PM1183-A-019-20

An Open-Label, Multicenter Study to Assess the Potential Effects of Bosentan (a Moderate CYP3A4 Inducer) on the Pharmacokinetics of Lurbinectedin in Patients with Advanced Solid Tumors

STATISTICAL ANALYSIS PLAN

INVESTIGATIONAL MEDICINAL PRODUCTS: Lurbinectedin (Zepzelca®), and Bosentan.
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-Confidential-

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ABBREVIATIONS AND GLOSSARY

AE(s)	Adverse Event(s)
ALT	Alanine Aminotransferase
AP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Concentration-time Curve
BIMO	Bioresearch Monitoring
BOS	Bosentan
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
IC_{50}	Half Maximal Inhibitory Concentration
ICH	International Conference on Harmonization
INR	International Normalized Ratio
i.v.	Intravenous
L	Liter
LDH	Lactate Dehydrogenase
LRB	Lurbinectedin
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
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
PS	Performance Status

PT	Preferred Term
q3wk	Every Three Weeks
RBC	Red Blood Cells
RT	Reference-Test Sequence
RTSM	Randomization and Trial Supply Management
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SCLC	Small Cell Lung Cancer
SmPC	Summary of Product Characteristics
SOC	System Organ Class
Std.	Standard Deviation
$T_{1/2}$	Terminal Half-life
TR	Test-Reference Sequence
ULN	Upper Limit of Normal
Vss	Volume of Distribution at Steady State
WBC	White Blood Cells
WHO	World Health Organization
wk	Week(s)

1 STUDY RATIONALE

Lurbinectedin 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 bosentan, a moderate CYP3A4 inducer, 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 bosentan administration) followed by a treatment phase consisting of two lurbinectedin cycles, one cycle in combination with bosentan 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.

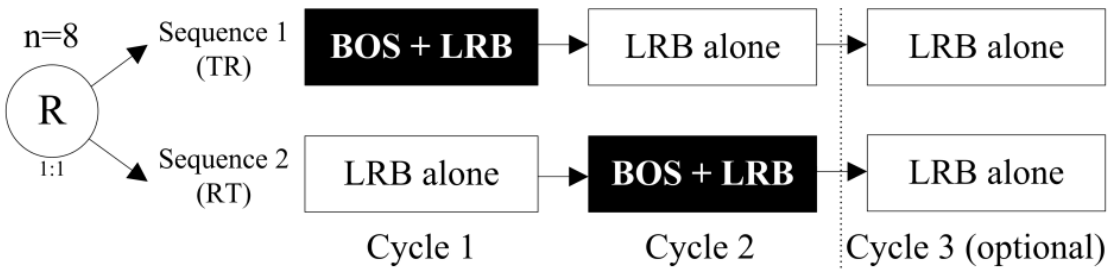
Patients will be treated as outpatients. At the discretion of the Investigator, patients may be admitted to the study center on Day –1 or Day 1 and monitored, at least, until completion of the Day 1 PK blood sample collections.

Patients will receive a maximum of three cycles: two consecutive cycles of lurbinectedin, one cycle with and one cycle without bosentan 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 every three weeks (q3wk) via a central or peripheral vein.

In the co-administration cycles, bosentan will be administered orally twice daily in the morning and evening during the prior five consecutive days, self-administered at home from Day -5 to Day -1 (i.e., five days before lurbinectedin infusion), and once daily on Day 1 (i.e., the day of lurbinectedin infusion), following recommendations at the Summary of Product Characteristics (SmPC). On Day 1 (i.e., the day of lurbinectedin infusion), bosentan will be given immediately prior to starting the lurbinectedin infusion. In fact, bosentan should be administered after obtaining the bosentan PK sample #1 and before the start of lurbinectedin infusion (-15 min to -1 min).
In case of lurbinectedin delay (≤ 2 days), bosentan could be administered twice daily during a maximum of seven consecutive days before lurbinectedin infusion, and supplied at the study center once daily on Day 1 (before lurbinectedin infusion).

All patients will receive a maximum of three cycles: two consecutive cycles of lurbinectedin, one cycle with and one cycle without bosentan 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).

Patients will be randomized in a 1:1 ratio to Sequence 1 (TR: Test- Reference; lurbinectedin + bosentan in Cycle 1) or Sequence 2 (RT: Reference-Test; lurbinectedin + bosentan in Cycle 2). Lurbinectedin will be administered as a 1-hour (-5/+20 min) intravenous (i.v.) infusion q3wk via a central or peripheral vein. The dose of lurbinectedin will be 3.2 mg/m² for all patients when administered with and without bosentan. If toxicity occurs, the appropriate intra-patient dose level (DL) reductions will be implemented in the subsequent cycle.



The enrollment of the patients will be simultaneous. However, if once the first three patients enrolled have completed Cycle 1 and Cycle 2, total lurbinectedin exposure does not allow an adequate PK assessment and if no unacceptable or life-threatening toxicities have occurred, the dose of lurbinectedin to be co-administered with bosentan in the remaining five patients can be adjusted accordingly.

This decision will be made by the Sponsor and the study Investigators. Therefore, the planned dose of lurbinectedin, when given with bosentan for the remaining five patients, will be based on the acceptability of the PK and safety results from the first three patients. 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 pharmacokinetics) to produce plasma lurbinectedin area under the curve (AUC) values that are comparable to those when lurbinectedin is given in the absence of bosentan. However, if toxicity occurs in the initial three patients, the appropriate dose-reduction of lurbinectedin will be implemented in the remaining five patients accordingly.

Patients will receive lurbinectedin until disease progression, unacceptable toxicity, consent withdrawal or while it is considered to be in their best interest, and for a maximum of three cycles. Treatment with lurbinectedin outside this study could be continued under a Compassionate Use Agreement after the completion of the optional third study cycle.

All patients will be randomly assigned to the corresponding sequences:

- Sequence 1 (TR):
  - Cycle 1: Bosentan + lurbinectedin
  - Cycle 2: Lurbinectedin alone
  - Cycle 3: Lurbinectedin alone (optional)

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

Lurbinectedin will be administered to eight evaluable patients and for a maximum of three cycles, while considered to be on the patient's best interest or until progressive disease (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 or any other reason at the physician's judgment that precludes lurbinectedin continuation.

If the patient responds to treatment after the first two cycles according to Investigator criteria for clinical benefit, 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 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 bosentan 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 enrolled 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 have been included in the trial and randomized, regardless 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 who have provided sufficient and interpretable PK parameters to calculate the non-compartmental PK parameters. Evaluable patients should have received the first two complete cycles regardless dose delays or reductions.
- The safety population will include all patients who received at least one dose of lurbinectedin. Patients who have received at least one dose of bosentan but who did not receive any dose of lurbinectedin will be excluded from the safety population and will be performed separately by narratives. The safety population will be used for all safety evaluations.

4 OBJECTIVES AND ENDPOINTS

4.1 Objectives

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

4.1.1 Primary Objective

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

4.1.2 Secondary Objective

- To assess the effect of bosentan on lurbinectedin unbound plasma exposure.
- To assess the effect of bosentan on lurbinectedin major metabolites (i.e., M1 and M4).
- To assess the effect of bosentan 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.

4.2 Endpoints

4.2.1 Primary Endpoint

- 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.

4.2.2 Secondary Endpoint

- Differences in dose-normalized total AUC_{0-t} and C_{max} and in Cl, Volume of Distribution at Steady State (V_{ss}) 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, $V_{ss,u}$ and $T_{1/2,u}$ of lurbinectedin between Cycle 1 and Cycle 2 will be explored.
- Differences in ratios between total $AUC_{0-\infty}$, AUC_{0-t} and C_{max}, 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 pharmacogenetic (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 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.

At least eight patients are expected to complete all study procedures, including the collection of sufficient and interpretable PK assessments. Although at least eight patients will be enrolled in this study; it is estimated that complete data from eight patients will be sufficient to estimate the drug-drug interaction of bosentan on the PK of lurbinectedin.

Randomization will apply for all patients.

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).

Randomization will be implemented in Medidata Rave RTSM. A randomization list will be generated to randomly allocate patients to Sequence 1 (TR: Test- Reference; lurbinectedin + bosentan in Cycle 1) or Sequence 2 (RT: Reference-Test; lurbinectedin + bosentan in Cycle 2). 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 bosentan on the PK of lurbinectedin in patients with advanced malignancies. The 90% confidence interval (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 + bosentan) / 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 Clinical Pharmacology department in a separate document. The present Statistical Analysis Plan (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 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 sequence and treatment (Sequence 1 [TR] vs. Sequence 2 [RT]) and treatment group (Test [lurbinectedin administered in combination with bosentan] vs. Reference [lurbinectedin alone]) .

6.1 Toxicity and Adverse Events

The toxicity evaluation will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v.5).

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 and PT.

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. Worst grade per patient and per cycle for applicable values during treatment will be shown.

The following hematological values will be displayed: hemoglobin, erythrocytes (RBC), white blood cells count (WBC), neutrophils, lymphocytes, monocytes, hematocrit and platelets count.

For the analysis by sequence, overall cross tabulation will be presented for the worst grade during treatment vs. the baseline toxicity grading of anemia, lymphopenia, neutropenia, leukopenia and thrombocytopenia.

If a grade ≥ 3 neutropenia or thrombocytopenia occurs during a treatment cycle, the first day it reaches grade 3 or 4 (counting from the start of the cycle) and the duration of the abnormality (i.e., until recovery to grade ≤ 2) will be tabulated. The information will be shown by means of median and range.

The following biochemical and coagulation values will be displayed: aspartate aminotransferase (AST), alanine aminotransferase (ALT), Alkaline Phosphatase, 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++), total calcium, total proteins, albumin, C-reactive protein count (CRP) and the international normalized ratio (INR).

If a grade ≥ 3 AST or ALT increase occurs during a treatment cycle, both the day it peaked and the duration of the abnormality will be tabulated. 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

Tables summarizing the performance status (PS), height, body weight and body surface area (BSA), vital signs, left ventricular ejection fraction (LVEF) at baseline and during the treatment will be prepared.

If appropriate, changes in the ECOG PS and body weight of each patient during the treatment compared with baseline will also be done.

Cardiac rhythm will be done in triplicate and identified ECG intervals of 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

Deaths and other serious adverse events (SAEs) will be tabulated following the same pattern than AEs. 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

Descriptive statistics (mean, median, standard deviation, range of value, frequencies and percentages) will be used to summarize the data. Counts and percentages will be used for categorical variables, and summary tables will be used for continuous variables.

7.1 Baseline and Demographics

Descriptive statistics will be used to summarize the patients' baseline characteristics

Baseline data such as demographics, cancer history, prior therapy, prior relevant history, signs and symptoms, ECG, 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 Section10, Appendix I).

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

For the cancer history, times from initial diagnosis, metastatic disease, from locally advanced disease and from last progression before the study entry will be summarized. These time calculations will be shown in months and summarized descriptively. Histology and characteristics of the disease at study entry will be tabulated.

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 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.

7.2 Patient Disposition and Treatment/Study Discontinuation

The number of patients included and treated in the study 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.

7.3 Protocol Deviations

Analysis of inclusion/exclusion criteria deviations, retreatment restrictions, concomitant medication and clinically relevant discontinuations, among others, will be done as described in Appendix I.

7.4 Treatment Administration

Exposure to treatment will be described by 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 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 bosentan, 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.

The items « Infusion delayed: yes/no» and « Dose reduced: yes/no» present 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).

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 subsequent therapies received after treatment discontinuation will be shown by total and treatment sequence group.

7.6 Subgroup Analyses

Safety analysis will be done by sequence (Sequence 1 [TR] vs Sequence 2 [RT]) and treatment group (Test [lurbinectedin administered in combination with bosentan] vs Reference [lurbinectedin alone]). Additional groups could be done (such a dose level in case dose of lurbinectedin was adjusted) if required, and a sequential number will be added at the end of the table number to differentiate them within each section.

No other subgroup analysis is planned.

7.7 Pharmacogenetics Analyses

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

7.8 Decimal places

By default, all results will be rounded to one decimal, except when variables are integers; in that case, they will be reported without decimals, (e.g. age in years or number of sites).

7.9 Imputation in Incomplete Dates

The 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.

Before randomization/treatment start date

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 be 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 study drug administration date plus 1 day.

7.10 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.

7.11 Decimal Places, Missing Values and Allowed Assessment Windows

By default, all numeric 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.). Four decimals will be used for p-values.

Missing values will not be included in the calculation of percentages. Assessment windows as specified in the clinical protocol will be respected.

7.12 Identification of Fixed or Random Effects Models

Not applicable (NA).

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

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

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

Main characteristics concerning 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

	S1 (TR)		S2 (RT)		Total	
	N	%	N	%	N	%
Institution 1						
Institution 2						
Total						

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

	S1 (TR)		S2 (RT)		Total	
	N	%	N	%	N	%
Evaluable for Safety						

Notes: Percentage is based on number of patients in total and by sequence, when applicable.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 10.1.1.4 Non-evaluable patients

Not Evaluable for	Sequence	Subject	Reason(s)
Safety			
PK			

10.1.2 Treatment Discontinuations

Table 10.1.2.1 Treatment discontinuation

	S1 (TR)		S2 (RT)		Total	
	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 in total and by sequence, when applicable.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 10.1.2.2 Treatment discontinuation due to related† Adverse Events

Sequence	Subject	AE reported	Preferred term	Grade	Relationship	Serious Event

Notes: † Related or unknown relationship.

Listing 10.1.2.3 Treatment discontinuation due to non-related Adverse Events

Sequence	Subject	AE reported	Preferred term	Grade	Relationship	Serious Event

Listing 10.1.2.4 Reasons for treatment discontinuation other than Progressive Disease

Sequence	Subject	Reason	Specify

Table 10.1.2.5 Reasons for study discontinuation

	S1 (TR)		S2 (RT)		Total	
	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 in total and by sequence, when applicable.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 10.1.2.6 Reasons for study discontinuation due to other reason

Sequence	Subject	Other, specify

Listing 10.1.2.7 Patients never treated

Sequence	Subject	Reason

10.1.3 Protocol Deviations

Classification will be based on the following group 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

Listing 10.1.3.1 Relevant protocol deviations

Sequence	Subject	Protocol deviation Type	Specify Deviation

10.2 Patient Characteristics

Demographics and other baseline characteristics will be carried out on the enrolled population.

10.2.1 Demographic and Other Baseline Characteristics

Table 10.2.1.1 Baseline characteristics: Gender

	S1 (TR)		S2 (RT)		Total	
	N	%	N	%	N	%
Gender						
Male						
Female						

Notes: Percentage is based on number of patients in total and by sequence, when applicable.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.1.2 Baseline characteristics: Race

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

Notes: Percentage is based on number of patients in total and by sequence, when applicable.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.1.3 Baseline characteristics: Age

	S1 (TR)	S2 (RT)	Total
Age at entry (years)			
N			
Mean, Std., Median, Range			

S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.1.4 Baseline characteristics: Pregnancy Test

	S1 (TR)		S2 (RT)		Total	
	N	%	N	%	N	%
Pregnancy Test						
Positive						
Negative						
NA (Specify)						

Notes: Percentage is based on number of patients in total and by sequence, when applicable.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.1.5 Baseline characteristics: Adequate contraception

	S1 (TR)		S2 (RT)		Total	
	N	%	N	%	N	%
Adequate contraception						
Yes						
No						
NA						

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

Sequence	Subject	Description	Onset date

10.2.3 Cancer History

Table 10.2.3.1 First diagnosis: Tumor type

	S1 (TR)		S2 (RT)		Total	
	N	%	N	%	N	%
Tumor Type						
Lung						
Kidney						
Prostate cancer						
…						

Notes: Percentage is based on number of patients in total and by sequence, when applicable.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.3.2 First diagnosis: Stage at diagnosis

	S1 (TR)		S2 (RT)		Total	
	N	%	N	%	N	%
Stage at Diagnosis						
Early						
Locally advanced						
Metastatic						

Notes: Percentage is based on number of patients in total and by sequence, when applicable.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.3.3 First diagnosis: Time from first diagnosis to first infusion

	S1 (TR)	S2 (RT)	Total
Time form first diagnosis to first infusion (months) †			
N			
Mean, Std., Median, Range			

† Time from first diagnosis to first infusion: defined as the date of first infusion minus date of first diagnosis.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.3.4 Current disease: Time from last PD to first infusion

	S1 (TR)	S2 (RT)	Total
Time from last PD† to first infusion (months)‡			
N			
Mean, Std., Median, Range			

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

Table 10.2.3.5 Current disease: Sites of disease involvement

	S1 (TR)		S2 (RT)		Total	
	N	%	N	%	N	%
Site of disease involvement						
Lung						
Liver						
Lymph node						
Pleura						
Bone						
…						
Other (Specify)						

Notes: Percentage is based on number of patients in total and by sequence, when applicable.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.3.6 No. of sites of disease involvement

	S1 (TR)		S2 (RT)		Total	
	N	%	N	%	N	%
No. of sites						
1						
2						
…						
≥ N sites						
Total						

Notes: Percentage is based on number of patients in total and by sequence, when applicable.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.3.7 Summary statistics: No. of sites of disease involvement

	S1 (TR)	S2 (RT)	Total
No. of sites			
N			
Mean, Std., Median, Range			

S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

10.2.4 Previous Anticancer Therapy Summary

Table 10.2.4.1 Patients with prior surgery

	S1 (TR)		S2 (RT)		Total	
	N	%	N	%	N	%
Prior surgery						
Yes						
No						

Notes: Percentage is based on number of patients in total and by sequence, when applicable.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.4.2 Patients with prior radiotherapy

	S1 (TR)		S2 (RT)		Total	
	N	%	N	%	N	%
Prior radiotherapy						
Yes						
No						

Notes: Percentage is based on number of patients in total and by sequence, when applicable.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.4.3 Prior anticancer medical therapy for study disease: No. of prior lines

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

Notes: Percentage is based on number of patients in total and by sequence, when applicable.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.4.4 Prior anticancer medical therapy for study disease: Summary of prior lines

	S1 (TR)	S2 (RT)	Total
No. of prior lines			
N			
Mean, Std., Median, Range			

S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.4.5 Prior anticancer medical therapy for study disease: No. of prior chemotherapy lines

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

Notes: Percentage is based on number of patients in total and by sequence, when applicable.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.4.6 Prior anticancer medical therapy for study disease: Summary of prior chemotherapy lines

	S1 (TR)	S2 (RT)	Total
No. of prior chemotherapy lines			
N			
Mean, Std., Median, Range			

S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.4.7 Prior anticancer medical therapy for study disease: No. of prior agents

	S1 (TR)		S2 (RT)		Total	
	N	%	N	%	N	%
No. of prior agents						
0 agents						
1 agent						
2 agents						
3 agents						
>= 4 agents						

Notes: Percentage is based on number of patients in total and by sequence, when applicable.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.4.8 Prior anticancer medical therapy for study disease: Summary of prior agents

	S1 (TR)	S2 (RT)	Total
No. of prior agents			
N			
Mean, Std., Median, Range			

S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.4.9 Prior anticancer medical therapy for study disease: Time to progression of last therapy

Time to progression (months)	S1 (TR)	S2 (TR)	Total
N			
Mean, Std., Median, Range			

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 Baseline physical examination

Physical examination	S1 (TR)		S2 (RT)		Total	
	N	%	N	%	N	%
Normal						
Abnormal						

Notes: Percentage is based on number of patients in total and by sequence, when applicable.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 10.2.5.2 Baseline physical examination: abnormalities

Sequence	Subject	Description

Table 10.2.5.3 Baseline physical examination: Weight, height and BSA

	S1 (TR)	S2 (RT)	Total
Weight (kg)			
N			
Mean, Std., Median, Range			
Height (cm)			
N			
Mean, Std., Median, Range			
BSA (m^2)			
N			
Mean, Std., Median, Range			

S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.5.4 Baseline physical examination: ECOG Performance Status

ECOG	S1 (TR)		S2 (RT)		Total	
	N	%	N	%	N	%
0						
1						
…						
Total						

Notes: Percentage is based on number of patients in total and by sequence, when applicable.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.5.5 Baseline characteristics: Vital signs

	S1 (TR)	S2 (RT)	Total
Heart rate (Beats/minute)			
N			
Mean, Std., Median, Range			
Temperature (ºC)			
N			
Mean, Std., Median, Range			
Blood pressure systolic (mmHg)			
N			
Mean, Std., Median, Range			
Blood pressure diastolic (mmHg)			
N			
Mean, Std., Median, Range			

S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.5.6 Baseline characteristics: ECG† pre infusion

	S1 (TR)		S2 (RT)		Total	
	N	%	N	%	N	%
Result						
Normal						
Abnormal						

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

Table 10.2.5.7 Baseline characteristics: Pre infusion ECG† values

	S1 (TR)		S2 (RT)		Total	
	N	%	N	%	N	%
PR interval (msec)						
N						
Mean, Std., Median, Range						
Heart rate (bpm)						
N						
Mean, Std., Median, Range						
QT interval (msec)						
N						
Mean, Std., Median, Range						
Bazett's corrected QT						
N						
Mean, Std., Median, Range						
Fridericia's corrected QT						
N						
Mean, Std., Median, Range						

† Mean of the three ECGs replicates will be used as baseline value.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.5.8 Baseline characteristics: Post-infusion ECG† values

	S1 (TR)		S2 (RT)		Total	
	N	%	N	%	N	%
PR interval (msec)						
N						
Mean, Std., Median, Range						
Heart rate (bpm)						
N						
Mean, Std., Median, Range						
QT interval (msec)						
N						
Mean, Std., Median, Range						
Bazett's corrected QT						
N						
Mean, Std., Median, Range						
Fridericia's corrected QT						
N						
Mean, Std., Median, Range						

† Mean of the three ECGs replicates will be used as baseline value.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 10.2.5.9 Patients with abnormal electrocardiogram

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

Table 10.2.5.10 Baseline characteristics: LVEF

	S1 (TR)		S2 (RT)		Total	
	N	%	N	%	N	%
Result						
Normal						
Abnormal						

Notes: Percentage is based on number of patients in total and by sequence, when applicable.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 10.2.5.11 Patients with abnormal LVEF

Sequence	Subject	Result	Method	Value (%)	Lower limit (%)	Abnormalities

Notes: Significant and non-significant abnormalities

Table 10.2.5.12 Baseline characteristics: LVEF value

LVEF (%) by Method	S1 (TR)		S2 (RT)		Total	
	N	%	N	%	N	%
MUGA						
N						
Mean, Std., Median, Range						
ECHO						
N						
Mean, Std., Median, Range						
Both						
N						
Mean, Std., Median, Range						

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†

	S1 (TR)						S2 (RT)						Total					
	All grades		Gr 1		...		All grades		Gr 1		…		All grades		Gr 1		…	
	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.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.6.2 Median and range for hematology parameters at baseline†

	S1 (TR)	S2 (RT)	Total
Hemoglobin (g/dL)			
N			
Mean, Std., Median, Range			
WBC (10^9/L)			
N			
Mean, Std., Median, Range			
Lymphocytes (10^9/L)			
N			
Mean, Std., Median, Range			
…			
N			
Mean, Std., Median, Range			

†Defined as the last value recorded before or on the date of first infusion.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 10.2.6.3 Hematological abnormalities at baseline (grade ≥ 2)

Sequence	Subject	Lab. Test	Examination date	Value	Unit	Std. Value	Std. Unit	Grade

Listing 10.2.6.4 Hematological tests not assessed at baseline

Sequence	Subject	Lab. Test

10.2.7 Biochemical Evaluation at Baseline

Table 10.2.7.1 Biochemical abnormalities at baseline†

	S1 (TR)						S2 (RT)						Total					
	All grades		Gr 1		...		All grades		Gr 1		…		All grades		Gr 1		…	
	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.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.7.2 Median and range for biochemical parameters at baseline†

	S1 (TR)	S2 (RT)	Total
ALT (xULN)			
N			
Mean, Std., Median, Range			
AST (xULN)			
N			
Mean, Std., Median, Range			
…			
N			
Mean, Std., Median, Range			

†Defined as the last value recorded before or on the date of first infusion.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 10.2.7.3 Biochemical abnormalities at baseline (grade ≥ 2)

Sequence	Subject	Lab. Test	Examination date	Value	Units	Std. Value	Std. Units	Grade

Listing 10.2.7.4 Biochemical abnormalities not assessed at baseline

Sequence	Subject	Lab. Test

10.2.8 Coagulation Evaluation at Baseline

Table 10.2.8.1 Coagulation abnormalities at baseline†

	S1 (TR)						S2 (RT)						Total					
	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.
If INR increase is observed, check listing of concomitant medication (anticoagulants) in section 13
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 10.2.8.2 INR increased at baseline (grade ≥ 2)

Sequence	Subject	Lab. Test	Examination date	Value	Std. Value	Grade

Listing 10.2.8.3 INR not assessed at baseline

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†	S1 (TR)		S2 (RT)		Total	
	N	%	N	%	N	%
…						

Notes: Percentage is based on number of patients in total and by sequence, when applicable.
†SOC: System Organ Class; PT: Preferred Term
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	S1 (TR)		S2 (RT)		Total	
	N	%	N	%	N	%
0						
1						
2						
≥ 3						
Total						

Notes: Percentage is based on number of patients in total and by sequence, when applicable.
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	S1 (TR)	S2 (RT)	Total
N			

No. of signs and symptoms per patient	S1 (TR)	S2 (RT)	Total
Mean, Std., Median, Range			

S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

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

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)

	S1 (TR)		S2 (RT)		Total	
	N	%	N	%	N	%
Alimentary tract and metabolism						
Antacids						
Magnesium compounds						
Magnesium adipate						
…						
Blood and blood forming organs						
Antithrombotic agents						
Vitamin K antagonists						
Acenocoumarol						
…						

Notes: Percentage is based on number of patients in total and by sequence, when applicable.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

11 APPENDIX II: SAFETY ANALYSIS

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

11.1 Extent of exposure

11.1.1 Treatment Administration

Table 11.1.1.1 Number of cycles administered†

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

Notes: Percentage is based on number of patients in total and by sequence, when applicable.
† Including when lurbinectedin is administered both alone and in combination with bosentan.
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

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

† Including when lurbinectedin is administered both alone and in combination with bosentan.
*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.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 11.1.1.3 Dose information by sequence

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

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

	S1 (TR)		S2 (RT)		Total	
	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
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 11.1.2.2 Length of dosing delay

	S1 (TR)		S2 (RT)		Total	
	N	%	N	%	N	%
Length of delay‡‡						
≤ 7 days						
> 7 to ≤ 14 days						
> 14 days						

‡‡ Denominator = Number of cycles susceptible to have dose delay
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 11.1.2.3 Dose delays

Sequence	Subject	Cycle	Delay (days)	Reason for delay

11.1.3 Dose Reductions

Table 11.1.3.1 Summary of lurbinectedin dose reductions

	S1 (TR)		S2 (RT)		Total	
	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
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 11.1.3.2 Dose reductions

Sequence	Subject	Cycle	Lurbinectedin intended dose (mg/m^2)	Reason for dose reduction	Specify

11.1.4 Any Other Dose Modifications

Listing 11.1.4.1 Dose interruptions for lurbinectedin

Sequence	Subject	Cycle	Date	Reason for interruption	Specify

Listing 11.1.4.2 Dose not taken according to protocol for Bosentan

Sequence	Subject	Cycle	Day	Reason

11.2 Adverse Events (AEs)

Adverse events tables will be listed by total and sequence or differentiating by treatment (Test, Reference or both).

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

	BOS+LRB		LRB alone	
	N	%	N	%
No. of patients with any AE				
No. of patients with any treatment-related† AE				
Patients with any grade ≥ 3 AE				
Patients with any grade ≥4 AE				
No. of patients with any grade ≥ 3 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 SAE				
No. of patients with any grade ≥4 SAE				
Any grade ≥3 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 AEs leading to treatment discontinuation				
No. of patients with treatment-related† AEs leading to treatment discontinuation				

† Related to combination, lurbinectedin or bosentan, or with unknown relationship
Number of patients with at least one event, treatment modification, withdrawal or death during the treatment with BOS+LRB or LRB alone.
BOS, bosentan; LRB, lurbinectedin.

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

SOC/PT	BOS+LRB						LRB alone					
	All grades		Gr ≥ 3		Gr ≥ 4		All grades		Gr ≥ 3		Gr ≥ 4	
	N	%	N	%	N	%	N	%	N	%	N	%
…												

Notes: Percentage is based on number of patients by treatment, when applicable.
† Related to both or lurbinectedin or bosentan or with unknown relationship
BOS, bosentan; LRB, lurbinectedin.

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

SOC/PT	BOS+LRB						LRB alone					
	All grades		Gr ≥ 3		Gr ≥ 4		All grades		Gr ≥ 3		Gr ≥ 4	
	N	%	N	%	N	%	N	%	N	%	N	%
…												

Notes: Percentage is based on number of patients by treatment, when applicable.
† Related to lurbinectedin or with unknown relationship
BOS, bosentan; LRB, lurbinectedin.

Table 11.2.1.4 Bosentan related Adverse Events. Worst grade per treatment

SOC/PT	BOS+LRB					
	All grades		Gr ≥ 3		Gr ≥ 4	
	N	%	N	%	N	%
…						

Notes: Percentage is based on number of patients by treatment, when applicable.
† Related to bosentan or with unknown relationship
BOS, bosentan; LRB, lurbinectedin.

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

SOC/PT	S1 (TR)						S2 (RT)						Total					
	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 in total and by sequence, when applicable.
† Related to both or lurbinectedin or bosentan or with unknown relationship
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 11.2.1.6 Adverse Events regardless of relationship. Worst grade per treatment

SOC/PT	BOS+LRB						LRB alone					
	All grades		Gr ≥ 3		Gr ≥ 4		All grades		Gr ≥ 3		Gr ≥ 4	
	N	%	N	%	N	%	N	%	N	%	N	%
…												

Notes: Percentage is based on number of patients by treatment, when applicable.
BOS, bosentan; LRB, lurbinectedin.

Table 11.2.1.7 Adverse Events regardless of relationship. Worst grade per patient

SOC/PT	S1 (TR)						S2 (RT)						Total					
	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 in total and by sequence, when applicable.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 11.2.1.8 AEs grade ≥ 3

Sequence	Treatment Group†	Cycle	Subject	SOC	PT	Grade	SAE (Y/N)	Start date	End date	Relationship study medication	Action taken	Serious Event	Outcome

†BOS+LRB/LRB alone

Listing 11.2.1.9 AEs related only to lurbinectedin

Sequence	Treatment group†	Cycle	Subject	SOC	PT	Grade	SAE (Y/N)	Start date	End date	Action taken	Serious Event	Outcome

†BOS+LRB/LRB alone

Listing 11.2.1.10 AEs related only to bosentan

Sequence	Treatment group†	Cycle	Subject	SOC	PT	Grade	SAE (Y/N)	Start date	End date	Action taken	Serious Event	Outcome

†BOS+LRB

11.3 Serious Adverse Events and Deaths

11.3.1 Serious Adverse Events

Serious adverse events tables will be listed by total and sequence or differentiating by treatment (Test, Reference or both).

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 per treatment

	BOS+LRB						LRB alone					
SOC/PT	All grades		Gr ≥ 3		Gr ≥ 4		All grades		Gr ≥ 3		Gr ≥ 4	
	N	%	N	%	N	%	N	%	N	%	N	%
…												

Notes: Percentage is based on number of patients by treatment, when applicable.
† Related to both or lurbinectedin or bosentan or with unknown relationship
BOS, bosentan; LRB, lurbinectedin.

Table 11.3.1.2 Lurbinectedin related† SAEs. Worst grade per treatment

	BOS+LRB						LRB alone					
SOC/PT	All grades		Gr ≥ 3		Gr ≥ 4		All grades		Gr ≥ 3		Gr ≥ 4	
	N	%	N	%	N	%	N	%	N	%	N	%
…												

Notes: Percentage is based on number of patients by treatment, when applicable.
† Related to lurbinectedin or with unknown relationship
BOS, bosentan; LRB, lurbinectedin.

Table 11.3.1.3 Bosentan related† SAEs. Worst grade per treatment

	BOS+LRB					
SOC/PT	All grades		Gr ≥ 3		Gr ≥ 4	
	N	%	N	%	N	%
…						

Notes: Percentage is based on number of patients by treatment, when applicable.
† Related to bosentan or with unknown relationship
BOS, bosentan; LRB, lurbinectedin.

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

	S1 (TR)						S2 (RT)						Total					
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 in total and by sequence, when applicable.
† Related to both or lurbinectedin or bosentan or with unknown relationship
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 11.3.1.5 SAEs regardless of relationship. Worst grade per treatment

SOC/PT	BOS+LRB						LRB alone					
	All grades		Gr ≥ 3		Gr ≥ 4		All grades		Gr ≥ 3		Gr ≥ 4	
	N	%	N	%	N	%	N	%	N	%	N	%
…												

Notes: Percentage is based on number of patients by treatment, when applicable.
BOS, bosentan; LRB, lurbinectedin..

Table 11.3.1.6 SAEs regardless of relationship. Worst grade per patient

SOC/PT	S1 (TR)						S2 (RT)						Total					
	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 in total and by sequence, when applicable.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 11.3.1.7 All SAEs†

Sequence	Treatment group*	Cycle	Subject	SOC	PT	Grade	AE Status	AE Relationship	AE consequences	Start date	End date

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

11.3.2 Deaths

Table 11.3.2.1 Cause of death

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

Notes: Percentage is based on number of patients who died by total and sequence, when applicable.
‡ Specify
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 11.3.2.2 Deaths

Sequence	Subject	Death date	Cause of death	No. of cycles administered	Time on treatment†	Time from last dose‡ (days)

† 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.
‡Time from last dose defined as date of death minus date of last infusion.

11.4 Clinical Laboratory Evaluation

11.4.1 Hematological Abnormalities

Table 11.4.1.1 Hematological abnormalities: Worst grade per treatment

	BOS+LRB						LRB alone					
	All grades		Gr ≥ 3		Gr ≥ 4		All grades		Gr ≥ 3		Gr ≥ 4	
	N	%	N	%	N	%	N	%	N	%	N	%
Anemia												
Leukopenia												
Lymphopenia												
Neutropenia												
Thrombocytopenia												

Notes: Percentage is based on number of patients by treatment, when applicable.
BOS, bosentan; LRB, lurbinectedin.

Listing 11.4.1.2 Hematological abnormalities grade ≥ 3

Treatment group[†]	Subject	Event	Grade

[†]BOS+LRB/LRB alone

Listing 11.4.1.3 Hematological tests not assessed by patient

Treatment group[†]	Subject	Lab. test

[†]BOS+LRB/LRB alone

Table 11.4.1.4 Hematological abnormalities: Worst grade per patient

	S1 (TR)						S2 (RT)						Total					
	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 in total and by sequence, when applicable.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 11.4.1.5 Hematological abnormalities by cycle grade ≥ 3

Sequence	Subject	Event	Cycle	Grade

Listing 11.4.1.6 Hematological tests not assessed by cycle

Sequence	Subject	Cycle	Lab. test

11.4.2 Biochemical Abnormalities

Table 11.4.2.1 Biochemical abnormalities: Worst grade per treatment

	BOS+LRB						LRB alone					
	All grades		Gr ≥ 3		Gr ≥ 4		All grades		Gr ≥ 3		Gr ≥ 4	
	N	%	N	%	N	%	N	%	N	%	N	%
ALT increase												
AST increase												
…*												

Notes: Percentage is based on number of patients by treatment, when applicable.
*Creatinine increased, hyperglycemia, hypoglycemia, CPK increased, GGT increased, bilirubin increased, hypoalbuminemia, hypernatremia, hyponatremia, hyperkalemia, hypokalemia, hypermagnesemia, hypomagnesemia, hypercalcemia, hypocalcemia.
BOS, bosentan; LRB, lurbinectedin.

Listing 11.4.2.2 Biochemical abnormalities grade ≥ 3

Treatment group†	Subject	Event	Grade

†BOS+LRB/LRB alone

Listing 11.4.2.3 Biochemical tests not assessed

Treatment group†	Subject	Lab. test

†BOS+LRB/LRB alone

Table 11.4.2.4 Biochemical abnormalities: Worst grade per patient

	S1 (TR)						S2 (RT)						Total					
	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 in total and by sequence, when applicable.
*Creatinine increased, hyperglycemia, hypoglycemia, CPK increased, GGT increased, bilirubin increased, hypoalbuminemia, hypernatremia, hyponatremia, hyperkalemia, hypokalemia, hypermagnesemia, hypomagnesemia, hypercalcemia, hypocalcemia
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 11.4.2.5 Biochemical abnormalities by cycle grade ≥ 3

Sequence	Subject	Event	Cycle	Grade

Listing 11.4.2.6 Biochemical tests not assessed by cycle

Sequence	Subject	Cycle	Lab. test

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	%
						S1 (TR)					
Anemia	Grade 0										
	…										
	Grade 4										
Leukopenia	Grade 0										
	…										
	Grade 4										
…*	Grade 0										
	…										
	Grade 4										
						S2 (RT)					
Anemia	Grade 0										
	…										
	Grade 4										
Leukopenia	Grade 0										
	…										
	Grade 4										
…*	Grade 0										
	…										
	Grade 4										
						Total					
Anemia	Grade 0										
	…										
	Grade 4										
Leukopenia	Grade 0										
	…										
	Grade 4										
…*	Grade 0										
	…										
	Grade 4										

Notes: Percentage is based on number of patients in total and by sequence, when applicable.
*Lymphopenia, Neutropenia and Thrombocytopenia.
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

	BOS+LRB		LRB alone		Total	
	N	Median (range)	N	Median (range)	N	Median (range)
Neutropenia (Grade≥3)						
Onset day						
Nadir day						
Recovery day						
Days of recovery to grade ≤2						
Thrombocytopenia (Grade≥3)						
Onset day						
Nadir day						
Recovery day						
Days of recovery to grade ≤2						

BOS, bosentan; LRB, lurbinectedin.

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	%
						S1 (TR)					
ALT increase	Grade 0										
	…										
	Grade 4										
AST increase	Grade 0										
	…										
	Grade 4										
…*	Grade 0										
	…										
	Grade 4										
						S2 (RT)					
ALT increase	Grade 0										
	…										
	Grade 4										
AST increase	Grade 0										
	…										
	Grade 4										
…*	Grade 0										
	…										
	Grade 4										
						Total					
ALT increase	Grade 0										
	…										
	Grade 4										
AST increase	Grade 0										
	…										
	Grade 4										
…*	Grade 0										
	…										
	Grade 4										

Notes: Percentage is based on number of patients in total and by sequence, when applicable.
†For ALT, AST, AP, GGT, and Bilirubin parameters, worst grade will be calculated compared to baseline.
*Creatinine increased, hyperglycemia, hypoglycemia, CPK increased, GGT increased, bilirubin increased, hypoalbuminemia, hypernatremia, hyponatremia, hyperkalemia, hypokalemia, hypermagnesemia, hypomagnesemia, hypercalcemia, hypocalcemia.
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

	BOS+LRB		LRB alone		Total	
	N	Median (range)	N	Median (range)	N	Median (range)
AST (Grade≥3)						
Onset day						
Peak day						
Recovery day						
Days of recovery to grade ≤2						
ALT (Grade≥3)						
Onset day						
Peak day						
Recovery day						
Days of recovery to grade ≤2						

BOS, bosentan; LRB, lurbinectedin.

If appropriate, inter-cycle time courses for neutropenia, thrombocytopenia or any other significant parameter will be displayed in graphs.

11.5 Linear Mixed-effects Model

If applicable, to compare the incidence of grade ≥4 or grade ≥3 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 ≥3AE			
Any grade ≥4 AE			
Any grade ≥3 treatment-related AE			
Any grade ≥4 treatment-related AE			
Any abnormality (G≥3) in laboratory value (hema, bio)			
Any abnormality (G≥4) 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

Sequence	Subject	PS†				
		Baseline	Cycle 1	Cycle 2	Cycle 3	EOT
S1 (TR)	…					
S2 (RT)	…					

† Worst of cycle determination
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test

Listing 11.6.1.2 Weight change during the study

Sequence	Subject	% Change†				
		Weight at Baseline	Cycle 1	Cycle 2	Cycle 3	EOT
S1 (TR)	…					
S2 (RT)	…					

† % compared to baseline
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

11.6.2 LVEF and ECG

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

Sequence	Subject	Assessment Date	Abnormality	Specify	Method	LVEF (%)	Lower limit of normality

Sequence	Subject	Assessment Date	Abnormality	Specify	Method	LVEF (%)	Lower limit of normality

Listing 11.6.2.2 Electrocardiogram evolution during the study

Sequence	Subject	% Change†					
		ECG parameters* Baseline	Cycle 1 Pre infusion	Cycle 1 Post infusion	Cycle 2 Pre infusion	Cycle 2 Post infusion	EOT
S1 (TR)	…						
S2 (RT)	…						

* PR interval (msec), Heart rate (bpm), QT interval (msec), QRS complex duration, Fridericia corrected QT
† % compared 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
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Listing 11.6.2.3 Patients with abnormal or clinically indicated Electrocardiogram during the study

Sequence	Subject	Assessment Date	Result	Specify	PR Interval (msec)	Heart rate (bpm)	QT interval (msec)	Bazett's corrected QT

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)

	BOS+LRB		LRB alone	
	N	%	N	%
Alimentary tract and metabolism				
Antacids				
Magnesium compounds				
Magnesium adipate				
…				
Blood and blood forming organs				
Antithrombotic agents				
Vitamin K antagonists				
Acenocoumarol				
…				

Notes: Percentage is based on number of patients by treatment, when applicable.
BOS, bosentan; LRB, lurbinectedin.

Table 11.7.1.2 Summary of concomitant medication during treatment by ATC

	BOS+LRB		LRB alone	
	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)				

BOS, bosentan; LRB, lurbinectedin.

11.7.2 Further Antitumor Therapies

Listing 11.7.2.1 First Antitumor Therapy

Sequence	Subject	End of treatment	First Antitumor Therapy	Start date

12 APPENDIX III: EFFICACY ANALYSIS

Not applicable.

13 APPENDIX IV: DB Listings

Listing 13.1 Screening (I)

Sequence	Subject	Informed consent	PGt sub-study	Planned initiation	EC3	EC4	PCR date	PCR result	Eligibility

Listing 13.2 Screening (II)

Sequence	Subject	Screening failure	Criterion not met	Details

Listing 13.3 Study registration/Randomization details

Sequence	Subject	Randomization	Date of Randomization	Treatment Sequence	Treatment Description	Screening failure date

Listing 13.4 Date of visit

Sequence	Subject	Visit	Date

Listing 13.5 Date of unscheduled visit

Sequence	Subject	Visit	Date	Clinically indicated repeat

Listing 13.6 Demographics

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

Listing 13.7 Childbearing potential and adequate contraception

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

Listing 13.8 Pregnancy test

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

Listing 13.9 Prior medical history

Sequence	Subject	Description	SOC	MedDRA PT	Onset date	Resolved date	Ongoing

Listing 13.10 Cancer history

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

Listing 13.11 Prior surgery

Sequence	Subject	None?	Site and procedures	Date

Listing 13.12 Prior radiotherapy

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

Listing 13.13 Prior anticancer medical therapy

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

Listing 13.14 Prophylactic medication

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

([†]) ATC1, ATC2, ATC3, ATC4

Listing 13.15 Lurbinectedin administration

Sequence	Subject	Visit	Date	Route	Start time	End time	Intended dose (mg/m^2)	Total intended dose (mg)	Total dose given	Total volume	BSA calculated for dose

Listing 13.16 Lurbinectedin treatment modification

Sequence	Subject	Visit	Any modification	Treatment Modification	Reason	Adverse Event	Other, specify

Listing 13.17 Lurbinectedin re-administration

Sequence	Subject	Visit	Date	Not done?	Route	Total dose given	Start time	End time

Listing 13.18 Bosentan administration prior to lurbinectedin infusion

Sequence	Subject	Visit	Day	Date	Time	No. of capsules (125 mg)	Taken accordingly?	Reason	Contact	Reason if No contacted

Listing 13.19 Hematological laboratory values

Sequence	Subject	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.

Listing 13.20 Coagulation Test

Sequence	Subject	Visit	Calculated cycle	Date	Repeat	INR (ratio)

Listing 13.21 Biochemical laboratory values

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

([†]) AP, Creatinine, CrCl, Glucose, CPK, CPK-MB fraction, GGT, Total Proteins, Albumin, CRP, Na, K, Mg, Ca

Listing 13.22 Performance status

Sequence	Subject	Not done	Visit	Date	ECOG

Listing 13.23 Physical examination

Sequence	Subject	Not done	Visit	Date	Weight	Height	BSA method	BSA calculated	Any Abnormalities?	Findings

Listing 13.24 Vital signs

Sequence	Subject	Not done	Visit	Date	Heart rate (bpm)	Systolic (mmHG)	Diastolic (mmHG)	Temperature (ºC)

Listing 13.25 Electrocardiogram

Sequence	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

Listing 13.26 Concomitant non-diagnostic procedures

Sequence	Subject	Procedure	Date	Indication	AE/MH	Comments

Listing 13.27 LVEF

Sequence	Subject	Reason clinically indicated	Not done	Visit	Date	Method	Value	Lower limit	Result	Abnormal specify

Listing 13.28 Signs and symptoms

Sequence	Subject	S&S Description	…[†]	Grade	Onset date	Still Ong.at C1D1?	End date	Related to:

([†])SOC, MedDRA PT

Listing 13.29 Adverse events

Sequence	Subject	AE.	…[†]	Grade	SAE	Onset date	Ong.	End date	Ong.	Relationship	Action taken	Seriousness criteria	Outcome

([†])SOC, MedDRA PT

Listing 13.30 SAE summary

Sequence	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

Listing 13.31 Concomitant medication

Sequence	Subject	Medication	…[†]	Route	Dose (units)	Frequency	Start date	End date	Ongoing	Indication	AE/MH

([†])ATC1, ATC4

Listing 13.32 Diagnostic procedures/Tests

Sequence	Subject	Test	Date	Result	Units	Comments

Listing 13.33 Pharmacokinetics

Sequence	Subject	Cycle	Day	Sample No	Sample time	Samp. window	Date	Time	Total (done)	Unbound (done)	Metabolites (done)	Bosentan (done)	Com.

Listing 13.34 Pharmacogenetics (Polymorphisms)

Sequence	Subject	Cycle	Date	Not done?	Comments

Listing 13.35 Alpha-1-acid glycoprotein and Interleukin 6

Sequence	Subject	Visit	Sample taken	Date	Comments

Listing 13.36 End of treatment

Sequence	Subject	Primary Reason End of Treatment	Specify

Listing 13.37 Follow up - Further antitumor therapies

Sequence	Subject	Antitumor Therapy description	Start date

Listing 13.38 Off study

Sequence	Subject	Off Study Date	Primary reason	Specify	Never treated, specify

Listing 13.39 Death report form

Sequence	Subject	Death date	Cause of death	Specify	Autopsy?

Listing 13.40 Investigator comments

Sequence	Subject	Page name	Instance	Variable	Comments

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	Subject	Informed Consent date	Screening failure?	Date of Screening failure	Met Eligibility	Criterion Identifier	Details	Treated	Date of First treatment

Listing 14.3 Sequence assignment by site

Site	Subject	Treatment Sequence	DA Start date	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 Protocol Deviations by Site

Site	Subject	Deviation type	Deviation

Listing 14.9 Concomitant medication

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

†ATC1, ATC4

Listing 14.10 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, AST, ALT, AP, LDH, Creatinine, CrCl, Glucose, CPK, CPK-MB fraction, GGT, Total Proteins, Total Bilirubin, Direct Bilirubin,Albumin, CRP, Na, K, Mg, Ca.

Listings 14.11 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 14.12 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 International Conference on Harmonization (ICH) E-3 guideline, patient listings specified as section 16.2 will be prepared.

Listing 16.2.1 Discontinued Patients

Subject	Institution	Treated	Cycles received	First infusion date	Last infusion date	Reason for end of treatment	Comments

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								Bosentan	
Subject	First Intended dose (mg/m^2)	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, AST, ALT, AP, LDH, Creatinine, CrCl, Glucose, CPK, CPK-MB fraction, GGT, Total Proteins, Total Bilirubin, Direct Bilirubin, Albumin, CRP, Na, K, Mg, Ca.

16 APPENDIX VI: VERSION HISTORY

16.1 History of Changes

Minor clarifications/modifications have been added to the SAP v1.0 date on 17 February 2021 during the programing tasks.

A brief summary is include below:

- In order to maintain the consistency in safety analysis groups (Sequence 1 vs Sequence 2 and lurbinectedin administered in combination vs lurbinectedin alone) some table's titles has been clarified and updated.

- Some listings/variables from Appendix IV: DB Listings have been deleted for containing duplicate information.

- Some minor comments for clarification have been added. Minor corrections will not be described below.

Detailed changes are presented in the next pages. Changes are highlighted in ***Italic bold*** and text removed has been ~~crossed out~~.

APPENDIX I (PATIENTS DISPOSITION)

10.1.1 Patients Disposition

Listing 10.1.1.4 Non-evaluable patients

Not Evaluable for	Sequence	Subject	Reason(s)
Safety			
PK			

10.2.1 Demographic and Other Baseline Characteristics

Table 10.2.1.1 Baseline characteristics: Adequate contraception

	S1 (TR)		S2 (RT)		Total	
	N	%	N	%	N	%
Adequate contraception						
Yes						
No						
NA ~~(For Male)~~						

Notes: Percentage ~~is based on number of patients by total and sequence~~ **is based on number of patients in total and by sequence**, when applicable.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

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

Table 10.2.5.6 Baseline characteristics: ECG† pre infusion

	S1 (TR)		S2 (RT)		Total	
	N	%	N	%	N	%
Result						
Normal						
Abnormal						
~~Significant abnormalities~~						
~~Non-significant abnormalities~~						

Notes: Percentage ~~is based on number of patients by total and sequence~~ **is based on number of patients in total and by sequence**, when applicable.
† Worst result of the three ECGs replicates will be used ~~as a baseline values~~ as baseline value.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

Table 10.2.5.10 Baseline characteristics: LVEF

	S1 (TR)		S2 (RT)		Total	
	N	%	N	%	N	%
Result						
Normal						
Abnormal						
~~Significant abnormalities~~						
~~Non-significant abnormalities~~						

Notes: Percentage is based on number of patients by total and sequence, when applicable.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

APPENDIX II (SAFETY ANALYSIS)

11.2.1 Display of Adverse Events

Table 11.2.1.2 **Treatment** Related† (or with unknown relationship) Adverse Events. Worst grade per ~~patient~~ **treatment**

	BOS+~~LURBI~~ **LRB**						**LRB** alone					
SOC/PT	All grades		Gr ≥ 3		Gr ≥ 4		All grades		Gr ≥ 3		Gr ≥ 4	
	N	%	N	%	N	%	N	%	N	%	N	%
…												

Notes: Percentage ~~is based on number of patients by total and sequence~~ **is based on number of patients by treatment**, when applicable.
† Related to both or lurbinectedin or bosentan or with unknown relationship
BOS, bosentan; LRB, lurbinectedin.

Table 11.2.1.3 Lurbinectedin related† Adverse Events. Worst grade per ~~patient~~ **treatment**

	BOS+~~LURBI~~ **LRB**						~~LURBI~~ **LRB** alone					
SOC/PT	All grades		Gr ≥ 3		Gr ≥ 4		All grades		Gr ≥ 3		Gr ≥ 4	
	N	%	N	%	N	%	N	%	N	%	N	%
…												

Notes: Percentage ~~is based on number of patients by total and sequence~~ **is based on number of patients by treatment**, when applicable
† Related to lurbinectedin or with unknown relationship
BOS, bosentan; LRB, lurbinectedin.

Table 11.2.1.4 Bosentan related Adverse Events. Worst grade per ~~patient~~ **treatment**

SOC/PT	BOS+ ~~LURB~~ **LRB**						~~LURBI alone~~					
	All grades		Gr ≥ 3		Gr ≥ 4		~~All grades~~		~~Gr ≥ 3~~		~~Gr ≥ 4~~	
	N	%	N	%	N	%	~~N~~	~~%~~	~~N~~	~~%~~	~~N~~	~~%~~
…												

Notes: Percentage ~~is based on number of patients by total and sequence~~ **is based on number of patients by treatment**, when applicable

† Related to bosentan or with unknown relationship
BOS, bosentan; LRB, lurbinectedin.

Table 11.2.1.5 Related† (or with unknown relationship) Adverse Events. Worst grade per ~~cycle~~ **patient**

SOC/PT	S1 (TR)						S2 (RT)						Total					
	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 total and sequence~~ **is based on number of patients in total and by sequence**, when applicable
† Related to both or lurbinectedin or bosentan or with unknown relationship
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

~~Table 11.2.1.6 Lurbinectedin related‡ Adverse Events. Worst grade per cycle~~

~~SOC/PT~~	~~S1 (TR)~~						~~S2 (RT)~~						~~Total~~					
	~~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 total and sequence, when applicable.~~
~~‡ Related to lurbinectedin or with unknown relationship~~
~~S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.~~

~~Table 11.2.1.7 Bosentan related‡ Adverse Events. Worst grade per cycle~~

~~SOC/PT~~	~~S1 (TR)~~						~~S2 (RT)~~						~~Total~~					
	~~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 total and sequence, when applicable.~~
~~‡ Related to bosentan or with unknown relationship~~
~~S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.~~

Table 11.2.1.~~8~~**6** Adverse Events regardless of relationship. Worst grade per ~~patient~~ **treatment**

SOC/PT	BOS+ ~~LURB~~ **LRB**						~~LURBI~~ **LRB** alone					
	All grades		Gr ≥ 3		Gr ≥ 4		All grades		Gr ≥ 3		Gr ≥ 4	
	N	%	N	%	N	%	N	%	N	%	N	%
…												

Notes: Percentage ~~is based on number of patients by total and sequence~~ **is based on number of patients by treatment**, when applicable
BOS, bosentan; LRB, lurbinectedin.

Table 11.2.1.~~9~~ **8**Adverse Events regardless of relationship. Worst grade per ~~cycle~~ **patient**

SOC/PT	S1 (TR)						S2 (RT)						Total					
	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 total and sequence, when applicable.
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

11.3.1 Serious Adverse Events

Table 11.3.1.1 **Treatment** Related† (or with unknown relationship) SAEs. Worst grade per ~~patient~~ **treatment**

SOC/PT	BOS+ ~~LURB~~ **LRB**						~~LURBI~~ **LRB** alone					
	All grades		Gr ≥ 3		Gr ≥ 4		All grades		Gr ≥ 3		Gr ≥ 4	
	N	%	N	%	N	%	N	%	N	%	N	%
…												

Notes: Percentage ~~is based on number of patients by total and sequence~~ **is based on number of patients by treatment**, when applicable
† Related to both or lurbinectedin or bosentan or with unknown relationship
BOS, bosentan; LRB, lurbinectedin.

Table 11.3.1.2 Lurbinectedin related† SAEs. Worst grade per ~~patient~~ **treatment**

SOC/PT	BOS+ ~~LURBI~~ **LRB**						~~LURBI~~ LRB alone					
	All grades		Gr ≥ 3		Gr ≥ 4		All grades		Gr ≥ 3		Gr ≥ 4	
	N	%	N	%	N	%	N	%	N	%	N	%
…												

Notes: Percentage ~~is based on number of patients by total and sequence~~ **is based on number of patients by treatment**, when applicable
† Related to lurbinectedin or with unknown relationship
BOS, bosentan; LRB, lurbinectedin.

Table 11.3.1.3 Bosentan related† SAEs. Worst grade per ~~patient~~ **treatment**

SOC/PT	BOS+~~LURBI~~ **LRB**						~~LURBI~~ **LRB** alone					
	All grades		Gr ≥ 3		Gr ≥ 4		~~All grades~~		~~Gr ≥ 3~~		~~Gr ≥ 4~~	
	N	%	N	%	N	%	~~N~~	~~%~~	~~N~~	~~%~~	~~N~~	~~%~~

…

Notes: Percentage ~~is based on number of patients by total and sequence~~ **is based on number of patients in total and by sequence**, when applicable
† Related to bosentan or with unknown relationship
BOS, bosentan; LRB, lurbinectedin.

Table 11.3.1.4 **Treatment** Related† (or with unknown relationship) SAEs. Worst grade per ~~cycle~~ **patient**

SOC/PT	S1 (TR)						S2 (RT)						Total					
	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 total and sequence~~ **is based on number of patients in total and by sequence**, when applicable
† Related to both or lurbinectedin or bosentan or with unknown relationship
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test

~~Table 11.3.1.5 Lurbinectedin related‡ SAEs. Worst grade per cycle~~

~~SOC/PT~~	~~S1 (TR)~~						~~S2 (RT)~~						~~Total~~					
	~~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 total and sequence, when applicable.~~
~~‡ Related to lurbinectedin or with unknown relationship~~
~~S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.~~

~~Table 11.3.1.6 Bosentan related‡ SAEs. Worst grade per cycle~~

~~SOC/PT~~	~~S1 (TR)~~						~~S2 (RT)~~						~~Total~~					
	~~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 total and sequence, when applicable.~~
~~‡ Related to bosentan or with unknown relationship~~
~~S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.~~

Table 11.3.1.~~7~~**5** SAEs regardless of relationship. Worst grade per ~~patient~~ **treatment**

SOC/PT	BOS+ ~~LURB~~ ~~I~~**LRB**						**LRB** ~~LURBI~~ alone					
	All grades		Gr ≥ 3		Gr ≥ 4		All grades		Gr ≥ 3		Gr ≥ 4	
	N	%	N	%	N	%	N	%	N	%	N	%

…

Notes: Percentage ~~is based on number of patients by total and sequence~~ **is based on number of patients by treatment**, when applicable
BOS, bosentan; LRB, lurbinectedin.

Table 11.3.1.~~8~~**6** SAEs regardless of relationship. Worst grade per ~~cycle~~ **patient**

SOC/PT	S1 (TR)						S2 (RT)						Total					
	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 total and sequence~~ **is based on number of patients in total and by sequence**, when applicable
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

11.4.1 Hematological Abnormalities

Table 11.4.1.1 Hematological abnormalities: Worst grade per ~~patient~~ **treatment**

	BOS+ ~~LURB~~ ~~I~~**LRB**						~~LURBI~~ **LRB** alone					
	All grades		Gr ≥ 3		Gr ≥ 4		All grades		Gr ≥ 3		Gr ≥ 4	
	N	%	N	%	N	%	N	%	N	%	N	%
Anemia												
Leukopenia												
Lymphopenia												
Neutropenia												
Thrombocytopenia												

Notes: Percentage ~~is based on number of patients by total and sequence~~ **is based on number of patients by treatment**, when applicable
BOS, bosentan; LRB, lurbinectedin.

Table 11.4.1.4 Hematological abnormalities: Worst grade per ~~cycle~~ **patient**

	S1 (TR)						S2 (RT)						Total					
	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 total and sequence~~ **is based on number of patients in total and by sequence**, when applicable
S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

11.4.2 Biochemical Abnormalities

Table 11.4.2.1 Biochemical abnormalities: Worst grade per ~~patient~~ **treatment**

	BOS+ ~~LURB~~ ~~H~~**LRB**			~~LURBI~~ **LRB** alone		
	All grades	Gr ≥ 3	Gr ≥ 4	All grades	Gr ≥ 3	Gr ≥ 4
	N %	N %	N %	N %	N %	N %
ALT increase						
AST increase						
…*						

Notes: Percentage ~~is based on number of patients by total and sequence~~ **is based on number of patients by treatment**, when applicable

*Creatinine increased, hyperglycemia, hypoglycemia, CPK increased, GGT increased, bilirubin increased, hypoalbuminemia, hypernatremia, hyponatremia, hyperkalemia, hypokalemia, hypermagnesemia, hypomagnesemia, hypercalcemia, hypocalcemia.

BOS, bosentan; LRB, lurbinectedin.

Table 11.4.2.4 Biochemical abnormalities: Worst grade per ~~cycle~~ **patient**

	S1 (TR)				S2 (RT)				Total			
	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 total and sequence~~ **is based on number of patients in total and by sequence**, when applicable.

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

*Creatinine increased, hyperglycemia, hypoglycemia, CPK increased, GGT increased, bilirubin increased, hypoalbuminemia, hypernatremia, hyponatremia, hyperkalemia, hypokalemia, hypermagnesemia, hypomagnesemia, hypercalcemia, hypocalcemia

S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.

11.4.3 Laboratory Values Over Treatment

Table 11.4.3.2 Time course for neutrophils and platelets

	~~S1 (TR)~~**BOS+LRB**		~~S2 (RT)~~**LRB alone**		Total	
	N	Median (range)	N	Median (range)	N	Median (range)
Neutropenia (Grade≥3)						
Onset day						
Nadir day						
Recovery day						
Days of recovery to grade ≤2						
Thrombocytopenia (Grade≥3)						
Onset day						
Nadir day						
Recovery day						
Days of recovery to grade ≤2						

~~S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.~~

BOS, bosentan; LRB, lurbinectedin.

Table 11.4.3.4 Time course for AST and ALT

	~~S1 (TR)~~**BOS+LRB**		~~S2 (RT)~~**LRB** alone		Total	
	N	Median (range)	N	Median (range)	N	Median (range)
AST (Grade≥3)						
Onset day						
Peak day						
Recovery day						
Days of recovery to grade ≤2						
ALT (Grade≥3)						
Onset day						
Peak day						
Recovery day						
Days of recovery to grade ≤2						

~~S1, Sequence 1; S2, Sequence 2; TR, test-reference; RT, reference-test.~~

BOS, bosentan; LRB, lurbinectedin.

APPENDIX IV (DB Listings)

Listing 13.1 Screening (I)

Sequence	Subject	Informed consent	PGt sub-study	Planned initiation	~~Age~~	~~Tumor type~~	EC3	EC4	PCR date	PCR result	Eligibility

~~Listing 13.3 Sponsor Approval Form~~

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

~~Listing 13.4 Randomization details~~

~~Sequence~~	~~Subject~~	~~Ready to be randomized~~	~~Treatment Sequence~~	~~Treatment Description~~	~~Date/Time of randomization~~

Listing 13.~~5~~**3** Study registration/**Randomization details**

Sequence	Subject	~~Registration~~ **Randomization**	**Date of** Randomization	Treatment Sequence	Treatment Description	Screening failure date