will be included in by-participant data listing using Safety analysis set.

## 8.6. Medical History

Medical conditions collected on the Medical History page of the CRF will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.0. Summary of medical history by system organ class (SOC) and preferred term (PT) will be provided using the Safety analysis set by cohort and across cohorts. A participant will only be counted once within a particular SOC (PT) even if he/she has multiple conditions/diseases in the same SOC (PT). Summary results will be ordered by descending frequency of SOC and PT within each SOC. If the frequencies tie, an alphabetic order will be applied.

A listing of medical history will be provided with the start date, ongoing (yes or no), and the end date, if not ongoing.

## 8.7. Prior Anti-Cancer Therapy

Prior anti-cancer therapy is defined as those taken by the participant prior to the administration of study treatment. Prior anti-cancer therapy, including systemic therapy, radiotherapy, and procedure or surgery, will be summarized descriptively by cohort for the safety analysis set.

### 8.7.1. Prior Systemic Anti-Cancer Therapy

Prior systemic anti-cancer therapy will be coded to Anatomical Therapeutic Chemical (ATC) Level 4 and PT using the World Health Organization Drug Dictionary (WHODrug) version Mar 2022.

For prior systemic anti-cancer therapy, the following summary results will be prepared:

- Number and percentage of participants with at least one prior systemic anti-cancer therapy
- Number and percentage of participants with 1, 2, 3, 4, and ≥ 5 previous lines of therapy
- Number of maximum number of regimens of prior systemic anti-cancer therapy
- Time (months) from completion of the most recent prior systemic anti-cancer therapy to study treatment (< 3, ≥ 3 - < 6, ≥ 6 months), which is calculated as (date of first dose of the study treatment –date of last dose of the most recent prior systemic anti-cancer therapy + 1)/ 30.4375.
- Characteristics of the most recent prior systemic anti-cancer therapy: type of prior systemic anti-cancer therapy, best response, reason therapy ended, and time (months) from completion of the most recent prior systemic anti-cancer therapy to progression/recurrence [calculated as date of progressions/recurrence –date of last dose of the most recent prior systemic anti-cancer therapy + 1)/ 30.4375].

All prior systemic anti-cancer therapy will be presented in a participant listing using Safety analysis set. Listing will include regimen number, route, start/stop date (or ongoing), best overall response (and date), progressive disease date, and reason therapy ended.

### 8.7.2. Prior Anti-Cancer Radiotherapy

The number and percentage of participants with at least one prior anti-cancer radiotherapy will be summarized by cohort using Safety analysis set.

All prior anti-cancer radiotherapy will be presented in participant listing using Safety analysis set. Listing will include treatment intent, start/stop date, and setting.

### 8.7.3. Prior Anti-cancer Procedure or Surgery

Prior anti-cancer procedure or surgery will be coded to SOC and PT using MedDRA version 25.0.

The prior anti-cancer procedure or surgery will be summarized by presenting the number and percentage of participants by PT and SOC. Participants with the same procedure or surgery

reported multiple times will only be counted once for that PT or SOC. Summary results will be ordered by descending order of incidence of SOC and PT within each SOC. If the frequencies tie, an alphabetic order will be applied.

All prior anti-cancer procedure or surgery will be presented in a participant listing including intent for procedure or surgery, date, and result.

## 8.8. Subsequent Anti-Cancer Therapy

Subsequent anti-cancer therapy is defined as an anti-cancer therapy administered after the discontinuation of the study treatment. Number and percentage of participants receiving subsequent anti-cancer therapies, where categories include subsequent systemic therapy, subsequent surgery for cancer treatment, and subsequent radiotherapy for cancer treatment, will be summarized descriptively by cohort for the Safety analysis set. Summary results will include:

- Number and percentage of participants with at least one subsequent anti-cancer therapy
- Number and percentage of participants by type of therapy
- Number and percentage of participants with 1, 2, and ≥ 3 subsequent anti-cancer therapy (agents)
- Number of maximum number of regimens (agents) of subsequent systemic anti-cancer therapy

All subsequent anti-cancer therapies will be presented in participant listing using Safety analysis set. Listing will include therapy type, regimen number, start/stop date (or ongoing), dose and units, progressive disease date.

## 8.9. Prior and Concomitant Medications

Prior and concomitant medications will be coded to ATC level 4 and PT using WHODrug version Mar 2022.

Medications taken and stopped prior to the first dose of study treatment are denoted “Prior”. Medications taken prior to the first dose of study treatment and continuing beyond the first dose of study treatment or those medications started on or after the first dose of study treatment but within 30 days of last dose received (the 30-day safety window) are denoted “Concomitant”.

Medication with start date/time being partially or completely missing will be assumed to be concomitant if it cannot be shown that the medication was not administered during the treatment period.

The prior medications will be summarized by presenting the number and percentage of participants by PT and ATC level for each cohort using Safety analysis set. Participants taking the same medication multiple times will only be counted once for that PT or ATC level. Each summary will be ordered by descending order of incidence of ATC level and PT within each ATC level. If the frequencies tie, an alphabetic order will be applied.

Concomitant medications will be summarized in a similar way.

All prior and concomitant medications will be presented in participant listing using Safety analysis set.

## 8.10. Concomitant Procedures

Medical or surgical procedures that started after the first dosing date of the study treatment and within 30 days of the last dose received (the 30-day safety window) are denoted “Concomitant”.

Concomitant medical or surgical procedures will be classified using the MedDRA version 25.0.

The concomitant medical or surgical procedures will be summarized by presenting the number and percentage of participants by PT and SOC. Participants having the same medical or surgical procedure multiple times will only be counted once for that PT or SOC. Each summary will be ordered by descending order of incidence of SOC and PT within each SOC. If the frequencies tie, an alphabetic order will be applied. Results will be presented by cohort using Safety analysis set.

All concomitant medical or surgical procedures will be presented in participant listing using Safety analysis set.

# 9. EFFICACY

All efficacy analyses will be performed using the Efficacy-Evaluable Analysis Set, separately for each of the 3 cohorts, unless otherwise specified.

Primary analysis of objective response rate (ORR) will be based on the investigators’ assessment, unless noted otherwise.

Alpha (α) for the confidence intervals (CI) will be the two-sided 0.05. CIs for all efficacy endpoints will be at the two-sided 95% level. Point estimates and confidence bounds for efficacy endpoints will be rounded to the second decimal place.

A by-participant listing of efficacy results will be presented for each of the cohorts including treatment duration, progression date, death date, and all the other efficacy endpoints.

## 9.1. Primary Efficacy Endpoint and Analysis

### 9.1.1. Primary Analysis

The primary efficacy endpoint is the objective response rate (ORR).

Best overall response (BOR) is defined as the best response recorded between the date of the first dose of study treatment and the date of objectively documented progression per RECIST v1.1, or the date of subsequent anticancer therapy, death due to any cause, loss to follow-up, or study discontinuation, whichever occurs first. Best overall response (BOR) will be determined programmatically in the analysis of the study results as the best timepoint response that a participant achieves during the study (recorded between the date of the first dose of study treatment and the date of objectively documented progression per RECIST v1.1), with the

response ranked according to the following order (from best to worst): complete response (CR) > partial response (PR) > stable disease (SD) > progressive disease (PD).

The first post-baseline tumor imaging assessment should occur 6 weeks (+/- 7 days) from the first dosing date. A response of SD can only be made after the participant is on-study for a minimum of 35 days from the date of the first dose. The number and percentage of participants in each category of BOR (CR, PR, SD, PD, not evaluable [NE]) will be presented by each cohort.

The ORR is defined as the proportion of participants whose BOR is investigator-assessed confirmed CR or PR using the RECIST v1.1. The ORR will be summarized by a binomial response rate for each cohort and its corresponding two-sided 95% exact CIs using the Clopper and Pearson method (Clopper 1934).

The calculation of the ORR and its corresponding two-sided 95% exact CIs will be carried out using the PROC FREQ procedure with the exact binomial option in SAS version 9.4.

A by-participant listing of best overall response will be presented by each cohort including best overall response and dates of CR/PR/progression.

#### 9.1.2. Sensitivity Analyses

Not applicable.

#### 9.1.3. Subgroup Analyses

The influence of baseline and demographic characteristics on the treatment effect may be explored via exploratory subgroup analyses if the number of subjects in a subgroup category is >=5.

### 9.2. Secondary Efficacy Endpoints and Analyses

#### 9.2.1. Duration of Response (DOR)

The investigator-assessed objective response will be further characterized by the DOR. DOR will be evaluated for responders (confirmed CR and PR) only.

DOR is defined as the time (months) from first confirmed response (CR or PR) to the date of the first documented tumor progression as determined using RECIST v1.1 criteria or death due to any cause, whichever occurs first.

The following censoring rules will be applied to DOR:

- Participants who do not progress or die will be censored on the date of their last evaluable tumor assessment.
- Participants who started a new anticancer therapy without a prior reported progression will be censored on the date of their last evaluable tumor assessment on or prior to the initiation of first subsequent anticancer therapy.

- Participants who are lost to follow-up or discontinued from the study without a prior reported progression and without start of subsequent anticancer therapy will be censored on the date of their last evaluable tumor assessment on or prior to the date of loss to follow-up or study discontinuation.

A by-participant listing will be presented including actual cohort, best response, duration of response, whether the participant was censored for duration of response, and if so, the reason.

[redacted]

# 10. SAFETY

Safety analyses will be based on the Safety Analysis Set.

## 10.1. Exposure

### 10.1.1. Extent of Exposure

Exposure of study treatment (duration of exposure, number of cycles of treatment received, cumulative dose, dose intensity, and relative dose intensity) will be summarized by cohort and listed by participant using Safety analysis set.

The summary results will include the following:

- Number of cycles administered per participant (median, range)
- Number and percentage of participants with 1, 2, 3, 4, 5, $\geq$ 6 cycles administered
- Duration of lurbinectedin exposure (weeks), derived as [(date of last dose - date of first dose) + 1]/7
- Cumulative lurbinectedin dose (mg/m$^2$), calculated as sum of the doses received from the first cycle until the last cycle, including the dose received in the last cycle, and corrected by BSA
- Intended dose intensity (mg/m$^2$/week), calculated as the planned dose per cycle divided by the planned number of weeks per cycle
- Absolute dose intensity (mg/m$^2$/week), calculated as the cumulative lurbinectedin dose divided by the number of weeks of treatment, where the number of weeks of treatment is derived as [(date of last dose - date of first dose) + 21]/7

- Relative dose intensity (%), calculated as the ratio of absolute dose intensity divided by the intended dose intensity
- Number and percentage of participants with dose reduction (at least one, 1 dose reduction, 2 dose reductions); reasons for dose reductions will be included in by-participant data listing only
- Number and percentage of participants with incomplete infusions (i.e., infusions noted as interrupted and not restarted on eCRF) at least once, 1 time, 2 times, 3 or more times)

### 10.1.2. Treatment Compliance

Not applicable.

## 10.2. Adverse Events

Adverse events recorded in the CRF will be coded to SOC and PT using MedDRA version 25.0.

Unless otherwise noted, the AE summaries will be provided by SOC and PT; SOCs will be ordered alphabetically, with PTs within an SOC sorted in descending order of frequency. A participant will be counted only once at each level of summarization. If a participant has multiple episodes of events coded to the same preferred term, the participant will be counted just once while summarizing for that preferred term and at maximum severity (when applicable).

All AE summary tables will be generated overall (across all cohorts).

### 10.2.1. Treatment Emergent Adverse Events (TEAEs)

Treatment-emergent adverse events (TEAE) are defined as AEs with an onset date on or after the date of the first dose of the study treatment and within 30 days of last dose received (the 30-day safety window). TEAEs can be pre-treatment AEs that worsen in CTCAE grade after the start of study treatment. For the purpose of determining treatment-emergent, incomplete and missing AE start dates will be imputed as specified in Section 7.4.3.

Treatment-related AEs are those for which investigators answer “Yes” to the question “Is this adverse event related to study treatment [lurbinectedin]?” in the CRF. Events for which investigators do not record the relationship to lurbinectedin will be considered as related to lurbinectedin for summary purposes. By-participant listings for those events for which the investigator does not record relationship to lurbinectedin will show treatment relationship as missing.

The severity of AEs will be recorded using the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Adverse events are graded by the investigator as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life threatening), or Grade 5 (fatal). The severity grade of events for which the severity was not recorded will be categorized as “missing” for summaries and listings and will be considered the least severe for the purposes of sorting for data presentation.

The following summaries of TEAEs (number and percentage of participants) will be provided overall (across all cohorts) using Safety analysis set:

- Summary of any TEAEs by worst CTCAE grade (any grade, grade 3-4, grade 5) presented by SOC/PT
- Summary of TEAEs by PT (decreasing frequency)
    - Any grade
    - Grade 3-4
    - ≥ Grade 3
- Summary of any non-serious TEAEs by worst CTCAE grade (any grade, grade 3-4, grade 5) presented by SOC/PT
- Summary of treatment-related TEAEs by worst CTCAE grade (any grade, grade 3-4, grade 5) presented by SOC/PT
- Summary of treatment-related TEAEs by PT (decreasing frequency)

A by-participant TEAE listing will be provided with participant identifier, cohort, SOC, PT, start date, end date, severity grade, seriousness, relationship to lurbinectedin, and outcome of the AE using Safety analysis set.

### 10.2.2. Serious Adverse Events (SAEs)

Serious AEs are those for which investigators answers "Yes" to the question "Was the adverse event serious?" in the CRF. The clinical database will be reconciled with the SAE database before the final database lock.

The following summaries of SAEs (number and percentage of participants) will be provided across the cohorts using Safety analysis set:

- Summary of SAEs by worst CTCAE grade (any grade, grade 3-4, grade 5) presented by SOC/PT
- Summary of treatment-related SAEs by worst CTCAE grade (any grade, grade 3-4, grade 5) presented by SOC/PT

All analyses will be conducted from the first dosing date of study treatment to the last date of the 30-day safety window.

A by-participant SAE listing will be provided using Safety analysis set.

### 10.2.3. TEAEs Leading to Study Treatment Discontinuation

TEAEs leading to study treatment discontinuation are those with "Action Taken with Study Treatment = Drug Withdrawn" recorded in the CRF.

The following summaries of TEAEs leading to study treatment discontinuation (number and percentage of participants) will be provided across the cohorts using Safety analysis set:

- Summary of TEAEs leading to study treatment discontinuation by worst CTCAE grade (any grade, grade 3-4, grade 5) presented by SOC/PT
- Summary of treatment-related TEAEs leading to study treatment discontinuation by worst CTCAE grade (any grade, grade 3-4, grade 5) presented by SOC/PT

The analyses will be conducted from the first dosing date of study treatment to the last date of the 30-day safety window.

All TEAEs leading to study treatment discontinuation will be included in a by-participant listing including but not limited to participant identifier, cohort, SOC, PT, start date, end date, severity grade, relationship to lurbinectedin, seriousness, and outcome of the AE using Safety analysis set.

### 10.2.4. TEAEs Leading to Dose Modification

TEAEs leading to dose modification (dose delay/reduction) are those with "Action Taken with Study Treatment = Drug Interrupted or Dose Reduced" recorded in the CRF.

The following summaries of TEAEs leading to dose modification (number and percentage of participants) will be provided across the cohorts using Safety analysis set:

- Summary of TEAEs leading to dose delay/reduction by worst CTCAE grade (any grade, grade 3-4 presented by SOC/PT
- Summary of treatment-related TEAEs leading to dose delay/reduction by worst CTCAE grade (any grade, grade 3-4) presented by SOC/PT

The analyses will be conducted from the first dosing date of study treatment to the last date of the 30-day safety window.

All TEAEs leading to dose modification will be included in a by-participant listing including but not limited to participant identifier, cohort, SOC, PT, start date, end date, severity grade, relationship to lurbinectedin, seriousness, and outcome of the AE using Safety analysis set.

### 10.2.5. Deaths

Deaths will be summarized descriptively across the cohorts:

- All deaths, reasons for death
- Deaths within 30 days of the last dose received (the 30-day safety window), reasons for death

A by-participant listing of deaths will be provided for all enrolled participants population, in which deaths within the 30-day safety window will be flagged.

### 10.2.6. Adverse Events of Special Interest

Not Applicable.

### 10.2.7. Overall Summary of Adverse Events

A general summary of AEs will be provided with the number and percentage of participants in the Safety analysis set who experienced the following types of events across the cohorts:

- Participants with any TEAE
- Participants with any Treatment-Related TEAE
- Participants with TEAE by Worst CTCAE Grade

- Participants with any TEAE CTCAE Grade ≥ 3
- Participants with any Serious TEAE
- Participants with any Serious Treatment-Related TEAE
- Participants with any TEAE Leading to Death
- Participants with any TEAE Leading to Study Treatment Discontinuation
- Participants with any Treatment-Related TEAE Leading to Study Treatment Discontinuation
- Participants with any TEAE Leading to Study Treatment Reduction/Delay/Interruption
- Participants with any Treatment-related TEAE Leading to Study Treatment Reduction/Delay/Interruption

## 10.3. Laboratory Assessments

Blood and urine samples for the determination of hematology, clinical chemistry, coagulation, thyroid function, and urinalysis laboratory variables described in Table 6 will be measured and reported across the cohorts using Safety analysis set.

**Table 6: Protocol Specified Laboratory Tests**

| **Laboratory Tests** | **Parameter** | | |
|---|---|---|---|
| Hematology | Platelet Count | White blood cell count with differential<br>Neutrophils<br>Lymphocytes<br>Monocytes | |
| | Red Blood cell Count | | |
| | Hemoglobin | | |
| | Hematocrit | | |
| Biochemistry – A | Serum electrolytes (Na+, K+, Cl-) | AST/ALT | GGT |
| | AP | Total bilirubin (and direct if total is > 1.5 × ULN) | LDH |
| | Creatinine | CPK | Glucose (random) |
| Biochemistry – B | Albumin | Total protein | Ca<br>Mg |
| Coagulation | PT/INR | PTT | |
| Pregnancy testing | Highly sensitive serum or urine hCG pregnancy test (as needed for women of childbearing potential) | | |

| | |
|---|---|
| Other Screening tests | Serology (HIV antibody, HBsAg, and hepatitis C virus antibody) |

ALT=alanine aminotransferase; AP=alkaline phosphokinase; AST=aspartate aminotransferase; CPK=creatinine phosphokinase; GGT=gamma-glutamyl transferase; HBcAb=hepatitis B core antibody; HBsAg=hepatis B surface antigen; hCG=human chorionic gonadotropin; HCV=hepatitis C virus; HIV=human immunodeficiency virus; LDH=lactate dehydrogenase; PT=prothrombin time; PTT=partial thromboplastin time; ULN=upper limit of normal.

For all hematology, coagulation and biochemistry tests, the laboratory values at baseline and each of the post-baseline assessments until EOT visit will be summarized and presented using descriptive statistics, along with the number and percentage of participants with tests not done.

For each of the post-baseline assessments, change between baseline and that assessment in a specific laboratory value will be calculated as follows,

Change in lab value = [Lab value at the post-baseline assessment] – [Lab value at baseline],

and will be summarized and presented using descriptive statistics.

If the laboratory value is not done or missing at either baseline or a specific post-baseline assessment for a participant, change between baseline and that assessment will be treated as unknown. For each of the post-baseline assessments, the number and percentage of participants with unknown changes between baseline and that assessment will also be presented.

The non-protocol specified tests (if any reported), and urinalysis results will not be summarized; they will only be included in by-participant listings.

Data recorded by the laboratory will be converted to the International System of Units (SI) and summary tables will be generated using both SI and Conventional units.

Quantitative laboratory measurements reported as "< X", i.e., below the lower limit of quantification (LLQ), or "> X", i.e., above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e., as "< X" or "> X" in the listings.

Clinical laboratory results will be graded according to CTCAE criteria, CTCAE v5.0 criteria (Appendix 2). The frequency and percentage of participants with each CTCAE grade for each visit during the treatment period will be described by cohort. Both the scheduled and unscheduled assessments will be used to identify the worst post-baseline values.

Listings of all laboratory data with results reported using SI and Conventional units, normal reference ranges, and CTCAE grades (when possible) will be provided using Safety analysis set.

Pregnancy test results and other screening tests will be included in by-participant listings only.

## 10.4. Vital Signs

Systolic blood pressure (mmHg), diastolic blood pressure (mmHg), pulse rate (beats/min), respiratory rate (breaths/min), body temperature (C) at baseline and each of the post-baseline assessments will be summarized and presented using descriptive statistics across the cohorts using Safety analysis set. For each of the post-baseline assessments, the change between baseline and that assessment in a specific vital sign will be calculated as follows:

Change in vital sign = [post-baseline assessment] – [baseline assessment],

and will be summarized and presented using descriptive statistics.

If a specific type of vital sign is not done or missing at either baseline or a specific post-baseline assessment for a participant, change between baseline and that assessment will be treated as unknown. For each of the post-baseline assessments, the number and percentage of participants with unknown changes between baseline and that assessment will also be presented.

A listing of clinically significant abnormalities post baseline as judged by the investigator will be provided. For each participant and each vital sign, if there is at least one abnormal result, all results at all visits for that vital sign will be included in the listing.

The following values will be summarized:

- Systolic pressure < 60 or > 160 mmHg
- Diastolic pressure < 50 or > 100 mmHg
- Pulse rate < 40 or > 120 beats per minute
- Respiratory rate < 10 or > 40 breaths per minute
- Temperature < 36 or > 39 degrees Centigrade

All vital signs will be listed by participant using Safety analysis set.

## 10.5. ECG

A single 12-lead ECG will be obtained during screening using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals. A by-participant listing including heart rate (beats/min, PR Interval (msec), QRS duration (msec), QT interval (msec), QTcB (msec), QTcF (msec), ECG Interpretation and any abnormal findings will be prepared using Safety analysis set.

## 10.6. ECOG Performance Status

ECOG will be assessed at screening, on Day 1 of each cycle, and at EOT. The frequency and percentage of participants with each ECOG score level will be summarized by visit and across cohorts using Safety analysis set.

A listing of ECOG score for all participants will be provided using Safety analysis set.

## 10.7. Physical Examination

A complete physical examination will be conducted at screening, on Day 1 of each cycle, and at EOT. Height will be collected at screening only. BSA will be recalculated on Day 1 of each treatment cycle and for any change (higher or lower) of the baseline value ≥10% the dose will be adjusted.

A listing of physical examination data for all participants will be provided using Safety analysis set. Listing will include height (screening value), weight, BSA, BSA change from baseline value for all post-baseline visits.

## 10.8. AAGP

One blood sample for the evaluation of Alpha-1 Acid Glycoprotein (AAGP) will be collected at the end of the lurbinectedin infusion (± 5 min) on Cycle 1 Day 1 (C1D1) from all participants. The serum AAGP will be summarized by cohort using Safety analysis set and analyzed using summary statistics such as mean, SD, median, minimum, and maximum values. A by-participant listing of serum AAGP data will be provided for each cohort using Safety analysis set.

[redacted]

- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

## 12. PHARMACODYNAMIC ANALYSES

Not applicable.

# REFERENCES

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics. 1982 Mar 1:29-41.

Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934 Dec 1;26(4):404-13.

Cockcroft D.W. · Gault M.H. Prediction of Creatinine Clearance from Serum Creatinine. Nephron 1976;16:31–41. https://doi.org/10.1159/000180580

Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. 27Nov2017 https://ctep.cancer.gov.protocoldevelopment

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer. 2009; 45:228-247.

Food and Drug Administration (FDA). FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. 2018. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-trialendpoints-approval-cancer-drugs-and-biologics

Greenwood M. The "errors of sampling" of the survivorship tables. Reports on public health and medical subjects. 1926.

ICH. Harmonised Tripartite Guideline: Statistical principles for clinical trials (E9). 05 February 1998.

Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. John Wiley & Sons;

1980.

Marubini E and Valsecchi MG. Analysing survival data from clinical trials and observational studies, statistics in practice, ed. Vic Barnett. Chichester: John Wiley & Sons, 1995.

# Appendix 1: Schedule of activities

| Procedure | Screening (window) | Intervention Period [Days] | | | | | | | EOT (30± 7D after last dose) or E/D | OS telephone call every 3 months | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | C1 | | | C2 | | | ≥ C3 | | | |
| | | D1 | D8 | D15 | D1 | D8 | D15 | D1 | | | • D–1 is the calendar day before C1D1.<br>• Screening assessments must be repeated if the first infusion of lurbinectedin is given outside the stated window.<br>• EOT is defined as 30 days after the last dose of lurbinectedin, unless the participants starts any subsequent anticancer therapy, in which case the EOT visit should be performed immediately before the start of new therapy.<br>• The EOT assessments will be performed if no recent data are available (ie, within the previous 10 days prior to the EOT visit) or if the last available data show a Grade ≥ 2 increase in AE severity. |
| Informed consent | X (–28 to -1) | | | | | | | | | | |
| Inclusion and exclusion criteria | X (–28 to -1) | | | | | | | | | | Note: for HRD-positive cohort, participants without mutational analysis results are not eligible for participation |
| Demography | X (–28 to -1) | | | | | | | | | | |
| Primary diagnosis and prior treatment(s) | X (–28 to -1) | | | | | | | | | | |
| Medical and cancer history/past and current medical conditions | X (–28 to -1) | | | | | | | | | | |
| Full physical examination including height, weight, and BSA | X (–7 to -1) | X | | | X | | | X | X | | BSA will be recalculated on Day 1 of each treatment cycle. The dose will be adjusted if BSA change is ≥ 10% (higher or lower) of the baseline value. Height is only required at Screening. |

| Procedure | Screening (window) | Intervention Period [Days] | | | | | | | EOT (30± 7D after last dose) or E/D | OS telephone call every 3 months | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | C1 | | | C2 | | | ≥ C3 | | | |
| | | D1 | D8 | D15 | D1 | D8 | D15 | D1 | | | • D–1 is the calendar day before C1D1.<br>• Screening assessments must be repeated if the first infusion of lurbinectedin is given outside the stated window.<br>• EOT is defined as 30 days after the last dose of lurbinectedin, unless the participants starts any subsequent anticancer therapy, in which case the EOT visit should be performed immediately before the start of new therapy.<br>• The EOT assessments will be performed if no recent data are available (ie, within the previous 10 days prior to the EOT visit) or if the last available data show a Grade ≥ 2 increase in AE severity. |
| Performance status (ECOG) | X (–7 to -1) | X | | | X | | | X | X | | –1 day window (except in Cycle 1) |
| Single 12-lead ECG | X (–7 to -1) | Repeat if clinically indicated | | | | | | | | | ECG: cardiac rhythm will be identified in ECG intervals of at least 30 seconds of duration, PR interval, QT interval (raw), heart rate (HR) and QRS complex. |
| Highly sensitive serum OR urine pregnancy test (WOCBP only) | X (–7 to -1) | X | | | X | | | X | X | | Beta subunit-human chorionic gonadotropin (β-hCG) (urine or serum). In WOCBP, if a urine pregnancy test is positive a serum test must be performed and confirmed negative prior to administering IP. See Section 8.4.5 for pregnancy reporting requirements. |
| HIV (antibody), Hepatitis B (surface antigen), and Hepatitis C (surface antigen, and RNA if positive by antibody) screening | X (–28 to -1) | | | | | | | | | | All participants will be tested for HIV prior to the enrollment into the study and HIV-positive participants will be excluded from the study. Participants with active hepatitis B (chronic or acute; defined as having a positive HBsAg test result at screening) will be excluded from the study. Participants with past or resolved HBV infection (defined as the presence of HBcAb and absence of HBsAg) are eligible; HBV DNA should be obtained in these participants prior to enrollment. Participants with HCV will be excluded from the study; participants who test positive for HCV antibody are eligible only if PCR is negative for HCV RNA. |

| Procedure | Screening (window) | Intervention Period [Days] | | | | | | | EOT (30± 7D after last dose) or E/D | OS telephone call every 3 months | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | C1 | | | C2 | | | ≥ C3 | | | |
| | | D1 | D8 | D15 | D1 | D8 | D15 | D1 | | | |
| | | | | | | | | | | | • D–1 is the calendar day before C1D1.<br>• Screening assessments must be repeated if the first infusion of lurbinectedin is given outside the stated window.<br>• EOT is defined as 30 days after the last dose of lurbinectedin, unless the participants starts any subsequent anticancer therapy, in which case the EOT visit should be performed immediately before the start of new therapy.<br>• The EOT assessments will be performed if no recent data are available (ie, within the previous 10 days prior to the EOT visit) or if the last available data show a Grade ≥ 2 increase in AE severity. |
| Coagulation tests | X (–7 to -1) | | | | X | | | X | X | | –3 day window (except in Cycle 1). Clinical laboratory tests are detailed in Appendix 3. |
| Hematology | X (–7 to -1) | X | X | X | X | X | X | X | X | | –3 day window (except in Cycle 1). Clinical laboratory tests are detailed in Appendix 3. Any participants with febrile neutropenia of any grade, Grade 4 neutropenia, and/or Grade 4 thrombocytopenia, should have relevant tests repeated daily until recovery to Grade ≤ 3 and through the day after fever resolution, if applicable.<br>**For Cycle 3 and after, Hematology and Biochemistry "A" tests on Days 8 and 15 are to be performed only in participants with Grade ≥ 3 biochemical Grade 4 hematological treatment-related toxicities, or who required dose adjustments due to hematological or biochemical abnormalities in the preceding cycle.** |
| Biochemistry-A | X (–7 to -1) | | X | X | X | X | X | X | X | | –3 day window (except in Cycle 1). Clinical laboratory tests are detailed in Appendix 3. |
| Biochemistry-B | X (–7 to -1) | X | | | X | | | X | X | | Albumin, total proteins, $Ca^{++}$ and $Mg^{++}$. Total proteins, $Ca^{++}$ and $Mg^{++}$ will be measured at Screening and repeated thereafter only in those participants with abnormal baseline values. Clinical laboratory tests are detailed in Appendix 3. |

**Note: reference to Appendix 3 corresponds to protocol appendix.**

| Procedure | Screening (window) | Intervention Period [Days] | | | | | | | EOT (30± 7D after last dose) or E/D | OS telephone call every 3 months | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | C1 | | | C2 | | | ≥ C3 | | | |
| | | D1 | D8 | D15 | D1 | D8 | D15 | D1 | | | • D–1 is the calendar day before C1D1.<br>• Screening assessments must be repeated if the first infusion of lurbinectedin is given outside the stated window.<br>• EOT is defined as 30 days after the last dose of lurbinectedin, unless the participants starts any subsequent anticancer therapy, in which case the EOT visit should be performed immediately before the start of new therapy.<br>• The EOT assessments will be performed if no recent data are available (ie, within the previous 10 days prior to the EOT visit) or if the last available data show a Grade ≥ 2 increase in AE severity. |
| Vital signs (HR, BP, temperature, respiratory rate) | X (–7 to -1) | X | | | X | | | X | X | | –1 day window (except in Cycle 1) |
| | | | | | | | | | | | Blood samples will be collected from participants who consent to provide PK samples at the following time points in cycle 1: |
| [redacted] | | | | | | | | | | | |
| AAGP | | X | | | | | | | | | One blood sample for the evaluation of AAGP will be collected at the end of the lurbinectedin infusion (± 5 min) from all participants. |
| **HRD-positive cohort only**: blood sample for confirmation of any pre-identified germline and/or somatic pathogenic mutations | X (–28 to -1) | | | | | | | | | | One blood sample will be collected before lurbinectedin administration in Cycle 1 from all participants in the HRD-positive cohort. |

| Procedure | Screening (window) | Intervention Period [Days] | | | | | | | EOT (30± 7D after last dose) or E/D | OS telephone call every 3 months | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | C1 | | | C2 | | | ≥ C3 | | | |
| | | D1 | D8 | D15 | D1 | D8 | D15 | D1 | | | • D–1 is the calendar day before C1D1.<br>• Screening assessments must be repeated if the first infusion of lurbinectedin is given outside the stated window.<br>• EOT is defined as 30 days after the last dose of lurbinectedin, unless the participants starts any subsequent anticancer therapy, in which case the EOT visit should be performed immediately before the start of new therapy.<br>• The EOT assessments will be performed if no recent data are available (ie, within the previous 10 days prior to the EOT visit) or if the last available data show a Grade ≥ 2 increase in AE severity. |
| Blood sample for ctDNA somatic mutational analysis (required) | | X | | | | | | | | | Required sample: the C1D1 sample should be collected before lurbinectedin administration. |
| Blood sample for longitudinal ctDNA somatic mutational analysis (optional) | | | | | X | | X | | X | | |
| Radiological tumor assessment | X (–28 to -1) | Every 6 weeks (±7 days) from the C1D1 for 36 weeks (±7 days). After completion of the Week 36 tumor assessment, every 12 weeks (±14 days) thereafter. The assessments will be performed at these time points until PD, start of a new anticancer therapy, death, EOT visit, or study termination, whichever occurs first. | | | | | | | X (if not performed within 7 days of last treatment evaluation visit for participants who discontinue treatment, see Section 7.1) | | Evaluation by contrast enhanced helical CT-scan or MRI, as clinically indicated, of all measurable sites of disease involvement and of all nonmeasurable sites of disease should be done prior to the first Lurbinectedin administration. While on treatment, evaluation of all original sites of disease involvement should be done per RECIST v1.1. The same initial method must be used throughout the study. For all LCNET of lung participants, CT-scan or MRI of brain will be requested before the planned treatment onset to rule out CNS involvement.<br>Participants showing a response must have a confirmatory assessment at least 4 weeks after initial response.<br>See Appendix 8 for tumor assessment guidelines. |

| Procedure | Screening (window) | Intervention Period [Days] | | | | | | | EOT (30± 7D after last dose) or E/D | OS telephone call every 3 months | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | C1 | | | C2 | | | ≥ C3 | | | |
| | | D1 | D8 | D15 | D1 | D8 | D15 | D1 | | | • D–1 is the calendar day before C1D1.<br>• Screening assessments must be repeated if the first infusion of lurbinectedin is given outside the stated window.<br>• EOT is defined as 30 days after the last dose of lurbinectedin, unless the participants starts any subsequent anticancer therapy, in which case the EOT visit should be performed immediately before the start of new therapy.<br>• The EOT assessments will be performed if no recent data are available (ie, within the previous 10 days prior to the EOT visit) or if the last available data show a Grade ≥ 2 increase in AE severity. |
| Pretreatment tumor sample (optional) | X (–28 to -1) | Tumor samples may be submitted at any time during the study. | | | | | | | | | Pretreatment tumor sample from primary tumor and/or metastasis, either obtained at diagnosis or at any time before the first lurbinectedin administration. Any tumor sample, sample from primary tumor and/or metastasis, (either formalin fixed paraffin-embedded [FFPE] tumor tissue or cytology slides) will be acceptable. Archived tumor samples, if available, can be submitted at any time during the study. |
| Administer lurbinectedin | | X | | | X | | | X | | | ± 3 day window (except in Cycle 1). Refer to criteria for treatment continuation (Section 5.5) and dose delay and reduction rules (Section 6.7) prior to each administration of lurbinectedin. |
| On-treatment tumor sample (optional) | | Optional biopsy 4 to 6 weeks after C1D1 | | | | | | | | | Optional samples are only obtained from those participants consenting to biomarker analyses via the corresponding option in the ICF. |
| OS | | | | | | | | | | X | |
| AE review | | ←═══════════→ | | | | | | | | | Adverse events resulting in study discontinuation will be followed until satisfactory resolution per the investigator. See Section 8.4.1. |

| Procedure | Screening (window) | Intervention Period [Days] C1 D1 | C1 D8 | C1 D15 | C2 D1 | C2 D8 | C2 D15 | ≥ C3 D1 | EOT (30± 7D after last dose) or E/D | OS telephone call every 3 months | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | • D–1 is the calendar day before C1D1.<br>• Screening assessments must be repeated if the first infusion of lurbinectedin is given outside the stated window.<br>• EOT is defined as 30 days after the last dose of lurbinectedin, unless the participants starts any subsequent anticancer therapy, in which case the EOT visit should be performed immediately before the start of new therapy.<br>• The EOT assessments will be performed if no recent data are available (ie, within the previous 10 days prior to the EOT visit) or if the last available data show a Grade ≥ 2 increase in AE severity. |
| SAE review | | ←═══ | ═══ | ═══ | ═══ | ═══ | ═══ | ═══→ | | | All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.<br>During the OS Follow-up, any spontaneous treatment-related SAEs will be collected and reported. |
| Prior/concomitant medications | ←═══ | ═══ | ═══ | ═══ | ═══ | ═══ | ═══ | ═══→ | | | |

Abbreviations: AAGP = alpha-1 acid glycoprotein; AE = adverse event; AP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; BSA = body surface area; C = cycle; CT = computed tomography; ctDNA = circulating tumor DNA; D = day; ECG = electrocardiogram; E/D = early discontinuation; ECOG = Eastern Cooperative Oncology Group; EOT = end-of-treatment; FFPE = formalin fixed paraffin-embedded; GGT = gamma-glutamyltransferase; HR = heart rate; INR = international normalized ratio; LDH = lactate dehydrogenase; LCNET = large cell neuroendocrine tumor; MRI = magnetic resonance imaging; NA = not applicable; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; OS = overall survival; PD = progressive disease; PT = prothrombin time; PTT = partial thromboplastin time; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; ULN = upper limit of normal; WBC = white blood cells.

# Appendix 2: NCI CTCAE Criteria v5.0 for Laboratory Parameters

| PARAMETER (SI Unit) | Hypo | Hyper | ATOXGR | | | |
|---|---|---|---|---|---|---|
| | | | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| Hemoglobin (g/L) | Anemia | Hemoglobin increased | Increase in >0 - 2 g/dL | Increase in >2 - 4 g/dL | Increase in >4 g/dL | ~ |
| | | | Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L | Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 – 80 g/L | Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L | ~ |
| Platelets (10^9/L) | Platelet count decreased | | <LLN - 75,000/mm$^3$; <LLN - 75.0 × 10e9 /L | <75,000 - 50,000/mm$^3$; <75.0 - 50.0 × 10e9 /L | <50,000 - 25,000/mm$^3$; <50.0 - 25.0 × 10e9 /L | <25,000/mm$^3$; <25.0 × 10e9 /L |
| Leukocytes (10^9/L) | White blood cell decreased | | <LLN - 3000/mm3; <LLN - 3.0 × 10e9 /L | <3000 - 2000/mm3; <3.0 - 2.0 × 10e9 /L | <2000 - 1000/mm3; <2.0 - 1.0 × 10e9 /L | <1000/mm3; <1.0 × 10e9 /L |
| Neutrophils (10^9/L) | Neutrophil count decreased | | <LLN - 1500/mm3; <LLN - 1.5 × 10e9 /L | <1500 - 1000/mm3; <1.5 - 1.0 × 10e9 /L | <1000 - 500/mm3; <1.0 - 0.5 × 10e9 /L | <500/mm3; <0.5 × 10e9 /L |
| Lymphocytes (10^9/L) | Lymphocyte count decreased | | <LLN - 800/mm3; <LLN - 0.8 × 10e9/L | <800 - 500/mm3; <0.8 - 0.5 × 10e9 /L | <500 - 200/mm3; <0.5 - 0.2 × 10e9 /L | <200/mm3; <0.2 x 10e9 /L |
| | | Lymphocyte count increased | ~ | >4000/mm3 - 20,000/mm3 | >20,000/mm3 | ~ |
| Eosinophils (%) | | Eosinophilia | >ULN and >Baseline | - | Steroids initiated | - |
| Activated Partial Thromboplastin Time (s) | | Activated partial thromboplastin time prolonged | >ULN - 1.5 × ULN | >1.5 - 2.5 × ULN | >2.5 × ULN; bleeding | ~ |
| International Normalized Ratio | | INR increased | >1.2 - 1.5 | >1.5 - 2.5 | >2.5 | ~ |

| PARAMETER (SI Unit) | Hypo | Hyper | ATOXGR | | | |
|---|---|---|---|---|---|---|
| | | | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| Albumin (g/L) | Hypoalbuminemia | | <LLN - 3 g/dL; <LLN - 30 g/L | <3 - 2 g/dL; <30 - 20 g/L | <2 g/dL; <20 g/L | ~ |
| Glucose (mmol/L) | Hypoglycemia | | <LLN - 55 mg/dL; <LLN - 3.0 mmol/L | <55 - 40 mg/dL; <3.0 - 2.2 mmol/L | <40 - 30 mg/dL; <2.2 - 1.7 mmol/L | <30 mg/dL; <1.7 mmol/L |
| Creatinine (umol/L) | | Creatinine increased | >ULN - 1.5 × ULN | >1.5 - 3.0 × baseline if baseline was abnormal; >1.5 - 3.0 × ULN if baseline was normal | >3.0 × baseline-6.0 × ULN if baseline was abnormal; >3.0 - 6.0 × ULN if baseline is normal | >6.0 × ULN |
| Creatine phosphokinase (IU/L) | | CPK increased | >ULN - 2.5 × ULN | >2.5 × ULN- 5 × ULN | >5.0 X ULN - 10.0 x ULN | >10.0 × ULN |
| Alkaline Phosphatase (uKat/L) | | Alkaline phosphatase increased | >ULN - 2.5 × ULN if baseline was normal; 2.0 - 2.5 × baseline if baseline was abnormal | >2.5 - 5.0 × ULN if baseline was normal; >2.5 - 5.0 × baseline if baseline was abnormal | >5.0 - 20.0 × ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal | >20.0 × ULN if baseline was normal; >20.0 x baseline if baseline was abnormal |
| Aspartate Aminotransferase (uKat/L) | | Aspartate aminotransferase increased | >ULN - 3.0 × ULN if baseline was normal; 1.5 - 3.0 × baseline if baseline was abnormal | >3.0 - 5.0 × ULN if baseline was normal; >3.0 - 5.0 × baseline if baseline was abnormal | >5.0 - 20.0 × ULN if baseline was normal; >5.0 - 20.0 × baseline if baseline was abnormal | >20.0 × ULN if baseline was normal; >20.0 × baseline if baseline was abnormal |
| Alanine Aminotransferase (uKat/L) | | Alanine aminotransferase increased | >ULN - 3.0 × ULN if baseline was normal; 1.5 - 3.0 × baseline if baseline was abnormal | >3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 × baseline if baseline was abnormal | >5.0 - 20.0 × ULN if baseline was normal; >5.0 - 20.0 × baseline if baseline was abnormal | >20.0 × ULN if baseline was normal; >20.0 × baseline if baseline was abnormal |

| PARAMETER (SI Unit) | Hypo | Hyper | ATOXGR | | | |
|---|---|---|---|---|---|---|
| | | | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| Serum Calcium (mmol/L) | Hypocalcemia | Hypercalcemia | >ULN - 2.9 mmol/L | >2.9 - 3.1 mmol/L | >3.1 - 3.4 mmol/L | >3.4 mmol/L |
| | | | <LLN - 2.0 mmol/L | <2.0 - 1.75 mmol/L | <1.75 - 1.5 mmol/L | <1.5 mmol/L |
| Magnesium (mmol/L) | Hypomagnesemia | Hypermagnesemia | >ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L | ~ | >3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L | >8.0 mg/dL; >3.30 mmol/L |
| | | | <LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L | <1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L | <0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L | <0.7 mg/dL; <0.3 mmol/L |
| Potassium (mmol/L) | Hypokalemia | Hyperkalemia | >ULN - 5.5 mmol/L | >5.5 - 6.0 mmol/L | >6.0 - 7.0 mmol/L | >7.0 mmol/L |
| | | | <LLN - 3.0 mmol/L | ~ | <3.0 - 2.5 mmol/L | <2.5 mmol/L |
| Sodium (mmol/L) | Hyponatremia | Hypernatremia | >ULN - 150 mmol/L | >150 - 155 mmol/L | >155 - 160 mmol/L | >160 mmol/L |
| | | | <LLN - 130 mmol/L | 125-129 mmol/L | 120-124 mmol/L | <120 mmol/L |
| Bilirubin (umol/L) | | Blood bilirubin increased | >ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal | >1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal | >3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal | >10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal |
| Urinary protein | | Proteinuria | 1+ proteinuria; urinary protein ≥ULN - <1.0 g/24 hrs | 2+ and 3+ proteinuria; urinary protein 1.0-<3.5g/24hrs | 4+ proteinuria; urinary protein ≥ 3.5g/24hrs | ~ |