PM1183-A-018-20

An Open-Label, Multicenter Study to Assess the Potential Effects of Itraconazole (a Strong CYP3A4 Inhibitor) on the Pharmacokinetics of Lurbinectedin (PM01183) in Patients with Advanced Solid Tumors

STATISTICAL ANALYSIS PLAN

INVESTIGATIONAL MEDICINAL PRODUCTS: Lurbinectedin and Itraconazole
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-Confidential-

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ABBREVIATIONS AND GLOSSARY

AE(s)	Adverse Event(s)
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Concentration-time Curve
BIMO	Bioresearch Monitoring
BSA	Body Surface Area
CI	Confidence Interval
Cl	Clearance
C_{max}	Maximum Plasma Concentration
CPK	Creatine Phosphokinase
CPK-MB	Creatine Phosphokinase Isoenzyme MB
CrCl	Creatinine Clearance
CRF	Case Report Form
CRP	C-reactive Protein
CV	Coefficient of Variation
CYP	Cytochrome P450
D	Day
DL	Dose Level
DSBs	Double-strand Breaks
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EDC	Electronic Data Capture
EOT	End of treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
HR	Heart Rate
IC	Informed Consent
IC_{50}	Half Maximal Inhibitory Concentration
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
i.v.	Intravenous
L	Liter
LDH	Lactate Dehydrogenase
LRB	Lurbinectedin
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minutes
Mg	Milligram
mL	Milliliter
MUGA	Multiple-gated Acquisition Scan
NA	Not Applicable
NCI-CTCAE	National Cancer Institute Common Toxicity Criteria
PD	Progressive Disease

PGt	Pharmacogenetic
PK	Pharmacokinetics
PN	Preferred Name
PS	Performance Status
PT	Preferred Term
q3wk	Every Three Weeks
R	Randomized
RBC	Red Blood Cells
RT	Reference-Test Sequence
RTSM	Randomization and Trial Supply Management
S	Sequence
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SCLC	Small Cell Lung Cancer
SmPC	Summary of Product Characteristics
SOC	System Organ Class
$T_{1/2}$	Terminal Half-life
TEAE(s)	Treatment-Emergent Adverse Events
TR	Test-Reference Sequence
ULN	Upper Limit of Normal
Vs.	*Versus*
Vss	Volume of Distribution at Steady State
WBC	White Blood Cells
WHO	World Health Organization
wk	Week(s)

1 STUDY RATIONALE

Lurbinectedin (PM01183) is a novel synthetic tetrahydroisoquinoline structurally related to ecteinascidins.

Lurbinectedin is a new chemical entity that binds the DNA leading to the formation of DNA double-strand breaks (DSBs). The binding to DNA is likely occurring in the minor groove region and induces apoptosis and delayed progression through the cellular phase S/G2. Lurbinectedin also induces the specific degradation of transcribing RNA Pol II in several human tumor cell lines.

In vitro, lurbinectedin demonstrated cytotoxic effects against a broad selection of tumor types with half maximal inhibitory concentration (IC50) values in the range of 1-10 nM. Although selectivity was also seen, a clustering of sensitive tumors has not been identified. Lurbinectedin also exhibited antitumor activity against different murine models of xenografted human-derived tumor types. Lurbinectedin has been tested as a single agent or in combination with different drugs in solid tumors; while antitumor activity in hematological tumors was deemed negligible, lurbinectedin has shown activity in different solid tumors; some of the most responsive tumor types were breast, small cell lung cancer (SCLC), ovarian and endometrial cancer.

Based on current clinical data, the toxicity of lurbinectedin is predictable, reversible and manageable. The most relevant toxicity is reversible myelosuppression with a nadir occurring in the middle of the second week after Day 1 infusion in an every-three-week cycle; overall, the incidence of febrile neutropenia is below 20% in all ongoing Phase II trials.

Lurbinectedin is extensively metabolized by the cytochrome P450 enzymes, primarily CYP3A4. Thus, potent inducers or inhibitors of this enzyme may alter the plasma concentrations of lurbinectedin. This study is designed to examine the pharmacokinetics (PK) and safety of lurbinectedin when co-administered with itraconazole, a strong CYP3A4 inhibitor, in comparison with lurbinectedin alone. The results of this study may be used to support future clinical studies in patients and prescribing information in future labeling.

A full rationale for the study may be found in the appropriate sections of the study's clinical protocol.

2 OVERALL STUDY DESIGN

This is a prospective, open-label, two-way crossover, phase Ib drug-drug interaction study in patients with advanced solid tumors.

The study will include a pre-treatment (screening) phase (within 14 days before the first lurbinectedin or itraconazole administration) followed by a treatment phase consisting of two lurbinectedin cycles, one cycle in combination with itraconazole and one cycle of lurbinectedin as single agent (in different order depending on the study sequence), and one additional third cycle of lurbinectedin as a single agent for patients who meet the continuation criteria and obtain a clinical benefit after the first two cycles, and then follow-up of adverse events if any.

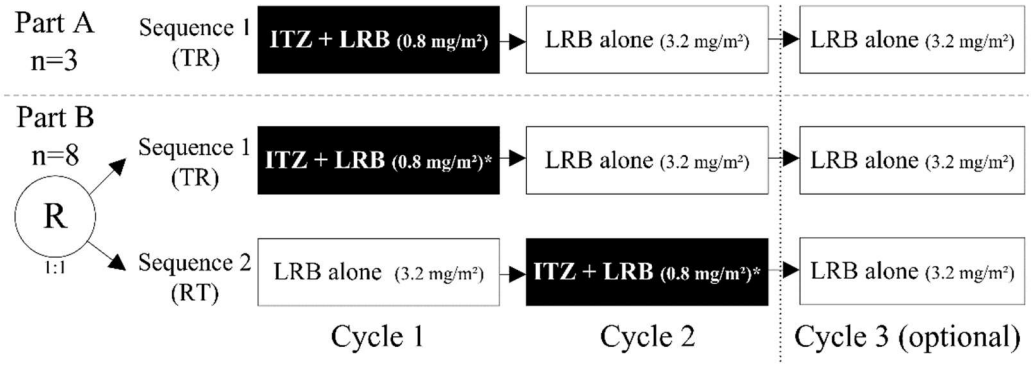
Patients who meet the continuation criteria and obtain a clinical benefit according to the Investigator's criteria will have the opportunity to continue treatment under a Compassionate Use Agreement after the completion of the optional third study cycle.

Patients will be treated as outpatients. At the discretion of the Investigator, patients may be admitted to the study center on Day –1 or Day 1 and monitored, at least, until completion of the Day 1 PK blood sample collections.

Patients will receive a maximum of three cycles: two consecutive cycles of lurbinectedin, one cycle with and one cycle without itraconazole co-administration (in different order depending on the study Sequence 1 or Sequence 2 of treatment), followed by a third cycle with lurbinectedin alone (this last optional for patients with clinical benefit). Lurbinectedin will be administered as a 1-hour (-5/+20 min) i.v. infusion q3wk via a central or peripheral vein.

In the co-administration cycles, itraconazole will be administered orally once daily in the morning after breakfast during 12 consecutive days, self-administered at home from Day -4 (i.e., four days before lurbinectedin infusion) until Day 8 (i.e., seven days after lurbinectedin infusion), and supplied at the study center on Day 1, following recommendations at the Summary of Product Characteristics (SmPC). On Day 1 (i.e., the day of lurbinectedin infusion), itraconazole will be given immediately prior to starting the lurbinectedin infusion. In fact, itraconazole should be administered after obtain the itraconazole PK sample #1 and before the start of lurbinectedin infusion (-15 min to -1 min).
In case of lurbinectedin delay (≤ 2 days), itraconazole could be administered during a maximum of 14 days.

This study will consist of two parts: Part A and B. The dose of lurbinectedin when given in combination with itraconazole for the initial three patients in Part A will be 0.8 mg/m², and in Part B is susceptible to be adjusted properly if deemed necessary based on exposure and safety experience in Part A. The dose of lurbinectedin during Parts A and B will be 3.2 mg/m² for all patients when administered without itraconazole. If toxicity occurs, the appropriate intra-patient dose level (DL) reductions will be implemented in the subsequent cycle.



In Part A, three patients will be enrolled to Sequence 1 (TR: Test-Reference) and will receive itraconazole with lurbinectedin in Cycle 1 followed by two consecutive cycles of lurbinectedin alone (the last cycle being optional for patients with clinical benefit according to the Investigator's criteria).

Enrollment for Part A will be sequential. Once the first patient enrolled has completed Cycle 1 and Cycle 2, the second and the third patients could be enrolled simultaneously, after the evaluation of lurbinectedin total PK parameters, and if no unacceptable or life-threatening toxicities have occurred for this first patient. However, if toxicity occurs, the

appropriate dose reductions will be implemented with the second and third patients based on the PK and safety information of first patient.

The dose of lurbinectedin when given in combination with itraconazole for the initial three patients in Part A will be 0.8 mg/m². However, if lurbinectedin exposure in the first patient of Part A does not allow an adequate PK assessment, the lurbinectedin dose of the following patients may be increased accordingly.

Upon exposure and safety assessments in Part A, the dose of lurbinectedin to be co-administered with itraconazole in Part B can be readjusted accordingly. This decision will be made by the Sponsor and study Investigators, and will be documented and communicated to the Independent Ethics Committee/Institutional Review Board (IEC/IRB).

Therefore, the planned dose of lurbinectedin, when given with itraconazole for the remaining eight patients in Part B will be based on the acceptability of the PK and safety results from the first three patients in Part A. If the initial three patients do not experience adverse events (AEs) which might require a dose reduction, the dose of lurbinectedin may still be adjusted (based on the assumption of dose-proportional PK) to produce plasma lurbinectedin AUC values that are comparable to those when lurbinectedin is given in the absence of itraconazole. However, if toxicity occurs in the initial three patients in Part A, the appropriate dose-reduction of lurbinectedin will be implemented in Part B accordingly.

If the safety and PK data obtained from the three patients in Part A is deemed acceptable as defined in the protocol, Part B of this study will begin enrollment. Therefore, once Part A is completed, patients in Part B will be enrolled based on the review of the safety following completion of the first cycle of the previous patient(s), and will be randomized in a 1:1 ratio to Sequence 1 (as used in Part A) or Sequence 2 (RT: Reference-Test; lurbinectedin + itraconazole in Cycle 2).

In Part A, all patients will receive itraconazole plus lurbinectedin in Cycle 1 and lurbinectedin alone in Cycles 2 and 3 (this last cycle being optional).

In Part B, patients will be randomly assigned to the corresponding sequences:

- Sequence 1 (TR) (same used in Part A):
    - Cycle 1: Itraconazole + lurbinectedin
    - Cycle 2: Lurbinectedin alone
    - Cycle 3: Lurbinectedin alone (optional)

- Sequence 2 (RT):
    - Cycle 1: Lurbinectedin alone
    - Cycle 2: Itraconazole + lurbinectedin
    - Cycle 3: Lurbinectedin alone (optional)

Lurbinectedin will be administered to 11 evaluable patients for PK analyses and for a maximum of three cycles, while considered to be on the patient's best interest or until PD, unacceptable toxicity, intercurrent illness of sufficient magnitude to preclude safe continuation of the study, patient's refusal and/or non-compliance with study requirements, a protocol deviation with an effect on the risk/benefit ratio of the clinical

study, more than one lurbinectedin dose reduction due to AEs related to lurbinectedin (unless clear clinical benefit has been documented and always with the Sponsor's agreement) or any other reason at the physician's judgment that precludes lurbinectedin continuation.

If the patient responds to treatment after the first two cycles, treatment with lurbinectedin may continue outside this study under a Compassionate Use Agreement at the same dose based on Investigator's decision and upon agreement with the Sponsor. Then, the treating center must request authorization to the relevant Health Authorities and notify the Sponsor in due time. In order to avoid a treatment discontinuation, during the Compassionate Use Agreement authorization an additional third cycle with lurbinectedin is allowed.

All adverse events (AEs) will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v.5. Treatment delays, dose reduction requirements and reasons for treatment discontinuation will be monitored throughout the study. The safety profile of patients will be monitored throughout the treatment and up to 31 days (±10 days) after the last lurbinectedin infusion (end of treatment, EOT), until the patient starts a new antitumor therapy or until the date of death, whichever occurs first. Any treatment-emergent AEs will be followed until recovery to at least grade 1 or stabilization of symptoms or until the start of a new antitumor therapy, until the continuation of treatment outside this study under a Compassionate Use Agreement or death, whichever occurs first. After treatment discontinuation, patients will be followed until resolution or stabilization of all toxicities, if any.

Patients will be evaluated at scheduled visits on three study periods: pre-treatment (screening), treatment (one cycle of lurbinectedin in combination with itraconazole and two as a single agent and the third cycle optional) and follow-up of adverse events if any.

3 PATIENTS EVALUABILITY CRITERIA

Patients must fulfill all the inclusion/exclusion criteria to be eligible to participate in the study.

The study will include the following analysis population set definitions:

- The enrolled population is defined as all patients recorded in the database who are included in the trial, independently of whether they have received the study drug or not. Screening failure patients will not be considered as part of this population.
- The PK population will include all patients enrolled in Part A and B who have sufficient and interpretable PK parameters to calculate the non-compartmental PK parameters. Only the patients in Part B who have completed the two cycles and have sufficient and interpretable PK assessments will be included in the statistical comparison to assess the effect of itraconazole on the PK of lurbinectedin.
- The safety population will include all patients who received at least one dose of lurbinectedin. Patients who have received at least one dose of itraconazole but who did not receive any dose of lurbinectedin will be excluded from the safety population. The analysis of data from these patients will be performed separately (e.g., by means of narratives). The safety population will be used for all safety evaluations.

4 STUDY OBJECTIVES AND PHARMACOKINETIC PARAMETERS

4.1 Objectives

This clinical pharmacology study is designed to assess the impact of itraconazole co-administration on lurbinectedin PK parameters administered alone.

4.1.1 Primary

- To assess the effect of itraconazole on lurbinectedin total plasma exposure in patients with advanced solid tumors.

4.1.2 Secondary

- To assess the effect of itraconazole on lurbinectedin unbound plasma exposure.
- To assess the effect of itraconazole on lurbinectedin major metabolites (i.e., M1 and M4).
- To assess the effect of itraconazole on the safety profile of lurbinectedin.
- To collect and store a blood sample for germline DNA extraction for future pharmacogenetic (PGt) analysis of variations on genes that may influence exposure and response (i.e., disposition, metabolism and safety) to lurbinectedin.

4.1 Endpoints

4.1.1 Primary

- Plasma dose-normalized C_{max} and $AUC_{0-\infty}$ of lurbinectedin will be compared between Cycle 1 and Cycle 2. Pharmacokinetic analyses will be evaluated in plasma by standard non-compartmental methods, or population methods, if necessary.

4.1.2 Secondary

- Differences in dose-normalized total AUC_{0-t} and Cmax and in Cl, Vss and $T_{1/2}$ of lurbinectedin between Cycle 1 and Cycle 2 will be explored.
- Differences in dose-normalized unbound $AUC_{u,0-\infty}$, $AUC_{u,0-t}$ and $C_{u,max}$ and in CL_u, Vss,u and $T_{1/2}$,u of lurbinectedin between Cycle 1 and Cycle 2 will be explored.
- Differences in ratios between total $AUC_{0-\infty}$, AUC0-t and Cmax, of main lurbinectedin metabolites relative to parent drug between Cycle 1 and Cycle 2 will be explored. Additional PK parameters will be calculated if deemed appropriate.
- Treatment safety, including AEs, serious adverse events (SAEs) and laboratory abnormalities will be graded according to the NCI-CTCAE v.5. Additionally, treatment compliance, in particular dose reductions requirements and/or treatment delays due to AEs, and reasons for treatment discontinuation will also be described. Patients will be evaluable for safety if they have received at least one partial or complete infusion of lurbinectedin.

- The presence or absence of PGt polymorphisms in genes relevant for lurbinectedin disposition (distribution, metabolism and excretion) from a single blood sample collected (only if written IC given) at any time during the trial (but preferably at the same time as the pre-treatments PK sample on Day 1 of Cycle 1), which will be stored to explain individual variability in main PK parameters in future analyses

5 SAMPLE CONSIDERATIONS

5.1 Randomization

A block randomization (1:1 ratio) will be performed only in Part B. Block randomization will be used to avoid bias in the assignment of patients to treatment sequence group, to increase the likelihood that known and unknown subject attributes (e.g., demographic and baseline characteristics) are evenly balanced across treatment sequence groups, and to enhance the validity of statistical comparisons across treatment sequence groups.

Patients must be replaced if they are not evaluable for the assessment of the primary endpoint (e.g., if they have not sufficient and interpretable PK parameters).

An evaluable patient for Part A should have completed sufficient study procedures until Day 8 of Cycle 1 (i.e., most itraconazole administration and PK assessments). For Part B, an evaluable patient for the main objective of the study (e.g., assessment of lurbinectedin PK) should have provided sufficient and interpretable PK parameters (e.g., AUC_{0-t} should cover at least 80% of $AUC_{0-\infty}$) of Cycle 1 and 2. Evaluable patients should have received the first two complete cycles regardless dose delays or reductions. For Part A and Part B, the compliance of itraconazole will be confirmed based on a patient's diary, the drug accountability and the expected individual plasma concentration at the steady state.

Randomization will be implemented in Medidata Rave RTSM for Part B of the study. A randomization list will be generated to randomly allocate patients to the sequence treatment. Additional randomization lists will be generated in case non-evaluable patients need to be replaced. Variable block sizes and allocation ratios will be used depending on the number of patients to be replaced in each case scenario in order to complete both sequence treatment groups while keeping balance across them. In order to achieve reproducible results, the seed used in the generation of each randomization list will be saved.

5.2 Sample Size

This study was designed to assess the potential effects of itraconazole on the PK of lurbinectedin in patients with advanced malignancies. The 90% CI will be used to help with the interpretation of the results. A sample size of eight patients was based on feasibility and clinical considerations. Based on previous studies, the intra-subject coefficient of variation (CV) of lurbinectedin PK parameters is estimated to be more than 30%. The precision (half-width) of the 90% CI for [(lurbinectedin + itraconazole) / lurbinectedin alone] comparison on the log-scale will extend 0.389 from the observed differences in means, assuming that the intra-subject CV around 40%. This half-width corresponds to a 90% CI in the range of 70% and 147% assuming the ratio of the means equal to unity for each PK parameter. This 90% CI will be used to help with the interpretation of the results.

6 STATISTICAL METHODOLOGY

The PK definitions and analysis plan will be described by the Pharmacology department in a separate document. The present SAP is focused on the statistical methodology for safety.

Safety analyses will consider treatment emergent AEs and SAEs, according to their relationship with study treatment, as well as analytical results, deaths and the reasons for treatment discontinuations, delays and/or dose reductions. All AEs and SAEs will be graded according to NCI-CTCAE v.5, and coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Descriptive statistics will be used to characterize the profiles of drug-related AEs, drug-related deaths, SAEs, clinical laboratory data, drug-related delays and/or treatment discontinuations. Tables will be displayed by study part and sequence of treatment (Test/Reference or Reference/Test).

6.1 Toxicity and Adverse Events

Treatment-emergent adverse events (TEAEs) are any adverse event aggravated in severity from baseline or having their onset between the first dose of the study drug and 31-day (±10 days) after the last treatment dose, death or date of further therapy, whichever came first. AEs related to the study treatment or with unknown relationship occurring more than 31 days after the last dose were also taken into account as TEAEs.

Summary of overall AEs will be done by system organ class (SOC) and preferred term (PT), by severity (worst toxicity grade) and by relationship to the study drug (any of them or both). Tables will be sorted by category of events using SOC (i.e. alphabetic order) and PT in descending frequencies (i.e. from higher to lower).

AEs, SAEs, deaths, laboratory evaluations, dose delays/omissions/reductions and study drug discontinuations due to AEs will be tabulated in a descriptive way. Counts and percentages will be used for categorical variables, and summary tables will be used for continuous variables.

Patients having any treatment-related grade $\geq$ 3 AEs should have relevant tests re-assessed at least every 72 hours until recovery to at least grade 2.

6.2 Clinical Laboratory Evaluation

Laboratory results will be classified according to the NCI-CTCAE v.5. All laboratory visits reported as “End of treatment” visit will be mapped to the last cycle visit for each patient.

The following hematological values will be displayed: white blood cells count (WBC), neutrophil count, lymphocyte count, monocyte count, erythrocytes, hemoglobin, hematocrit and platelet count. Worst grade per patient and per cycle for anaemia, lymphopenia, neutropenia, leukopenia and thrombocytopenia during treatment will be shown.

Overall cross tabulation will be presented for the worst grade during treatment vs. the baseline toxicity grading of anaemia, lymphopenia, neutropenia, leukopenia and thrombocytopenia.

If a grade 3/4 neutropenia or thrombocytopenia increase occurs during a treatment cycle, the first day the onset value is reached (counting from the start of the cycle) will be tabulated. Time to recovery of the abnormality (i.e., grade 3/4 neutropenia or thrombocytopenia) will be assessed and defined as the time, in days, from the start of the grade 3/4 abnormality until the abnormality is recovered (grade ≤ 2). The analysis will be carried out taking into account all events, including those that occur in a same cycle. The information will be shown by means of median and range.

Likewise, the following biochemical and coagulation values will be displayed: aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), creatinine, creatinine clearance, glucose, creatine phosphokinase (CPK), CPK-MB fraction, gamma glutamyltransferase (GGT), total bilirubin, direct bilirubin, serum electrolytes (Na+, K+, Mg++, Ca++), total proteins, albumin, C-reactive protein count (CRP) and the international normalized ratio (INR). Worst grade per patient and per cycle for applicable values during treatment will be shown.

Time to recovery of the abnormality (grade 3/4 AST or ALT) will be assessed and defined as the time, in days, from the start of the grade 3/4 abnormality until recovery to grade $\leq$ 2. The analysis will be carried out taking into account all events, including those that occur in a same cycle. The information will be shown by means of median and range.

Overall cross tabulation will be presented for the worst grade during treatment vs. the baseline toxicity grading of biochemical abnormalities.

6.3 Physical Examination, Vital signs, Left Ventricular Ejection Fraction and Electrocardiogram Findings

Summary tables will be prepared with the performance status, physical examination, body weight and BSA, vital signs, left ventricular ejection fraction (LVEF) and electrocardiogram (ECG) abnormalities. If appropriate, a "change from baseline" summary will also be done.

ECG will be collected in triplicate allowing rhythm definition (at least 30 seconds of duration), PR interval and QT interval (raw and corrected by HR using Bazett's formula). Mean of all ECGs collected on each time point will be used for analysis.

6.4 Deaths and other Serious Adverse Events

Serious adverse events (SAEs) will be tabulated following the same pattern than AEs. Reason of death will be tabulated. In addition, all deaths within 60 days from the first dose of treatment or within 30 days from the last dose of treatment will be listed.

7 OTHER ANALYSES

Continuous variables will be tabulated and presented with summary statistics (i.e., mean, StD, median and range).

Categorical variables will be summarized in frequency tables by means of counts and percentages. Percentages in the summary tables will be rounded and may therefore not always add up to exactly 100%.

7.1 Patient Disposition and Treatment/Study Discontinuation

The number of patients included in the study, the number of patients treated and the number of patients evaluable for the main endpoint will be shown. Also, accrual by center and the main dates of the study will be displayed. Reasons for treatment discontinuation and for study discontinuation will be tabulated.

7.2 Protocol Deviations

Protocol deviations will be listed and categorized according to the following categories:

- Inclusion/exclusion criteria not met
- Incorrect treatment, dose or schedule received
- Excluded concomitant medication received
- Withdrawal criteria met, but treatment continued
- Failure to comply study procedures
- Any other Ethical/GCP issues

In addition, they will be classified as Relevant/Non-relevant according to clinical criteria.

7.3 Baseline and Demographic Data

Baseline data such as demographics, cancer history, prior therapy, prior relevant history, signs and symptoms, electrocardiogram, LVEF, physical examination, vital signs, laboratory values and concomitant medication, coded according to the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system, will be described following standard tables detailed in Appendix I.

Age, baseline weight, height and BSA values will be summarized descriptively. Age categories, sex, race and baseline ECOG PS score will be summarized with frequency counts.

For the cancer history, time from initial diagnosis, time from metastatic disease, time from locally advanced disease and time from last progression before the study entry will be summarized. This time calculations will be shown in months and summarized descriptively. Tumor type and other characteristics of the primary and current disease will be described using standard tables detailed in Appendix I.

Previous relevant medical history (other than cancer) will be listed.

A frequency tabulation of the number of patients with the different types of previous surgery, radiotherapy or therapy (number of lines) will be given.

Signs and symptoms will be displayed by tabulation of frequencies according to NCI-CTCAE v.5 toxicity grades. Signs and symptoms will be listed.

In case of pre-treatment characteristics with multiple measurements per subject before the start of treatment (e.g. laboratory assessments or vital signs), the last value prior to or on the first day of treatment will be considered the baseline measurement.

7.4 Treatment Administration

Exposure to treatment will be described by sequence treatment group.

Total cumulative dose, time on treatment, dose intensity and relative dose intensity, administration delay and dose reductions/omissions will be described following standard

tables (detailed in Section 11, Appendix II). The reported cycle information on the case report form (CRF) pages will be used for the analysis.

Time on treatment, expressed in weeks, is defined as the last administration date of lurbinectedin minus the first administration date of lurbinectedin plus 31 days, except if the patient dies or starts a new antitumor therapy within 31 days from the last administration date, in which case the time on treatment will be the date of death or the start date of the new antitumor therapy minus the date of the first administration of the study treatment.

Total cumulative dose by drug, expressed in mg for both lurbinectedin and itraconazole, is the sum of all the product doses received during the study, including the dose received in the last cycle.

For lurbinectedin, intended dose intensity is the planned dose per cycle divided by the planned number of weeks by cycle.

Absolute dose intensity is the actual cumulative dose divided by the number of weeks of treatment. As a convention, for this calculation, the duration of the last cycle will be the predefined cycle length (e.g, 21 days). Relative dose intensity (%) is the ratio of absolute dose intensity divided by the intended dose intensity. In those cases where the relative dose intensity is over 100% due to permitted dose anticipation (i.e. patients receiving more dose than planned), this ratio will be adjusted to 100%.

The options "Dose Reduced" and "Dose Delayed" available in the Treatment Modification item on the treatment exposure CRF pages will be used to calculate delays and dose reductions, respectively. For cycles considered as delayed by the Investigator, the length of the delay will be calculated as:

Duration of cycle delay: Date of the current drug administration – Date of the previous drug administration – the predefined cycle length (i.e., 21 days).

For itraconazole, the percentage of compliance will be calculated by dividing the actual total dose by the intended dose.

If the number of delays or dose reductions are very low, tables will not be presented and only listings will be shown.

7.5 Subsequent Therapies

A listing of the first subsequent therapies received after treatment discontinuation will be shown by study part and treatment sequence group.

7.6 Imputation in Incomplete Dates

Dates of certain historical or current clinical activities are key component for statistical analysis. An incomplete date results from a missing day, month or year; in that case, the missing figure can be imputed allowing for the calculation of variables, such duration and time to certain event. However, when all of them, day, month and year, are missing no imputation will be done.

<u>Before randomization/treatment start date</u>

All variables needed to summarize for example prior information (e.g. first diagnosis date) where partial information is available will be subject of imputation by means of SAS programming. If the day of a date is unknown then the imputed day will be 1, if the month is also unknown then the imputed date will 1/July. This assumption will be valid if the imputed date is earlier than the randomization date; otherwise, the imputed date will be the first day of the month of the randomization date (i.e. 01/Randomization month date/year).

Between treatment start and end of treatment

All date variables during treatment where information is needed and is not fully available, for example adverse events or concomitant medications, will be subject of imputation by means of SAS programming. If the day of a date is unknown then the imputed day will be 1, if the month and/or year is also unknown then the imputed date will 1/January (this assumption will be valid if the imputed date is not earlier than the treatment start date; otherwise, the imputed date will be the treatment start date).

After end of treatment

A conservative approach for the variables collecting information after end of treatment where partial information is available (e.g., follow-up AEs) will be imputed by means of SAS programming. The following rules will be implemented: if the day of a date is unknown then the imputed day will be 1; if the month is also unknown, then the imputed date will be 1/July. This assumption will be valid if the imputed date occurs later than the last drug administration date; otherwise, the imputed date will be the last drug administration date plus 1 day.

7.7 Variable Unit Standardization

Variables reported with different units will be homogenized to standardized variables following the International System of Units (e.g. laboratory tests, biometrical assessments...) unless otherwise specified in the following sections.

7.8 Decimal Places, Missing Values and Allowed Assessment Windows

By default, all results will be rounded to one decimal place, except when variables are integer, which will be reported without decimals (e.g., age in years, number of sites, etc.). For representing p-values four decimals will be selected as default but they could be rounded to fewer decimals if necessary.

Missing values will not be imputed. Assessment windows as specified in the clinical protocol will be respected.

7.9 Subgroup Analyses

Safety analysis will be done by study part and sequence treatment arm.

No other subgroup analysis is planned.

7.10 Pharmacogenetic Analysis

The analysis of pharmacogenetic data will be detailed and reported in a separate document.

7.11 Identification of Fixed or Random Effects Models

Not applicable.

7.12 Data Analysis Conventions

All data analysis conventions, data calculations and grouping needed to perform the statistical analysis not included in this SAP will be described in separate document.

8 STATISTICAL SOFTWARE

Medidata Rave® EDC will be used for data entry and clinical data management.

Medidata Rave® RTSM will be used for permuted block randomization design and management.

SAS® v.9.4 or superior will be used for all statistical analysis outputs.

9 REFERENCES

1. Food and Drug Administration (FDA).2001. Guidance for Industry. Statistical approaches to establishing bioequivalence.

2. SAS OnlineDoc.

10 APPENDIX I: PATIENTS DISPOSITION

10.1 General Characteristics

The general characteristics analysis will be carried out on the enrolled population.

10.1.1 Patient Disposition

The main characteristics of the enrolled patients (inclusion in the study, withdrawal from the study and protocol deviations) will be displayed in this section.

Table 10.1.1.1 Patient accrual by institution

	Part A		Part B				Part A+B		Total	
	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)			
	N	%	N	%	N	%	N	%	N	%
Institution 1										
Institution 2										
Total										

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.1.1.2 Disposition of patients

Relevant study dates
Date of first consent
Date of first dose/first patient
Date of last consent
Date of first dose/last patient
Date of last dose
Date of last follow up*

(*) Last follow up date, examination date or procedure before study closure.

Table 10.1.1.3 Number of patients evaluable for analysis

	Part A		Part B				Part A+B		Total	
	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)			
	N	%	N	%	N	%	N	%	N	%
Included										
Evaluable for PK										
Evaluable for Safety										

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 10.1.1.4 Non-evaluable patients

Not Evaluable for	Study Part	Sequence	Subject	Max. Cycle received	Reason(s)
PK					
….					
Safety					
…					

10.1.2 Treatment Discontinuations

Table 10.1.2.1 Treatment discontinuation

	Part A		Part B				Part A+B		Total	
	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)			
	N	%	N	%	N	%	N	%	N	%
Protocol Treatment Completed										
Patient moved to Compassionate Use										
Progressive disease										
Adverse Events										
Patient refusal to treatment										
Investigator's decision										
Death										
Other										
Total										

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 10.1.2.2 Treatment discontinuation due to related† Adverse Events

Study Part	Sequence	Treatment Group*	Subject	Cycle	AE reported	Preferred term	Grade	Relationship	Serious Event

Notes: † Related or unknown relationship.
* ITZ+LRB / LRB

Listing 10.1.2.3 Treatment discontinuation due to non-related Adverse Events

Study Part	Sequence	Treatment Group*	Subject	Cycle	AE reported	Preferred term	Grade	Relationship	Serious Event

* ITZ+LRB / LRB

Listing 10.1.2.4 Reasons for treatment discontinuation other than Progressive Disease

Study Part	Sequence	Subject	Max. Cycle received	Reason	Specify

Table 10.1.2.5 Reasons for study discontinuation

	Part A		Part B				Part A+B		Total	
	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)			
	N	%	N	%	N	%	N	%	N	%
Patient's follow-up completed										
Patient moved to Compassionate Use Study termination (clinical cut-off)										
Withdrawal of consent										
Death										
Never treated										
Lost to follow up										
Other										
Total										

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 10.1.2.6 Reasons for treatment discontinuation due to other reason

Study Part	Sequence	Subject	Max. Cycle received	Other, specify

Listing 10.1.2.7 Patients never treated

Study Part	Sequence	Subject	Reason

10.1.3 Protocol Deviations

Listing 10.1.3.1 Relevant protocol deviations

Study Part	Sequence	Subject	Cycle	Protocol deviation Type	Specify Deviation

Notes: See 16.2.2 for a full listing (relevant and non-relevant).

10.2 Patient Characteristics

Baseline/screening characteristics of all enrolled patients (enrolled population) will be described.

10.2.1 Demographic and Other Baseline Characteristics

Table 10.2.1.1 Patients characteristics at baseline: Gender

	Part A		Part B				Part A+B		Total	
	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)			
	N	%	N	%	N	%	N	%	N	%
Gender										
Male										
Female										

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.1.2 Patients characteristics at baseline: Race

	Part A		Part B				Part A+B		Total	
	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)			
	N	%	N	%	N	%	N	%	N	%
Race										
White										
Black										
Asian										
…										
Other (Specify)										

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.1.3 Patients characteristics at baseline: Age

	Part A	Part B		Part A+B	Total
	S1 (TR)	S1 (TR)	S2 (RT)	S1 (TR)	
Age at entry (years)					
N					
Median (range)					

Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.1.4 Patients characteristics at baseline: Pregnancy Test

	Part A		Part B				Part A+B		Total	
	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)			
	N	%	N	%	N	%	N	%	N	%
Pregnancy Test										

	Part A		Part B				Part A+B		Total	
	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)			
	N	%	N	%	N	%	N	%	N	%
Positive										
Negative										
NA (Specify)										

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.1.5 Patients characteristics at baseline: Adequate contraception

	Part A		Part B				Part A+B		Total	
	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)			
	N	%	N	%	N	%	N	%	N	%
Adequate contraception										
Yes										
No										
NA (Specify)										

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

10.2.2 Medical History

Listing 10.2.2.1 Ongoing medical history

Study Part	Sequence	Subject	Description	Onset date

10.2.3 Cancer History

Table 10.2.3.1 First diagnosis: Tumor type and stage at diagnosis

	Part A		Part B				Part A+B		Total	
	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)			
	N	%	N	%	N	%	N	%	N	%
Tumor Type										
Lung										
Kidney										
Prostate cancer										
…										
Stage at Diagnosis										
Early										
Locally advanced										
Metastatic										

Notes: Percentage is based on number of patients by study part and sequence, when applicable.

Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.3.2 First diagnosis: Time from first diagnosis to first infusion

	Part A	Part B		Part A+B	Total
	S1 (TR)	S1 (TR)	S2 (RT)	S1 (TR)	
Time form first diagnosis to first infusion (years) †					
N					
Median (range)					

† Time from first diagnosis to first infusion: defined as the date of first infusion minus date of first diagnosis.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.3.3 Current disease: Time from last PD to first infusion

	Part A	Part B		Part A+B	Total
	S1 (TR)	S1 (TR)	S2 (RT)	S1 (TR)	
Time from last PD† to first infusion (months)‡					
N					
Median (range)					

† Last PD will be taken from the Cancer history form.
‡ Time from last PD to first infusion: date first infusion minus date of last progression before study entry.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.3.4 Current disease: Sites of disease involvement

	Part A		Part B				Part A+B		Total	
	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)			
	N	%	N	%	N	%	N	%	N	%
Site of disease involvement										
Lung										
Liver										
Lymph node										
…										
Other (Specify)										

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.3.5 No. of sites of disease involvement

	Part A		Part B				Part A+B		Total	
	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)			
	N	%	N	%	N	%	N	%	N	%
1										
2										

	Part A		Part B				Part A+B		Total	
	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)			
	N	%	N	%	N	%	N	%	N	%
…										
≥ N sites										
Total										

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.3.6 Summary statistics: No. of sites of disease involvement

	Part A	Part B		Part A+B	Total
	S1 (TR)	S1 (TR)	S2 (RT)	S1 (TR)	
N					
Median (range)					

Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

10.2.4 Previous Anticancer Therapy Summary

Table 10.2.4.1 Prior surgery

	Part A		Part B				Part A+B		Total	
	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)			
	N	%	N	%	N	%	N	%	N	%
Prior surgery										
Yes										
No										

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.4.2 Prior radiotherapy

	Part A		Part B				Part A+B		Total	
	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)			
	N	%	N	%	N	%	N	%	N	%
Prior radiotherapy										
Yes										
No										

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.4.3 Prior anticancer medical therapy for study disease: Setting

	Part A		Part B				Part A+B		Total	
	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)			
	N	%	N	%	N	%	N	%	N	%
Setting										
Neoadjuvant										
Adjuvant										
Advanced										

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.4.4 Prior anticancer medical therapy for study disease: No. of prior lines

	Part A		Part B				Part A+B		Total	
	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)			
	N	%	N	%	N	%	N	%	N	%
No. of prior lines										
1 line										
2 lines										
3 lines										
>= 4 lines										

Notes: Percentage is based on number of patients by study part and sequence, when applicable.

Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.4.5 Prior anticancer medical therapy for study disease: Summary of prior lines

	Part A	Part B		Part A+B	Total
	S1 (TR)	S1 (TR)	S2 (RT)	S1 (TR)	
No. of prior chemotherapy lines					
N					
Median (range)					

Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.4.6 Prior anticancer medical therapy for study disease: Best response to last therapy

Best response to last prior therapy	Part A		Part B				Part A+B		Total	
	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)			
	N	%	N	%	N	%	N	%	N	%
Complete Response										
Partial Response										
Stable Disease										
Progressive Disease										
Not Evaluable										
Unknown										
Not Applicable										

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.4.7 Prior anticancer medical therapy for study disease: Time to progression of last therapy

Time to progression (months)	Part A	Part B		Part A+B	Total
	S1 (TR)	S1 (TR)	S2 (RT)	S1 (TR)	
N					
Median (range)					

Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

10.2.5 Physical Examination, ECOG, Vital Signs, LVEF and ECG

Table 10.2.5.1 Physical examination at baseline

Physical examination	Part A		Part B				Part A+B		Total	
	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)			
	N	%	N	%	N	%	N	%	N	%
Normal										
Abnormal										

Notes: Percentage is based on number of patients by study part and sequence, when applicable.

Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 10.2.5.2 Physical examination at baseline: abnormalities

Study Part	Sequence	Subject	Description

Table 10.2.5.3 Weight, height and BSA at baseline

	Part A	Part B		Part A+B	Total
	S1 (TR)	S1 (TR)	S2 (RT)	S1 (TR)	
Weight (kg)					
N					
Median (range)					
Height (cm)					
N					
Median (range)					
BSA (m^2)					
N					
Median (range)					

Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.5.4 ECOG Performance Status at baseline

	Part A		Part B				Part A+B		Total	
ECOG	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)			
	N	%	N	%	N	%	N	%	N	%
0										
1										
…										
Total										

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.5.5 Vital signs at baseline

	Part A	Part B		Part A+B	Total
	S1 (TR)	S1 (TR)	S2 (RT)	S1 (TR)	
Heart rate (Beats/minute)					
N					
Median (range)					
Temperature (ºC)					
N					
Median (range)					
Blood pressure systolic (mmHg)					
N					
Median (range)					
Blood pressure diastolic (mmHg)					

	Part A	Part B		Part A+B	Total
	S1 (TR)	S1 (TR)	S2 (RT)	S1 (TR)	
N					
Median (range)					

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.5.6 ECG† pre infusion at baseline

	Part A		Part B				Part A+B		Total	
	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)			
	N	%	N	%	N	%	N	%	N	%
Result										
Normal										
Abnormal										

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
† Worst result of the three ECGs replicates will be used as baseline value.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.5.7 ECG† pre infusion at baseline

	Part A		Part B				Part A+B		Total	
	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)			
	N	%	N	%	N	%	N	%	N	%
PR interval (msec)										
N										
Median (range)										
Heart rate (bpm)										
N										
Median (range)										
QT interval (msec)										
N										
Median (range)										
Bazett's corrected QT										
N										
Median (range)										

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
† Mean of the three ECGs replicates will be used as a baseline value.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 10.2.5.8 Patients with abnormal electrocardiogram

Study Part	Sequence	Subject	ECG no.	Abnormality	PR interval (msec)	Heart rate (bpm)	QT interval (msec)	Bazett's corrected QT
…								

Table 10.2.5.9 LVEF at baseline

	Part A		Part B				Part A+B		Total	
	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)			
	N	%	N	%	N	%	N	%	N	%
Result										
Normal										
Abnormal										

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 10.2.5.10 Patients with abnormal LVEF

Study Part	Sequence	Subject	Result	Method	Value (%)	Lower limit (%)	Abnormalities
…							

Notes: Significant and non-significant abnormalities

Table 10.2.5.11 LVEF value at baseline

	Part A		Part B				Part A+B		Total	
LVEF (%)	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)			
	N	%	N	%	N	%	N	%	N	%
MUGA										
N										
Median (range)										
ECHO										
N										
Median (range)										
Both										
N										
Median (range)										

Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

10.2.6 Hematological Evaluation at Baseline

Table 10.2.6.1 Hematology abnormalities at baseline†

	Part A						Part B						Part A+B						Total			
	S1 (TR)						S1 (TR)				S2 (RT)				S1 (TR)							
	All grades		Gr 1		...*		All grades		Gr 1		…*		All grades		Gr 1		…*		All grades		Gr 1	…*	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Anemia																								
Leukopenia																								
Lymphopenia																								
Neutropenia																								
Thrombocytopenia																								

†Defined as the last value recorded before or on the date of first infusion.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.
* Gr 1, Gr 2, Gr 3, Gr 4

Table 10.2.6.2 Median and range for hematology parameters at baseline†

	Part A	Part B		Part A+B	Total
	S1 (TR)	S1 (TR)	S2 (RT)	S1 (TR)	
Hemoglobin (g/dL)					
N					
Median (range)					
WBC (10^9/L)					
N					
Median (range)					
Lymphocytes (10^9/L)					
N					
Median (range)					
…					
N					
Median (range)					

†Defined as the last value recorded before or on the date of first infusion.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 10.2.6.3 Hematological abnormalities at baseline (grade ≥ 2)

Study Part	Sequence	Subject	Lab. Test	Examination date	Value	Std. Value	Std. Unit	Grade
…								

Listing 10.2.6.4 Hematological tests not assessed at baseline

Study Part	Sequence	Subject	Lab. Test
…			

10.2.7 Biochemical Evaluation at Baseline

Table 10.2.7.1 Biochemical abnormalities at baseline†

	Part A				Part B				Part A+B				Total			
	S1 (TR)				S1 (TR)				S2 (RT)				S1 (TR)			
	All grades		Gr 1		...**		All grades		Gr 1		…**		All grades		Gr 1		…**		All grades		Gr 1		…**	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
ALT increased																								
AST increased																								
…*																								

†Defined as the last value recorded before or on the date of first infusion.
*Creatinine increased, hyperglycemia, hypoglycemia, CPK increased, GGT increased, bilirubin increased, hypoalbuminemia, hypernatremia, hyponatremia, hyperkalemia, hypokalemia, hypermagnesemia, hypomagnesemia, hypercalcemia, hypocalcemia.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.
** Gr 1, Gr 2, Gr 3, Gr 4

Table 10.2.7.2 Median and range for biochemical parameters at baseline†

	Part A	Part B		Part A+B	Total
	S1 (TR)	S1 (TR)	S2 (RT)	S1 (TR)	
ALT (xULN)					
N					
Median (range)					
AST (xULN)					
N					
Median (range)					
…					
N					
Median (range)					

†Defined as the last value recorded before or on the date of first infusion.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 10.2.7.3 Biochemical abnormalities at baseline (grade ≥ 2)

Study Part	Sequence	Subject	Lab. Test	Examination date	Value	Std. Value	Grade
…							

Listing 10.2.7.4 Biochemical abnormalities not assessed at baseline

Study Part	Sequence	Subject	Lab. Test
…			

10.2.8 Coagulation Evaluation at Baseline

Table 10.2.8.1 Coagulation abnormalities at baseline†

	Part A				Part B				Part A+B				Total			
	S1 (TR)				S1 (TR)				S2 (RT)				S1 (TR)			
	All grades		Gr 1		…*		All grades		Gr 1		…*		All grades		Gr 1		…*	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
INR increased																		

†Defined as the last value recorded before or on the date of first infusion.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.
*Gr 1, Gr 2, Gr 3, Gr 4

Listing 10.2.8.2 INR increased at baseline (grade ≥ 2)

Study Part	Sequence	Subject	Lab. Test	Examination date	Value	Std. Value	Grade
…							

Listing 10.2.8.3 INR not assessed at baseline

Study Part	Sequence	Subject	Lab. Test
…			

10.2.9 Signs and Symptoms at Baseline

Signs and symptoms refer to any AE with onset date before the first treatment dose.

Table 10.2.9.1 Signs and symptoms at baseline (MedDRA coded)

MedDRA SOC/PT†	Part A		Part B				Part A+B		Total	
	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)			
	N	%	N	%	N	%	N	%	N	%
…										

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
†SOC: System Organ Class; PT: Preferred Term
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.9.2 Signs and symptoms at baseline

No. of signs and symptoms per patient	Part A		Part B				Part A+B		Total	
	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)			
	N	%	N	%	N	%	N	%	N	%
0										
1										
2										
≥ 3										
Total										

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.9.3 Summary of signs and symptoms at baseline

No. of signs and symptoms per patient	Part A	Part B		Part A+B	Total
	S1 (TR)	S1 (TR)	S2 (RT)	S1 (TR)	
N					
Median (range)					

Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 10.2.9.4 Signs and symptoms at baseline (grade ≥ 2)

Study Part	Sequence	Subject	Sign/symptom	MedDRA Preferred Term	Grade	Onset date	Relationship
…							

10.2.10 Concomitant Medication at Baseline

Concomitant medication at baseline according to the ATC classification.

Table 10.2.10.1 Concomitant medication at baseline (ATC levels1, 2 and 4)

	Part A		Part B				Part A+B		Total	
Concomitant medication	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)			
	N	%	N	%	N	%	N	%	N	%
Alimentary tract and metabolism										
Antacids										
Magnesium compounds										
Magnesium adipate										
…										

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

11 APPENDIX II: SAFETY ANALYSIS

11.1 Extent of Exposure

This analysis will be carried out on evaluable patients for the safety population.

11.1.1 Treatment Administration

Table 11.1.1.1 Number of cycles administered†

No. of cycles administered	Part A		Part B				Part A+B		Total	
	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)			
	N	%	N	%	N	%	N	%	N	%
1 cycle										
2 cycles										
3 cycles										

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
† Including when lurbinectedin is administered both alone and in combination with itraconazole.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 11.1.1.2 Summary of number of cycles administered† and time on treatment

	Part A	Part B		Part A+B	Total
	S1 (TR)	S1 (TR)	S2 (RT)	S1 (TR)	
No. of cycles administered per patient					
N					
Median (range)					
Time on treatment (weeks)*					
N					
Median (range)					

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
† Including when lurbinectedin is administered both alone and in combination with itraconazole.
*Time on treatment is defined as the last administration date of lurbinectedin plus 31 days, death or the start date of the new therapy, whichever comes first, minus the first administration date of lurbinectedin.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 11.1.1.3 Dose information by study part and sequence

	Part A	Part B		Part A+B	Total
	S1 (TR)	S1 (TR)	S2 (RT)	S1 (TR)	
			Lurbinectedin		
Cumulative dose (mg/m^2)					
N					
Median (range)					
Dose intensity (mg/m^2/week)					
N					
Median (range)					
Relative dose intensity (%)					
N					
Median (range)					

	Part A	Part B		Part A+B	Total
	S1 (TR)	S1 (TR)	S2 (RT)	S1 (TR)	
			Itraconazole		
Cumulative dose (mg)					
N					
Median (range)					
Compliance (%)					
N					
Median (range)					

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

11.1.2 Cycle Delays

Table 11.1.2.1 Summary of lurbinectedin dose delays

	Part A		Part B				Part A+B		Total	
	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)			
	N	%	N	%	N	%	N	%	N	%
No. of patients treated										
No. of patients susceptible to have dose delay †										
No. of patients with any dose delay										
Drug related‡ AE										
Non-drug related AE										
Other reason										
No. of cycles administered										
No. of cycles susceptible to have dose delay††										
No. of cycles with any dose delay‡‡										
Drug related‡ AE										
Non-drug related AE										
Other reason										

† Excluding patients who received only the first cycle.
‡ Related or unknown relationship
†† All cycles excluding first cycle
‡‡ Denominator = Number of cycles susceptible to have dose delay
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 11.1.2.2 Length of delay

	Part A		Part B				Part A+B		Total	
	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)			
	N	%	N	%	N	%	N	%	N	%
Length of delay‡‡										
≤ 2 days										
≤ 7 days										
> 7 to ≤ 14 days										

‡‡ Denominator = Number of cycles susceptible to have dose delay
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 11.1.2.3 Dose delays

Study Part	Sequence	Treatment Group*	Subject	Cycle	Delay (days)	Reason for delay
…						

* ITZ+LRB / LRB

11.1.3 Dose Reductions

Table 11.1.3.1 Summary of lurbinectedin dose reductions

	Part A		Part B				Part A+B		Total	
	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)			
	N	%	N	%	N	%	N	%	N	%
No. of patients treated										
No. of patients susceptible to have dose reduction †										
No. of patients with any dose reduction										
Drug related‡ AE										
Non-drug related AE										
Other reason										
No. of cycles administered										
No. of cycles susceptible to have dose reduction††										
No. of cycles with any dose reduction‡‡										
Drug related‡ AE										
Non-drug related AE										
Other reason										

† Excluding patients who received only the first cycle.
‡ Related or unknown relationship
†† All cycles excluding first cycle
‡‡ Denominator = Number of cycles susceptible to have dose delay/reduction
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 11.1.3.2 Dose reductions

Study Part	Sequence	Treatment Group*	Subject	Cycle	Lurbinectedin intended dose (mg/m^2)	Reason for dose reduction	Specify
…							

* ITZ+LRB / LRB

11.1.4 Any Other Dose Modifications

Listing 11.1.4.1 Dose interruptions for lurbinectedin

Study Part	Sequence	Treatment Group*	Subject	Cycle	Date	Reason for interruption	Specify
…							

* ITZ+LRB / LRB

Listing 11.1.4.2 Dose Omissions for lurbinectedin

Study Part	Sequence	Treatment Group*	Subject	Cycle	Date	Reason for omission	Specify
…							

* ITZ+LRB / LRB

Listing 11.1.4.3 Dose not taken according to protocol for Itraconazole

Study Part	Sequence	Treatment Group*	Subject	Cycle	Date	Reason for omission	Specify
…							

* ITZ+LRB / LRB

11.2 Adverse Events (AEs)

This analysis will be carried out on evaluable patients for the safety population.

All adverse events tables will be listed by study part and sequence and differentiating by treatment (Test, Reference or both). Additional groups could be done (such as PM01183 alone or in combination) if required, and a sequential number will be added at the end of the table number.

AEs consisting of laboratory abnormalities (e.g., neutropenia) may be under-reported as AEs. Since these events are better evaluated using objective laboratory results, laboratory abnormalities will be discussed in Section 11.4.

The type of toxicity and worst grade or severity by cycle and by patient will be summarized according to System Organ Class (SOC) and Preferred Term (PT) as per the MedDRA dictionary. Subsequent grouping of similar or clinically related items might be appropriate at the time of the analysis. Tables will be organized by category of events using SOC and PT. Grades could be presented by separate or any other grouping at the time of the analysis.

11.2.1 Display of Adverse Events

Table 11.2.1.1 Summary of adverse events

	Part A		Part B			
	S1		S1		S2	
	T	R	T	R	R	T
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
No. of patients with any AE						
No. of patients with any treatment-related† AE						
Patients with any grade 3/4 AE						
Patients with any grade 4 AE						
No. of patients with any grade 3/4 treatment-related† AE						
No. of patients with any grade 4 treatment-related† AE						
No. of patients with any SAE						
No. of patients with any treatment-related† SAE						
No. of patients with any grade 3/4 SAE						
No. of patients with any grade 4 SAE						
Any grade 3/4 treatment-related† SAE						
Any grade 4 treatment-related† SAE						
No. of patients with deaths associated with AEs						
No. of patients with deaths associated with treatment-related† AEs						
No. of patients with dose delays associated with AEs						
No. of patients with dose delays associated with treatment-related† AEs						
No. of patients with dose reductions associated with AEs						
No. of patients with dose reductions associated with treatment-related†AEs						
No. of patients with dose interruptions associated with AEs						
No. of patients with dose interruptions associated with treatment-related† AEs						

	Part A+B		Total
	S1		
	T	R	
	N(%)	N(%)	N(%)
No. of patients with any AE			
No. of patients with any treatment-related† AE			
Patients with any grade 3/4 AE			
Patients with any grade 4 AE			
No. of patients with any grade 3/4 treatment-related† AE			
No. of patients with any grade 4 treatment-related† AE			
No. of patients with any SAE			
No. of patients with any treatment-related† SAE			
No. of patients with any grade 3/4 SAE			
No. of patients with any grade 4 SAE			
Any grade 3/4 treatment-related† SAE			
Any grade 4 treatment-related† SAE			
No. of patients with deaths associated with AEs			
No. of patients with deaths associated with treatment-related† AEs			
No. of patients with dose delays associated with AEs			
No. of patients with dose delays associated with treatment-related† AEs			
No. of patients with dose reductions associated with AEs			
No. of patients with dose reductions associated with treatment-related†AEs			
No. of patients with dose interruptions associated with AEs			
No. of patients with dose interruptions associated with treatment-related† AEs			

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
† Related to both or lurbinectedin or itraconazole or with unknown relationship.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2.
T, Test (ITZ+LRB); R, Reference (LRB alone).

Supplementary tables describing the adverse event toxicity grades or laboratory abnormality grades 1,2,3,4,5 and grade 1-5 will be added below the tables with aggregated severity grades show in sections 11.2.1, 11.3.1, 11.4.1 and 11.4.2 as shown in table 11.2.1.2

Table 11.2.1.2 Treatment related† (or with unknown relationship) Adverse Events. Worst grade by treatment

	Part A					
	T			R		
SOC/PT	All grades	Gr ≥ 3	Gr ≥4	All grades	Gr ≥ 3	Gr≥4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
…						

	Part B											
	S1						S2					
	T			R			R			T		
SOC/PT	All grades	Gr ≥ 3	Gr≥4	All grades	Gr ≥ 3	Gr≥4	All grades	Gr ≥ 3	Gr≥4	All grades	Gr ≥ 3	Gr≥4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
…												

	Part A+B (S1)						Total		
	T			R					
SOC/PT	All grades	Gr ≥ 3	Gr≥4	All grades	Gr ≥ 3	Gr≥4	All grades	Gr ≥ 3	Gr≥4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
…									

	Part A											
	T						R					
SOC/PT	Gr1	Gr2	Gr3	Gr4	Gr5	Gr 1- 5	Gr1	Gr2	Gr3	Gr4	Gr5	Gr 1- 5
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
…												

	Part B (S1)											
	T						R					
SOC/PT	Gr1	Gr2	Gr3	Gr4	Gr5	Gr 1- 5	Gr1	Gr2	Gr3	Gr4	Gr5	Gr 1- 5
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
…												

	Part B (S2)											
	R						T					
SOC/PT	Gr1	Gr2	Gr3	Gr4	Gr5	Gr 1- 5	Gr1	Gr2	Gr3	Gr4	Gr5	Gr 1- 5
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
…												

	Part A+B (S1)											
	T						R					
SOC/PT	Gr1	Gr2	Gr3	Gr4	Gr5	Gr 1- 5	Gr1	Gr2	Gr3	Gr4	Gr5	Gr 1- 5
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
…												

Total

SOC/PT	Gr1	Gr2	Gr3	Gr4	Gr5	Gr 1- 5
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
…						

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
† Related to both or lurbinectedin or itraconazole or with unknown relationship.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2.
T, Test (ITZ+LRB); R, Reference (LRB alone).

Table 11.2.1.3 Lurbinectedin related† Adverse Events. Worst grade by treatment

	Part A					
	T			R		
SOC/PT	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
…						

	Part B											
	S1						S2					
	T			R			R			T		
SOC/PT	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
…												

	Part A+B (S1)						Total		
	T			R					
SOC/PT	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
…									

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
† Related to both or lurbinectedin or itraconazole or with unknown relationship.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2.
T, Test (ITZ+LRB); R, Reference (LRB alone).

Table 11.2.1.4 Itraconazole related Adverse Events. Worst grade by treatment

	Part A					
	T			R		
SOC/PT	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
…						

	Part B											
	S1						S2					
	T			R			R			T		
SOC/PT	All grades	Gr ≥ 3	Gr ≥4	All grades	Gr ≥ 3	Gr ≥4	All grades	Gr ≥ 3	Gr ≥4	All grades	Gr ≥ 3	Gr ≥4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
…												

	Part A+B (S1)						Total		
	T			R					
SOC/PT	All grades	Gr ≥ 3	Gr ≥4	All grades	Gr ≥ 3	Gr ≥4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
…									

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
† Related to both or lurbinectedin or itraconazole or with unknown relationship.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2.
T, Test (ITZ+LRB); R, Reference (LRB alone: NA).

Table 11.2.1.5 Treatment related† (or with unknown relationship) Adverse Events. Worst grade per patient

	Part A					
	T			R		
SOC/PT	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
…						

	Part B											
	S1						S2					
	T			R			R			T		
SOC/PT	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
…												

	Part A+B (S1)						Total		
	T			R					
SOC/PT	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
…									

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
A supplementary Table 11.2.1.5supp will be created with grades 1,2,3,4,5.
† Related to both or lurbinectedin or itraconazole or with unknown relationship.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2.
T, Test (ITZ+LRB); R, Reference (LRB alone).

Table 11.2.1.6 Lurbinectedin related† Adverse Events. Worst grade per patient

SOC / PT	Part A						Part B								Part A+B				Total			
	S1 (TR)						S1 (TR)				S2 (RT)				S1 (TR)							
	All grades		Gr ≥ 3		Gr ≥ 4		All grades		Gr ≥ 3		Gr ≥ 4		All grades		Gr ≥ 3		Gr ≥ 4		All grades		Gr ≥ 3		Gr ≥ 4	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
…																								

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
† Related to both or lurbinectedin or with unknown relationship
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 11.2.1.7 Itraconazole related Adverse Events. Worst grade per patient

SOC / PT	Part A						Part B								Part A+B				Total			
	S1 (TR)						S1 (TR)				S2 (RT)				S1 (TR)							
	All grades		Gr ≥ 3		Gr ≥ 4		All grades		Gr ≥ 3		Gr ≥ 4		All grades		Gr ≥ 3		Gr ≥ 4		All grades		Gr ≥ 3		Gr ≥ 4	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
…																								

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
† Related to both or itraconazole or with unknown relationship
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 11.2.1.8 Adverse Events regardless of relationship. Worst grade by treatment

	Part A					
	T			R		
SOC/PT	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
…						

	Part B											
	S1						S2					
	T			R			R			T		
SOC/PT	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
…												

	Part A+B (S1)						Total		
	T			R					
SOC/PT	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
…									

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
† Related to both or lurbinectedin or itraconazole or with unknown relationship.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2.
T, Test (ITZ+LRB); R, Reference (LRB alone).

Table 11.2.1.9 Adverse Events regardless of relationship. Worst grade per patient

SOC / PT	Part A				Part B				Part A+B				Total			
	S1 (TR)				S1 (TR)				S2 (RT)				S1 (TR)			
	All grades		Gr ≥ 3		Gr ≥ 4		All grades		Gr ≥ 3		Gr ≥ 4		All grades		Gr ≥ 3		Gr ≥ 4	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
…																		

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 11.2.1.10 AEs grade ≥ 3

Study Part	Sequence	Treatment Group*	Subject	Cycle	Literal term	SOC	PT	Grade	SAE (Y/N)	Start date	End date	Relationship to study medication	Action taken	Serious Event	Outcome
…															

Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
* ITZ+LRB / LRB

Listing 11.2.1.11 AEs related only to lurbinectedin

Study Part	Sequence	Treatment Group*	Subject	Cycle	Literal term	SOC	PT	Grade	SAE (Y/N)	Start date	End date	Action taken	Serious Event	Outcome
…														

Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
* ITZ+LRB / LRB

Listing 11.2.1.12 AEs related only to itraconazole

Study Part	Sequence	Treatment Group*	Subject	Cycle	Literal term	SOC	PT	Grade	SAE (Y/N)	Start date	End date	Action taken	Serious Event	Outcome
…														

Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
* ITZ+LRB / LRB

11.2.2 Evolution of Signs and Symptoms during the Treatment

Worst grade of signs and symptoms present at baseline and their evolution during treatment will be shown regardless of relationship.

Table 11.2.2.1 Shift of signs and symptoms during treatment

MedDRA PT	Baseline grade	Worst grade per patient during treatment									
		Grade 1		Grade 2		Grade 3		Grade 4		Grade 5	
		N	%	N	%	N	%	N	%	N	%
Part A - S1 (TR)											
…	1										
	2										
	…										
…	1										
	…										
Part B - S1 (TR)											
…	1										
	…										
…	1										
	…										
Part B - S2 (RT)											
…	1										
	…										
…	1										
	…										

Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.
Test, ITZ+LRB; Reference, LRB alone.

11.3 Serious Adverse Events and Deaths

11.3.1 Serious Adverse Events

This analysis will be carried out on evaluable patients for the safety population.

All serious adverse events tables will be listed by study part and sequence and differentiating by treatment (Test, Reference or both). Additional groups could be done (such as PM01183 alone or in combination) if required, and a sequential number will be added at the end of the table number.

The type of toxicity and worst grade or severity by cycle and by patient will be summarized according to System Organ Class (SOC) and Preferred Term (PT) as per the MedDRA dictionary. Subsequent grouping of similar or clinically related items might be appropriate at the time of the analysis. Tables will be organized by category of events using SOC and PT. Grades could be presented by separate or any other grouping at the time of the analysis.

If the number of SAEs are very low, these tables will not be presented and only listings will be shown.

Table 11.3.1.1 Treatment related† (or with unknown relationship) SAEs. Worst grade by treatment

	Part A					
	T			R		
SOC/PT	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
…						

	Part B											
	S1						S2					
	T			R			R			T		
SOC/PT	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
…												

	Part A+B (S1)						Total		
	T			R					
SOC/PT	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
…									

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
† Related to both or lurbinectedin or itraconazole or with unknown relationship.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2.
T, Test (ITZ+LRB); R, Reference (LRB alone).

Table 11.3.1.2 Lurbinectedin related† SAEs. Worst grade by treatment

	Part A					
	T			R		
SOC/PT	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
…						

	Part B											
	S1						S2					
	T			R			R			T		
SOC/PT	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
…												

	Part A+B (S1)						Total		
	T			R					
SOC/PT	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
…									

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
† Related to both or lurbinectedin or itraconazole or with unknown relationship.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2.
T, Test (ITZ+LRB); R, Reference (LRB alone).

Table 11.3.1.3 Itraconazole related† SAEs. Worst grade by treatment

	Part A					
	T			R		
SOC/PT	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
…						

	Part B											
	S1						S2					
	T			R			R			T		
SOC/PT	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
…												

	Part A+B (S1)						Total		
	T			R					
SOC/PT	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4

	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
…									

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
† Related to both or lurbinectedin or itraconazole or with unknown relationship.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2.
T, Test (ITZ+LRB); R, Reference (LRB alone).

Table 11.3.1.4 Treatment related† (or with unknown relationship) SAEs. Worst grade per patient

SOC / PT	Part A			Part B						Part A+B			Total		
	S1 (TR)			S1 (TR)			S2 (RT)			S1 (TR)					
	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %
…															

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
† Related to both or lurbinectedin or itraconazole or with unknown relationship
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 11.3.1.5 Lurbinectedin related† SAEs. Worst grade per patient

SOC / PT	Part A			Part B						Part A+B			Total		
	S1 (TR)			S1 (TR)			S2 (RT)			S1 (TR)					
	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %
…															

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
† Related to both or lurbinectedin or with unknown relationship
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 11.3.1.6 Itraconazole related SAEs. Worst grade per patient

SOC / PT	Part A			Part B						Part A+B			Total		
	S1 (TR)			S1 (TR)			S2 (RT)			S1 (TR)					
	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %
…															

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
† Related to both or itraconazole or with unknown relationship
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.
T, Test (ITZ+LRB); R, Reference (LRB alone: NA).

Table 11.3.1.7 SAEs regardless of relationship. Worst grade by treatment

	Part A					
	T			R		
SOC/PT	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
…						

	Part B											
	S1						S2					
	T			R			R			T		
SOC/PT	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
…												

	Part A+B (S1)						Total		
	T			R					
SOC/PT	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
…									

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
† Related to both or lurbinectedin or itraconazole or with unknown relationship.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2.
T, Test (ITZ+LRB); R, Reference (LRB alone).

Table 11.3.1.8 SAEs regardless of relationship. Worst grade per patient

SOC / PT	Part A			Part B						Part A+B			Total		
	S1 (TR)			S1 (TR)			S2 (RT)			S1 (TR)					
	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %
…															

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 11.3.1.9 All SAEs†

Study Part	Sequence	Treatment Group*	Subject	SOC	PT	Grade	AE Status	AE Relationship	AE consequences	Start date	End date
…											

† SAE narratives will be provided by the pharmacovigilance department
* ITZ+LRB / LRB

11.3.2 Deaths

Table 11.3.2.1 Cause of death

	Part A		Part B				Part A+B		Total	
	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)			
	N	%	N	%	N	%	N	%	N	%
Malignant disease										
Adverse Event(s)										
Other‡										
Total										

Notes: Percentage is based on number of patients who died by study part and sequence, when applicable.
‡ Specify.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 11.3.2.2 Deaths

Study Part	Sequence	Treatment Group*	Subject	Cycle	Death date	Cause of death	No. of cycles administered	Time on treatment†	Time from first dose (days)	Time from last dose (days)
…										

* ITZ+LRB / LRB

11.4 Clinical Laboratory Evaluation

Tables will be listed by study part and sequence, however, additional groups could be done (such as PM01183 alone or in combination) if required, and a sequential number will be added at the end of the table number.
Grades could be presented by separate or any other grouping at the time of the analysis.

11.4.1 Hematological Abnormalities

Table 11.4.1.1 Hematological abnormalities: Worst grade by treatment

	Part A					
	T			R		
SOC/PT	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
Anemia						
Leukopenia						
Lymphopenia						
Neutropenia						
Thrombocytopenia						

	Part B											
	S1						S2					
	T			R			R			T		
SOC/PT	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
Anemia												
Leukopenia												
Lymphopenia												
Neutropenia												
Thrombocytopenia												

	Part A+B (S1)						Total		
	T			R					
SOC/PT	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
Anemia									
Leukopenia									
Lymphopenia									
Neutropenia									
Thrombocytopenia									

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
† Related to both or lurbinectedin or itraconazole or with unknown relationship.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2.
T, Test (ITZ+LRB); R, Reference (LRB alone).

Listing 11.4.1.2 Hematological abnormalities grade ≥ 3 by treatment

Study Part	Sequence	Treatment Group*	Subject	Cycle	Event	Grade
…						

* ITZ+LRB / LRB

Listing 11.4.1.3 Hematological tests not assessed by treatment

Study Part	Sequence	Treatment Group*	Subject	Cycle	Lab. test
…					

* ITZ+LRB / LRB

Table 11.4.1.4 Hematological abnormalities: Worst grade per patient

	Part A			Part B						Part A+B			Total		
	S1 (TR)			S1 (TR)			S2 (RT)			S1 (TR)					
	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %
Anemia															
Leukopenia															
Lymphopenia															
Neutropenia															
Thrombocytopenia															

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 11.4.1.5 Hematological abnormalities per patient grade ≥ 3

Study Part	Sequence	Treatment Group*	Subject	Cycle	Event	Cycle	Grade
…							

* ITZ+LRB / LRB

Listing 11.4.1.6 Hematological tests not assessed per patient

Study Part	Sequence	Treatment Group*	Subject	Cycle	Lab. test
…					

* ITZ+LRB / LRB

11.4.2 Biochemical Abnormalities

Table 11.4.2.1 Biochemical abnormalities: Worst grade per treatment

	Part A					
	T			R		
	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
ALT increase						
AST increase						
…*						

	Part B											
	S1						S2					
	T			R			R			T		
	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
ALT increase												
AST increase												
…*												

	Part A+B (S1)						Total		
	T			R					
	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
ALT increase									
AST increase									
…*									

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
*Creatinine increased, hyperglycemia, hypoglycemia, CPK increased, GGT increased, bilirubin increased, hypoalbuminemia, hypernatremia, hyponatremia, hyperkalemia, hypokalemia, hypermagnesemia, hypomagnesemia, hypercalcemia, hypocalcemia.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2.
T, Test (ITZ+LRB); R, Reference (LRB alone).

Listing 11.4.2.2 Biochemical abnormalities grade ≥ 3 by treatment

Study Part	Sequence	Treatment Group*	Subject	Event	Grade
…					

* ITZ+LRB / LRB

Listing 11.4.2.3 Biochemical tests not assessed by treatment

Study Part	Sequence	Treatment Group*	Subject	Lab. test
…				

* ITZ+LRB / LRB

Table 11.4.2.4 Biochemical abnormalities: Worst grade per patientpatientpatientpatientpatient

	Part A			Part B						Part A+B			Total	
	S1 (TR)			S1 (TR)			S2 (RT)			S1 (TR)				
	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %
ALT increase															
AST increase															
…*															

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 11.4.2.5 Biochemical abnormalities per patientpatientpatientpatientpatient grade ≥ 3

Study Part	Sequence	Treatment Group*	Subject	Cycle	Event	Cycle	Grade
…							

* ITZ+LRB / LRB

Listing 11.4.2.6 Biochemical tests not assessed per patientpatientpatientpatientpatient

Study Part	Sequence	Treatment Group*	Subject	Cycle	Lab. test
…					

* ITZ+LRB / LRB

11.4.3 Laboratory Values Over Treatment

Table 11.4.3.1 Shift of hematological abnormalities, worst grade per patient vs. baseline

	Baseline grade	Worst grade per patient during treatment									
		Grade 1		Grade 2		Grade 3		Grade 4		Grade 5	
		N	%	N	%	N	%	N	%	N	%
						Part A - S1 (TR)					
Anemia	G0										
	…										
	G4										
Leukopenia	G0										
	…										
	G4										
…	G0										
	…										
	G4										
						Part B - S1 (TR)					
Anemia	G0										
	…										
	G4										
Leukopenia	G0										
	…										
	G4										
…	G0										
	…										
	G4										
						Part B - S2 (RT)					
Anemia	G0										
	…										
	G4										
Leukopenia	G0										
	…										
	G4										
…	G0										
	…										
	G4										

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

If a low number of patients with grade ≥3 neutropenia or thrombocytopenia, the following table will be omitted and the information will be provided in a listing.

Table 11.4.3.2 Time course for neutrophils and platelets

	Part A		Part B				Part A+B		Total
	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)		
	N	Median (range)	N	Median (range)	N	Median (range)	N	Median (range)	
Neutropenia (Grade≥3)									
Onset day									
Nadir day									
Recovery day									
Days to recovery									
Thrombocytopenia (Grade≥3)									
Onset day									
Nadir day									
Recovery day									
Days to recovery									

Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 11.4.3.3 Shift of biochemical abnormalities, worst grade per patient vs baseline

	Baseline grade	Worst grade per patient during treatment									
		Grade 1		Grade 2		Grade 3		Grade 4		Grade 5	
		N	%	N	%	N	%	N	%	N	%
		Part A - S1 (TR)									
ALT increase	G0										
	…										
	G4										
AST increase	G0										
	…										
	G4										
…	G0										
	…										
	G4										
		Part B - S1 (TR)									
ALT increase	G0										
	…										
	G4										
AST increase	G0										
	…										
	G4										
…	G0										
	…										
	G4										
		Part B - S2 (RT)									
ALT increase	G0										
	…										
	G4										
AST increase	G0										
	…										
	G4										
…	G0										
	…										
	G4										

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

If a low number of patients with grade ≥3 ALT or AST increased, the following table will be omitted and the information will be provided in a listing.

Table 11.4.3.4 Time course for AST and ALT

	Part A		Part B				Part A+B		Total	
	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)			
	N	%	N	%	N	%	N	%	N	%

	Part A		Part B				Total	
			S1 (TR)		S2 (RT)			
	N	Median (range)	N	Median (range)	N	Median (range)	N	Median (range)
AST (Grade≥3)								
Onset day								
Peak day								
Recovery day								
Days to recovery								
ALT (Grade≥3)								
Onset day								
Peak day								
Recovery day								
Days to recovery								

Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

11.5 Linear Mixed-effects Model

If applicable, to compare the incidence of grade 4 or grade 3/4 between the combination and lurbinectedin alone, a generalized linear mixed-effects model will be fit to the data with treatment (Combination or lurbinectedin alone), period and sequence as fixed effects, and patients nested in sequences as a random effect

Table 11.5.1.1 Safety comparison between combination and lurbinectedin alone†

	Combination	Lurbinectedin alone	p-value‡
Any grade 3/4 AE			
Any grade 4 AE			
Any grade 3/4 treatment-related AE			
Any grade 4 treatment-related AE			
Any abnormality (G3-4) in laboratory value (hema, bio)			
Any abnormality (G4) in laboratory value (hema, bio)			

† A generalized mixed-effects model will be fit for each safety evaluation
‡ p-values will be provided for the comparison between treatments (combination vs. Lurbinectedin alone) or including the sequence effect if deemed necessary.

11.6 Physical Findings, ECOG PS, LVEF and ECG

11.6.1 Physical Findings and ECOG PS

Listing 11.6.1.1 ECOG Performance status during the study

Study part / Sequence		Subject	PS				
			Baseline	Cycle 1	Cycle 2	Cycle 3	EOT
Part A	S1 (TR)	…					
Part B	S1 (TR)	…					
	S2 (RT)	…					

Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 11.6.1.2 Weight change during the study

Study part / Sequence		Subject	Weight (kg) at baseline	% Change†			
				Cycle 1	Cycle 2	Cycle 3	EOT
Part A	S1 (TR)	…					
Part B	S1 (TR)	…					
	S2 (RT)	…					

† % of change with respect to baseline
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 11.6.1.3 BSA during the study

Study part / Sequence		Subject	BSA (m^2)†				
			Baseline	Cycle 1	Cycle 2	Cycle 3	EOT
Part A	S1 (TR)	…					
Part B	S1 (TR)	…					
	S2 (RT)	…					

† Calculated according to DuBois formula: BSA (m^2) = Weight $(kg)^{0.425}$ x Height $(cm)^{0.725}$ x 0.007184
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.
* ITZ+LRB / LRB

11.6.2 LVEF and ECG

Listing 11.6.2.1 Patients with abnormal or clinically indicated LVEF during the study

Study Part	Sequence	Treatment Group*	Subject	Date	Visit	Abnormality	Specify	Method	LVEF (%)	Lower limit of normality
…										

* ITZ+LRB / LRB

Listing 11.6.2.2 Electrocardiogram: PR interval evolution during the study by study part and sequence

Study part / Sequence		Subject	PR interval (msec)‡ at baseline	% Change†				EOT
				Cycle 1		Cycle 2		
				Pre infusion	Post infusion	Pre infusion	Post infusion	
Part A	S1 (TR)	…						
Part B	S1 (TR)	…						
	S2 (RT)	…						

† % of change with respect to baseline
‡ Triplicate ECG values obtained at each time point (baseline, Day 1 of Cycle 1 pre-infusion and post-infusion, Day 1 of Cycle 2 pre-infusion and post-infusion and end of treatment) are averaged
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 11.6.2.3 Electrocardiogram: Heart rate evolution during the study

Study part / Sequence		Subject	Heart rate (bpm)‡ at baseline	% Change†				EOT
				Cycle 1		Cycle 2		
				Pre infusion	Post infusion	Pre infusion	Post infusion	
Part A	S1 (TR)	…						
Part B	S1 (TR)	…						
	S2 (RT)	…						

† % of change with respect to baseline
‡ Triplicate ECG values obtained at each time point (baseline, Day 1 of Cycle 1 pre-infusion and post-infusion, Day 1 of Cycle 2 pre-infusion and post-infusion and end of treatment) are averaged
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 11.6.2.4 Electrocardiogram: QT interval evolution during the study

Study part / Sequence		Subject	QT interval (msec)‡ at baseline	% Change†				EOT
				Cycle 1		Cycle 2		
				Pre infusion	Post infusion	Pre infusion	Post infusion	
Part A	S1 (TR)	…						
Part B	S1 (TR)	…						
	S2 (RT)	…						

† % of change with respect to baseline
‡ Triplicate ECG values obtained at each time point (baseline, Day 1 of Cycle 1 pre-infusion and post-infusion, Day 1 of Cycle 2 pre-infusion and post-infusion and end of treatment) are averaged
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 11.6.2.5 Electrocardiogram: QTc (Bazett's) [††] evolution during the study

Study part / Sequence		Subject	QTc (Bazett's)[‡] at baseline	% Change[†]				
				Cycle 1		Cycle 2		EOT
				Pre infusion	Post infusion	Pre infusion	Post infusion	
Part A	S1 (TR)	…						
Part B	S1 (TR)	…						
	S2 (RT)	…						

[†] % of change with respect to baseline
[‡] Triplicate ECG values obtained at each time point (baseline, Day 1 of Cycle 1 pre-infusion and post-infusion, Day 1 of Cycle 2 pre-infusion and post-infusion and end of treatment) are averaged
[††] QTc (Bazett's) = QT interval / √(60/Heart rate)
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 11.6.2.6 Patients with abnormal or clinically indicated Electrocardiogram during the study

Study Part	Sequence	Treatment Group*	Subject	Cycle	Assessment date	Visit	ECG #[‡]	Result	Specify	PR interval (msec)	Heart rate (bpm)	QT interval (msec)	QTc[†] (Bazett's)
…													

[†] QTc (Bazett's) = QT interval / √(60/Heart rate)
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.
* ITZ+LRB / LRB
[‡] # of ECGs triplicates: ECG 1-3 (Pre infusion) and ECG 1-3 (Post infusion) identification.

11.7 Concomitant Therapies

11.7.1 Concomitant Medication during the Study

Table 11.7.1.1 Concomitant medication during treatment (ATC1/ATC2/ATC4/PN)

Part A		Part B				Part A+B (S1)		Total
T	R	T	R	T	R	T	R	
N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
ATC1								
ATC 2								
ATC4								
PN								
...								
ATC1								
ATC 2								
ATC4								
PN								
...								

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 11.7.1.2 Concomitant medication during treatment by ATC

Part A		Part B				Part A+B (S1)		Total
T	R	T	R	T	R	T	R	
N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
No. of systems (ATC1 level)								
0								
1								
2								
≥ 3								
Median (range)								
No. of indications (ATC2 level)								
0								
1								
2								
≥ 3								
Median (range)								
No. of agent families (ATC4 level)								
0								
1								
2								
≥ 3								
Median (range)								
No. of agents (PN level)								
0								
1								
2								
≥ 3								
Median (range)								

Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 11.7.1.3 Summary of concomitant medication during treatment by ATC

	Part A		Part B		Part A+B (S1)				Total
	T	R	T	R	T	R	T	R	
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
No. of systems (ATC1 level)									
N									
Median (range)									
No. of indications (ATC2 level)									
N									
Median (range)									
No. of agent families (ATC4 level)									
N									
Median (range)									
No. of agents (PN level)									
N									
Median (range)									

Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

11.7.2 Further Antitumor Therapies

Listing 11.7.2.1 First Antitumor Therapy

Study Part	Sequence	Subject	End of treatment	First Antitumor Therapy	Start date
…					

* ITZ+LRB / LRB

12 APPENDIX III: EFFICACY EVALUATION

Not applicable.

13 APPENDIX IV: DB Listings

Listing 13.1 Screening (I)

Part / Sequence	Subject	Informed consent	PGt sub-study	Planned initiation	Age	Tumor type	No. of prior lines	EC3	EC4	PCR date	PCR result	Elegibility

Listing 13.2 Screening (II)

Part / Sequence	Subject	Screening failure	Criterion not met	Details

Listing 13.3 Sponsor Approval Form

Part / Sequence	Subject	Approval	Comments	Study Part	Lurbinectedin in combination (mg/m2)	Lurbinectedin alone (mg/m2)

Listing 13.4 Randomization details

Part / Sequence	Subject	Ready to be randomized	Treatment Sequence	Description	Date/Time

Listing 13.5 Study registration

Part / Sequence	Subject	Registration	Randomization	Sequence	Description	Screening failure date

Listing 13.6 Date of visit

Part / Sequence	Treatment Group*	Subject	Cycle	Visit	Date

* ITZ+LRB / LRB

Listing 13.7 Date of unscheduled visit

Part / Sequence	Treatment Group*	Subject	Cycle	Visit	Date	Clinically indicated repeat

* ITZ+LRB / LRB

Listing 13.8 Demographics

Part / Sequence	Subject	Date of birth	Age (years)	Sex	Race	Other Race, specify

Listing 13.9 Childbearing potential and adequate contraception

Part / Sequence	Subject	Childbearing potential?	No, Reason	Adequate contraception?	Specify

Listing 13.10 Pregnancy test

Part / Sequence	Subject	Not applicable?	Reason	Not done?	Sample date	Result

Listing 13.11 Prior medical history

Part / Sequence	Subject	Description	SOC	MedDRA PT	Onset date	End date	Ongoing

Listing 13.12 Cancer history

				First diagnosis		Current disease		
Part / Sequence	Subject	Date of diagnosis	Tumor type	Stage	Date of advanced disease	Date of metastatic disease	Date of last PD	Sites

* ITZ+LRB / LRB

Listing 13.13 Prior surgery

Part / Sequence	Subject	None?	Site and procedures	Date

Listing 13.14 Prior radiotherapy

Part / Sequence	Subject	None?	Site	Total dose (Gy)	Date of first dose	Date of last dose

Listing 13.15 Prior anticancer medical therapy

Part / Sequence	Subject	None?	Regimen	Agent	Agent Coded	Agent Class	Setting	Start date	Stop date	Best response	PD date	Non PD

Listing 13.16 Prophylactic medication

Part / Sequence	Subject	Visit	Type	Medication	…†	Route	Daily dose	Units	Start date	Stop date	Time	Taken per protocol	Specify

(†) ATC1, ATC2, ATC3, ATC4
* ITZ+LRB / LRB

Listing 13.17 Lurbinectedin administration

Part / Sequence	Treatment Group*	Subject	Cycle	Visit	Date	Route	Start time	End time	Intended dose (mg/m2)	Total intended dose (mg)	Total dose given	Total volume	BSA calculated for dose

* ITZ+LRB / LRB

Listing 13.18 Lurbinectedin treatment modification

Part / Sequence	Treatment Group*	Subject	Cycle	Visit	Any modification	Modification	Reason	Adverse Event	Other, specify

Listing 13.19 Lurbinectedin re-administration

Part / Sequence	Treatment Group*	Subject	Cycle	Visit	Date	Not done?	Route	Total dose given	Start time	End time

* ITZ+LRB / LRB

Listing 13.20 Itraconazole administration prior to lurbinectedin infusion

Part / Sequence	Treatment Group*	Subject	Cycle	Visit	Day	Date	Time	No. of capsules	Taken accordingly?	Reason	Contact

* ITZ+LRB / LRB

Listing 13.21 Itraconazole administration D1 to D8

Part / Sequence	Treatment Group*	Subject	Cycle	Visit	Day	Date	Time	No. of capsules	Taken accordingly?	Reason	Contact

* ITZ+LRB / LRB

Listing 13.22 Hematological laboratory values

Part / Sequence	Treatment Group*	Subject	CRF Visit	Calc. cycle	Date	Hemoglobin (g/dl)	…†	WBC (x10*9/L)	Neutrophils (x10*9/L)	Lymphocytes (x10*9/L)	Platelets (x10*9/L)

(†)Hematocrit, RBC and monocytes.
* ITZ+LRB / LRB

Listing 13.23 Coagulation Test

Part / Sequence	Treatment Group*	Subject	Cycle	Visit	Calculated cycle	Date	Repeat	INR (ratio)

* ITZ+LRB / LRB

Listing 13.24 Biochemical laboratory values

Part / Sequence	Treatment Group*	Subject	Visit	Calc. Cycle	Date	n	Total Bilirubin (mg/dl)	Direct Bilirubin (mg/dl)	AST (IU/L)	ALT (IU/L)	LDH (xULN)	…†

(†)Creatinine, CrCl, Glucose, CPK, CPK-MB fraction, GGT, Total Proteins, Albumin, CRP, Na, K, Mg, Ca, Alpha-1-Acid Glycoprotein, Interleukin 6.
* ITZ+LRB / LRB

Listing 13.25 Performance status

Part / Sequence	Treatment Group*	Subject	Cycle	Not done	Visit	Date	ECOG

* ITZ+LRB / LRB

Listing 13.26 Physical examination

Part / Sequence	Treatment Group*	Subject	Cycle	Not done	Visit	Date	Weight	Height	BSA method	BSA	Any abnormalities?	Findings

* ITZ+LRB / LRB

Listing 13.27 Vital signs

Part / Sequence	Treatment Group*	Subject	Cycle	Not done	Visit	Date	Heart rate (bpm)	Systolic (mmHG)	Diastolic (mmHG)	Temperature (ºC)

* ITZ+LRB / LRB

Listing 13.28 Electrocardiogram

Part / Sequence	Treatment Group*	Subject	Cycle	Visit	Date	#	Pre/Post	Not done	Result	Specify	PR interval (msec)	Heart rate (bpm)	QT interval (msec)	Bazett's corrected QT	Not done within protocol, specify

* ITZ+LRB / LRB

Listing 13.29 Concomitant non-diagnostic procedures

Part / Sequence	Treatment Group*	Subject	Cycle	Procedure	Date	Indication	AE/MH	Comments

* ITZ+LRB / LRB

Listing 13.30 LVEF

Part / Sequence	Treatment Group*	Subject	Cycle	Reason clinically indicated	Not done	Visit	Date	Method	Value	Lower limit	Result	Abnormal specify

* ITZ+LRB / LRB

Listing 13.31 Signs and symptoms

Part / Sequence	Treatment Group*	Subject	AE. …†	Grade	SAE	Onset date	Ong.	End date	Ong.	Relationship	Action taken	Seriousness criteria	Outcome

(†)SOC, MedDRA PT
* ITZ+LRB / LRB

Listing 13.32 Adverse events

Part / Sequence	Treatment Group*	Subject	Cycle	S&S	…†	Grade	Ongoing at C1D1	Onset date	End date	Relationship

(†)SOC, MedDRA PT
* ITZ+LRB / LRB

Listing 13.33 SAE summary

Part / Sequence	Treatment Group*	Subject	Case id.	AE	…†	Outcome	Start date	Death	Life threatening	Requires/ prolongs hospitalization	Admission date	Discharge date	…‡

(†)SOC, MedDRA PT
(‡)Persistent/significant disability/incapacity, congenital anomaly, other medically important serious event, infectious agent transmitted, narrative, nullification reason
* ITZ+LRB / LRB

Listing 13.34 Concomitant medication

Part / Sequence	Treatment Group*	Subject	Cycle	Medication	…†	Route	Dose (units)	Frequency	Start date	End date	Ongoing	Indication	AE/MH

(†)ATC1, ATC4
* ITZ+LRB / LRB

Listing 13.35 Diagnostic procedures/Tests

Part / Sequence	Treatment Group*	Subject	Cycle	Test	Date	Result	Units	Comments

* ITZ+LRB / LRB

Listing 13.35.1 Pharmacokinetics

Part / Sequence	Treatment Group*	Subject	Cycle	Day	Samp. time	Samp. window	Date	Time	Total (done)	Unbound (done)	Metabolites (done)	Itraconazole (done)	Comments

* ITZ+LRB / LRB

Listing 13.36 Alpha-1-acid glycoprotein and Interleukin 6

Part / Sequence	Treatment Group*	Subject	Visit	Sample taken	Date	Comments

* ITZ+LRB / LRB

Listing 13.37 Pharmacogenetics (Polymorphisms)

Part / Sequence	Subject	Cycle	Date	Not done?	Comments

Listing 13.38 End of treatment

Part / Sequence	Subject	Primary Reason End of Treatment	Specify

Listing 13.39 Follow up - Further antitumor therapies (after end of treatment)

Part / Sequence	Subject	Antitumor Therapy description	Start date

Listing 13.40 Off study

Part / Sequence	Max. Cycle received	Subject	Date	Primary reason	Specify

Listing 13.41 Death report form

Part / Sequence	Max. Cycle received	Subject	Death date	Cause	Specify	Autopsy?

Listing 13.42 Investigator comments

Part / Sequence	Treatment Group*	Subject	Page name	Instance	Variable	Comments

* ITZ+LRB / LRB

14 APPENDIX V: BIMO Listings

The following listings will be provided following the recommended standardized formats according to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications.

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf

Table 14.1 Site level summary

Site	Patients Screened	Patients Treated	Patients End of Treatment	Patients Off Study

Listing 14.2 Consented subjects by site

Site	Part / Sequence	Treatment Group*	Subject	Informed Consent date	Screening failure?	Date of Screening failure	Treated	Date of First treatment

* ITZ+LRB / LRB

Listing 14.3 Sequence assignment by site

Site	Subject	Study Part	Treatment Sequence	First Intended dose

Listing 14.4 Discontinuations by site

Site	Subject	End of treatment Reason	End of treatment, specify	Off-study date	Off study Reason	Off-study Specify

Listing 14.5 Study population by site

Site	Subject	Enrolled population	PK population	Reason	Safety population	Reason

Listing 14.6 Inclusion and exclusion criteria by Site

Site	Subject	Eligibility requirements?	Criterion identifier I/E	I/E details

Listing 14.7 Adverse events by site

Site	Subject	Adverse Event	NCI-CTC Grade	SAE	Onset date	End date	Relationship Specify	Action taken	Seriousness Criteria	Outcome

Listing 14.8 Deaths by site

Site	Subject	Date	Reason	Time from first dose (days)	Time from last dose (days)

Listing 14.9 Protocol Deviations by Site

Site	Subject	Deviation type	Deviation

Listing 14.10 Concomitant medication

Site	Subject	Medication type	Medication	Reason	…[†]	Route/Dose(Units)/Time interval	Start date	End date	Indication	AE/MH

[†]ATC1, ATC4

Listing 14.11 Individual Laboratory Measurements by site

Site	Subject	Cycle	Examination date	Laboratory	Hematocrit	RBC	WBC (x10*9/L)	Neutrophils (x10*9/L)	…[†]

[†]Lymphocytes, Monocytes, Platelets, INR, Creatinine, CrCl, Glucose, CPK, CPK-MB fraction, GGT, Total Proteins, Albumin, CRP, Na, K, Mg, Ca, Alpha-1-Acid Glycoprotein, Interleukin 6.

Listings 14.12 Electrocardiogram by Site

Site	Subject	Visit	Date	ECG#	Not done	Result	Specify	PR interval (msec)	Heart rate (bpm)	QT interval (msec)	Bazett's corrected QT	Not done within protocol, specify

Listings 14.13 LVEF by Site

Site	Subject	Visit	Date	Not Done	Method	LVEF (%)	Range Lower Limit	Abnormality	Specify	Reason for Clinically Indicated Repeat

15 APPENDIX VI: ICH Listings

In accordance with the ICH E-3 guideline, patient listings specified as section 16.2 will be prepared.

Listing 16.2.1 Discontinued Patients

Part / Sequence	Treatment Group*	Subject	Institution	Treated	Cycles received	First infusion date	Last infusion date	Reason for end of treatment	Comments

* ITZ+LRB / LRB

Listing 16.2.2 Protocol Deviations

Subject	Deviation type	Description

Listing 16.2.3 Patients excluded from the efficacy analysis

Not applicable

Listing 16.2.4 Demographic data

Subject	Tumor type	Stage†	Age	Gender	Race	ECOG	Weight (kg)	Height (cm)	BSA (m^2)	Prior radiotherapy	Prior surgery	Prior agents

†At diagnosis

Listing 16.2.5 Compliance and/or drug concentration data

	Lurbinectedin								Itraconazole	
Subject	First Intended dose (mg/m2)	Start date (First cycle)	Start date (Second cycle)	Total dose (mg/m^2)	Dose intensity (mg/m^2/ wk)	Relative dose intensity (%)	Delays†	Reductions †	Taken by protocol	Reason

†Delays/reductions will be nested for each patient (cycle and reason of delay/reduction), e.g. C2 hematological toxicity

Listing 16.2.6 Individual efficacy response data

Not applicable

Listing 16.2.7 Adverse Event listing (each patient)

Subject	Adverse Event	SOC	PT	Grade	SAE	Onset date	End date	Relationship	Action taken	Seriousness criteria	Outcome

Listing 16.2.8 Individual Laboratory Measurements by Patient

				Hematocrit	RBC	WBC (x10*9/L)	Neutrophils (x10*9/L)	…†
Subject	Cycle	Examination date	Laboratory	Std. value	Std. value	Std. value	Std. value	Std. value

†Lymphocytes, Monocytes, Platelets, INR, Creatinine, CrCl, Glucose, CPK, CPK-MB fraction, GGT, Total Proteins, Albumin, CRP, Na, K, Mg, Ca, Alpha-1-Acid Glycoprotein, Interleukin 6.

15.1 History of Changes

Clarifications and modifications have been added to the SAP v2.0 on date 25 May 2022.

A summary of such changes are include below:

1. On Appendix I (Patients Disposition) columns and footnotes to the tables and listings have been included in order to clarify. See below (*).

2. On Appendix II (Safety Analysis) some tables headers have been clarified and updated. Also new footnotes have been included. See below (**).

3. On Appendix IV (DB Listings) columns Treatment Group and Cycle have been included, where applicable. See below (***).

Changes are presented in the following pages. Inclusions are highlighted in ***Italic bold*** and text removed has been ~~crossed out~~. Minor corrections will not be described below.

(*) Appendix I (Patients Disposition)

All Sections

On tables 10.1.1.1, 10.1.1.3, 10.1.2.1, 10.1.2.5, 10.2.1.1-5, 10.2.3.1-6, 10.2.4.1-7, 10.2.5.1, 10.2.5.3-7, 10.2.5.9, 10.2.5.11, 10.2.6.1-2, 10.2.7.1-2, 10.2.8.1, 10.2.9.1-3 and 10.2.10.1, the following footnote has been included:
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.

On listings 10.1.2.2, 10.1.2.1 and 10.1.2.3, the following column has been included:
Treatment Group*.

On listings 10.1.2.2, 10.1.2.1 and 10.1.2.3, the following footnote has been included:
**** ITZ+LRB / LRB.***

On tables 10.2.6.1, 10.2.7.1 and 10.2.8.1 the following footnote has been included:
*** Gr 1, Gr 2, Gr 3, Gr 4**

Section 10.1.1 Patient Disposition

Original text: On table 10.1.1.3, the following rows:

Evaluable for PK
Evaluable for Safety

Changes to:

Included
Evaluable for PK
Evaluable for Safety

Original text: On table 10.1.1.4, the following header:

Not Evaluable for	Study Part	Sequence	Subject	Reason(s)

Changes to:

Not Evaluable for	Study Part	Sequence	Subject	**Max. Cycle received**	Reason(s)

Original text: On table 10.1.2.4, the following header:

Study Part	Sequence	Subject	Reason	Specify

Changes to:

Study Part	Sequence	Subject	**Max. Cycle received**	Reason	Specify

Original text: On table 10.2.1.1, the following rows:

	Part A		Part B				Part A+B		Total	
	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)			
	N	%	N	%	N	%	N	%	N	%
Gender										
Male										
Female										
Race										
White										
Black										
Asian										
…										
Other (Specify)										

Change to these two different following tables:

	Part A		Part B				Part A+B		Total	
	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)			
	N	%	N	%	N	%	N	%	N	%
Gender										
Male										
Female										

	Part A		Part B				Part A+B		Total	
	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)			
	N	%	N	%	N	%	N	%	N	%
Race										
White										
Black										
Asian										
…										
Other (Specify)										

(**) Appendix II (Safety Analysis)

All Sections

On tables 11.1.1.1-3, 11.1.2.1-2, 11.1.3.1, 11.2.1.1, 11.2.1.2-5, 11.2.1.8, 11.2.1.9, 11.3.1.1-8, 11.3.2.1, 11.4.1.1, 11.4.1.4, 11.4.2.1, 11.4.2.4, 11.4.3.1-4 and 11.7.1.1-3, the following footnote has been included:
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.

On tables and listings 11.1.2.3, 11.1.3.2, 11.1.4.1-3, 11.2.1.10-12, 11.3.1.9, 11.3.2.2, 11.4.1.2-3, 11.4.1.5-6, 11.4.2.2-3, 11.4.2.5-6, and 11.6.2.6 the following column has been included:
Treatment Group*.

On tables and listings 11.1.2.3, 11.1.3.2, 11.1.4.1-3, 11.2.1.10-12, 11.3.1.9, 11.3.2.2, 11.4.1.2-3, 11.4.1.5-6, 11.4.2.2-3, 11.4.2.5-6, and 11.6.2.6 the following footnote has been included:
**** ITZ+LRB / LRB.***

On tables and listings 11.2.1.2-4, 11.2.1.8, 11.3.1.1-3, 11.3.1.7, 11.4.1.1-3, 11.4.2.1-3 the title:
Worst grade per patient.
Changes to:
Worst grade by treatment.

On tables and listings 11.2.1.5-7, 11.2.1.9, 11.3.1.4-6, 11.3.1.8, 11.4.1.4-6, 11.4.2.4-6 the title:
Worst grade per cycle.
Changes to:
Worst grade per patient.

Section 11.2.1 Display of Adverse Events

Original text: On table 11.2.1.1, the following header:

	Part A		Part B				Part A+B		Total	
	S1 ~~(TR)~~		S1 ~~(TR)~~		S2 ~~(RT)~~		S1 ~~(TR)~~			
	N	%	N	%	N	%	N	%	N	%

Changes to:

	Part A		Part B			
	S1		S1		S2	
	T	**R**	**T**	**R**	**R**	**T**
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)

	Part A+B		Total
	S1		
	T	**R**	
	N(%)	N(%)	N(%)

Original text: On table 11.2.1.1, the duplicated rows:

No. of patients with dose interruptions associated with treatment-related† AEs
~~No. of patients with dose interruptions associated with treatment-related† AEs~~

Changes to:

No. of patients with dose interruptions associated with treatment-related† AEs

The following text has been added: Below table 11.2.1.1:

Supplementary tables describing the adverse event toxicity grades or laboratory abnormality grades 1,2,3,4,5 and grade 1-5 will be added below the tables with aggregated severity grades show in sections 11.2.1, 11.3.1, 11.4.1 and 11.4.2 as shown in table 11.2.1.2

Original text: On table 11.2.1.2 the following header:

SOC / PT	Part A			Part B						Part A+B			Total		
	S1 ~~(TR)~~			S1 ~~(TR)~~			S2 ~~(RT)~~			S1 ~~(TR)~~					
	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %

Changes to:

	Part A					
	T			**R**		
SOC/PT	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)

	Part B											
	S1						S2					
	T			**R**			**R**			**T**		
SOC/PT	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)

	Part A+B **(S1)**						Total		
	T			**R**					
SOC/PT	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)

	Part A											
	T						**R**					
SOC/PT	**Gr1**	**Gr2**	**Gr3**	**Gr4**	**Gr5**	**Gr 1- 5**	**Gr1**	**Gr2**	**Gr3**	**Gr4**	**Gr5**	**Gr 1-5**
	N(%)	**N(%)**	**N(%)**	**N(%)**	**N(%)**	**N(%)**	**N(%)**	**N(%)**	**N(%)**	**N(%)**	**N(%)**	**N(%)**
…												

	Part B (S1)											
	T						**R**					
SOC/PT	**Gr1**	**Gr2**	**Gr3**	**Gr4**	**Gr5**	**Gr 1- 5**	**Gr1**	**Gr2**	**Gr3**	**Gr4**	**Gr5**	**Gr 1-5**
	N(%)	**N(%)**	**N(%)**	**N(%)**	**N(%)**	**N(%)**	**N(%)**	**N(%)**	**N(%)**	**N(%)**	**N(%)**	**N(%)**
…												

	Part B (S2)											
	R						T					
SOC/PT	Gr1	Gr2	Gr3	Gr4	Gr5	Gr 1- 5	Gr1	Gr2	Gr3	Gr4	Gr5	Gr 1-5
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
…												

	Part A+B (S1)											
	T						R					
SOC/PT	Gr1	Gr2	Gr3	Gr4	Gr5	Gr 1- 5	Gr1	Gr2	Gr3	Gr4	Gr5	Gr 1-5
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
…												

	Total					
SOC/PT	Gr1	Gr2	Gr3	Gr4	Gr5	Gr 1- 5
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
…						

Notes: Percentage is based on number of patients by study part and sequence, when applicable.
† Related to both or lurbinectedin or itraconazole or with unknown relationship.
Part A, patients assigned to Sequence 1; Part B, sequence assigned randomly.
S1, Sequence 1; S2, Sequence 2.
T, Test (ITZ+LRB); R, Reference (LRB alone).

Original text: On tables 11.2.1.3-5, 11.2.1.8, 11.3.1.1-3, 11.3.1.7, 11.4.1.1, 11.4.2.1 the following header:

SOC / PT	Part A			Part B			Part A+B			Total		
	S1 ~~(TR)~~			S1 ~~(TR)~~			S2 ~~(RT)~~			S1 ~~(TR)~~		
	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %

Changes to:

	Part A					
	T			R		
SOC/PT	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)

	Part B											
	S1						S2					
	T			R			R			T		
SOC/PT	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4

	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)

	Part A+B **(S1)**						Total		
	T			**R**					
SOC/PT	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)

Section 11.2.2 Evolution of Signs and Symptoms during the Treatment

Original text: On table 11.2.2.1 the following header:

MedDRA PT	Baseline grade	Worst grade per patient during treatment									
		Grade 1		Grade 2		Grade 3		Grade 4		Grade 5	
		N	%	N	%	N	%	N	%	N	%
		Part A									
…	1										
	2										
	…										
…	1										
	…										
		Part B - S1 (TR)									
…	1										
	…										
…	1										
	…										
…	1										
	…										
…	1										
	…										

Changes to:

MedDRA PT	Baseline grade	Worst grade per patient during treatment									
		Grade 1		Grade 2		Grade 3		Grade 4		Grade 5	
		N	%	N	%	N	%	N	%	N	%
		Part A - **S1 (TR)**									
…	1										
	2										
	…										
…	1										
	…										
		Part B - S1 (TR)									
…	1										
	…										
…	1										
	…										
		Part B - S2 (RT)									
…	1										
	…										
…	1										
	…										

Section 11.3.1 Serious Adverse Events

Original text: On tables 11.3.1.1-3 and 11.3.1.7 the following header:

SOC / PT	Part A				Part B								Part A+B				Total			
	S1 (TR)				S1 (TR)				S2 (RT)				S1 (TR)							
	All grades		Gr ≥ 3		Gr 4		All grades		Gr ≥ 3		Gr 4		All grades		Gr ≥ 3		Gr 4		All grades		Gr ≥ 3		Gr 4	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
…																								

Changes to:

SOC/PT	Part A					
	T			**R**		
	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
…						

SOC/PT	Part B											
	S1						**S2**					
	T			**R**			**R**			**T**		
	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
…												

SOC/PT	Part A+B **(S1)**						Total		
	T			**R**					
	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
…									

Section 11.4.1 Hematological Abnormalities

Original text: On tables 11.4.1.1 the following content:

	Part A				Part B								Part A+B				Total			
	S1 (TR)				S1 (TR)				S2 (RT)				S1 (TR)							
	All grades		Gr ≥ 3		Gr 4		All grades		Gr ≥ 3		Gr 4		All grades		Gr ≥ 3		Gr 4		All grades		Gr ≥ 3		Gr 4	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Anemia																								
Leukopenia																								
Lymphopenia																								
Neutropenia																								
Thrombocytopenia																								

Changes to:

Table 1. Hematological abnormalities: Worst grade by treatment

	Part A					
	T			**R**		
SOC/PT	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
Anemia						
Leukopenia						
Lymphopenia						
Neutropenia						
Thrombocytopenia						

	Part B											
	S1						S2					
	T			**R**			**R**			**T**		
SOC/PT	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
Anemia												
Leukopenia												
Lymphopenia												
Neutropenia												
Thrombocytopenia												

	Part A+B (S1)						Total		
	T			**R**					
SOC/PT	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
Anemia									
Leukopenia									
Lymphopenia									
Neutropenia									
Thrombocytopenia									

Section 11.4.2 Biochemical Abnormalities

Original text: On tables 11.4.2.1 the following content:

	Part A				Part B				Part A+B				Total		
	S1 (TR)				S1 (TR)				S2 (RT)				S1 (TR)						
	All grades		Gr ≥ 3		Gr 4		All grades		Gr ≥ 3		Gr 4		All grades		Gr ≥ 3		All grades		Gr ≥ 3		Gr 4	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
ALT increase																						
AST increase																						
…*																						

Changes to:

	Part A					
	T			**R**		
	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
ALT increase						
AST increase						
…*						

	Part B											
	S1						S2					
	T			**R**			**R**			**T**		
	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
ALT increase												
AST increase												
…*												

	Part A+B **(S1)**						Total		
	T			R					
	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
ALT increase									
AST increase									
…*									

Section 11.4.3 Laboratory Values Over Treatment

Original text: On table 11.4.3.1 the following content:

	Baseline grade	Worst grade per patient during treatment									
		Grade 1		Grade 2		Grade 3		Grade 4		Grade 5	
		N	%	N	%	N	%	N	%	N	%
		Part A									
Anemia	0										
	…										
	4										
Leukopenia	0										
	…										
	4										
…	0										
	…										
	4										
		Part B - S1 (TR)									
Anemia	0										
	…										
	4										
Leukopenia	0										
	…										
	4										
…	0										
	…										
	4										
		…									
Anemia	0										
	…										
	4										
Leukopenia	0										
	…										
	4										
…	0										
	…										
	4										

Changes to:

	Baseline grade	Worst grade per patient during treatment									
		Grade 1		Grade 2		Grade 3		Grade 4		Grade 5	
		N	%	N	%	N	%	N	%	N	%
						Part A - **S1 (TR)**					
Anemia	**G**0										
	…										
	G4										
Leukopenia	**G**0										
	…										
	G4										
…	**G**0										
	…										
	G4										
						Part B - S1 (TR)					
Anemia	**G**0										
	…										
	G4										
Leukopenia	**G**0										
	…										
	G4										
…	**G**0										
	…										
	G4										
						Part B - S2 (RT)					
Anemia	**G**0										
	…										
	G4										
Leukopenia	**G**0										
	…										
	G4										
…	**G**0										
	…										
	G4										

Original text: On table 11.4.3.3 the following content:

	Baseline grade	Worst grade per patient during treatment									
		Grade 1		Grade 2		Grade 3		Grade 4		Grade 5	
		N	%	N	%	N	%	N	%	N	%
						Part A					
ALT increase	0										
	…										
	4										
AST increase	0										
	…										
	4										
…	0										
	…										
	4										
						Part B - S1 (TR)					
ALT increase	0										
	…										
	4										
AST increase	0										
	…										
	4										
…	0										
	…										
	4										
						…					
ALT increase	0										
	…										
	4										
AST increase	0										
	…										
	4										
…	0										
	…										
	4										

Changes to:

	Baseline grade	Worst grade per patient during treatment									
		Grade 1		Grade 2		Grade 3		Grade 4		Grade 5	
		N	%	N	%	N	%	N	%	N	%
						Part A - **S1 (TR)**					
ALT increase	**G**0										
	…										
	G4										
AST increase	**G**0										
	…										
	G4										
…	**G**0										
	…										
	G4										
						Part B - S1 (TR)					
ALT increase	**G**0										
	…										
	G4										
AST increase	**G**0										
	…										
	G4										
…	**G**0										
	…										
	G4										
						Part B - S2 (RT)					
ALT increase	**G**0										
	…										
	G4										
AST increase	**G**0										
	…										
	G4										
…	**G**0										
	…										
	G4										

Section 11.6.1 Physical Findings, ECOG PS

Original text: On listings 11.6.1.1-3, 11.6.2.2-5 the following content:

Study part / Sequence		Subject
Part A		…
Part B	S1 (TR)	…
	S2 (RT)	…

Changes to:

Study part / Sequence		**Treatment Group***	Subject
Part A	**S1 (TR)**		…
Part B	S1 (TR)		…
	S2 (RT)		…

Section 11.6.2 LVEF and ECG

Original text: On listings 11.6.2.2 the following header:

Study part / Sequence	Subject	PR interval (msec)‡ at baseline	% Change†			
			Cycle 1 Pre infusion	Cycle 1 Post infusion	…	EOT

Changes to:

Study part / Sequence	Subject	PR interval (msec)‡ at baseline	% Change†				
			Cycle 1		**Cycle 2**		EOT
			Pre infusion	Post infusion	**Pre infusion**	**Post infusion**	

Original text: On listings 11.6.2.3 the following header:

Study part / Sequence	Subject	Heart rate (bpm)‡ at baseline	% Change†			
			Cycle 1	Cycle 2 Pre infusion	Cycle 2 Post infusion	EOT

Changes to:

Study part / Sequence	Subject	Heart rate (bpm)‡ at baseline	% Change†				
			Cycle 1		Cycle 2		EOT
			Pre infusion	**Post infusion**	Pre infusion	Post infusion	

Original text: On listings 11.6.2.4 the following header:

Study part / Sequence	Subject	QT interval (msec)‡ at baseline	% Change†			
			Cycle 1	Cycle 2 Pre infusion	Cycle 2 Post infusion	EOT

Changes to:

Study part / Sequence	Subject	QT interval (msec)‡ at baseline	% Change†				
			Cycle 1		Cycle 2		EOT
			Pre infusion	**Post infusion**	Pre infusion	Post infusion	

Original text: On listings 11.6.2.5 the following header:

Study part / Sequence	Subject	QTc (Bazett's)‡ at baseline	% Change†			
			Cycle 1	Cycle 2 Pre infusion	Cycle 2 Post infusion	EOT

Changes to:

Study part / Sequence	Subject	QTc (Bazett's)‡ at baseline	% Change†				
			Cycle 1		Cycle 2		EOT
			Pre infusion	**Post infusion**	Pre infusion	Post infusion	

Original text: On listings 11.6.2.6 the following header:

Study Part	Sequence	Subject	Assessment date	Visit	ECG #	Result	Specify	PR interval (msec)	Heart rate (bpm)	QT interval (msec)	QTc† (Bazett's)

Changes to:

Study Part	Sequence	**Treatment Group***	Subject	**Cycle**	Assessment date	Visit	ECG #‡	Result	Specify	PR interval (msec)	Heart rate (bpm)	QT interval (msec)	QTc† (Bazett's)

Section 11.7.1 Concomitant medication during treatment (ATC1/ATC2/ATC4/PN)

Original text: On table 11.7.1.1 the following header:

	Part A		Part B				Part A+B		Total	
	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)			
	N	%	N	%	N	%	N	%	N	%

Changes to:

Part A		Part B				Part A+B (S1)		Total
T	**R**	**T**	**R**	**T**	**R**	**T**	**R**	
N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

Original text: On listings 11.7.1.2 the following header:

	Part A		Part B				Part A+B		Total	
	S1 (TR)		S1 (TR)		S2 (RT)		S1 (TR)			
	N	%	N	%	N	%	N	%	N	%

Changes to:

Part A		Part B				Part A+B (S1)		Total
T	**R**	**T**	**R**	**T**	**R**	**T**	**R**	
N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

Original text: On listings 11.7.1.3 the following header:

	Part A	Part B		Part A+B	Total
	S1 (TR)	S1 (TR)	S2 (RT)	S1 (TR)	

Changes to:

Part A		Part B				Part A+B (S1)		Total
T	**R**	**T**	**R**	**T**	**R**	**T**	**R**	
N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

(***) Appendix IV (DB Listings)

All Sections

On listings 13.6, 13.7, 13.12, 13.16, 13.17, 13.19-36, 13.42 from Appendix IV the following footnote has been included:
**** ITZ+LRB / LRB.***

Also on the same listings from Appendix IV the following column has been included:
Treatment Group*.

Column ***Cycle***, has been included also on these listings, where applicable.