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RESEARCH**

APPLICATION NUMBER:

213702Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	213702
Priority or Standard	Priority
Submit Date(s)	December 16, 2019
Received Date(s)	December 16, 2019
PDUFA Goal Date	August 16, 2020
Division/Office	DO2/OOD
Review Completion Date	June 12, 2020
Established/Proper Name	Lurbinectedin
(Proposed) Trade Name	ZEPZELCA
Pharmacologic Class	Alkylating drug
Code name	PM01183
Applicant	Pharma Mar USA, Inc.
Doseage form	For injection: 4 mg lyophilized powder in a single-dose vial
Applicant proposed Dosing Regimen	3.2 mg/m ² intravenously over 1 hour every 21 days
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adult patients with metastatic small cell lung cancer (SCLC) with disease progression on or after (b) (4) platinum-based chemotherapy
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	
Recommended Dosing Regimen	3.2 mg/m ² intravenously over 1 hour every 3 weeks

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OPQ=Office of Pharmaceutical Quality

OPDP=Office of Prescription Drug Promotion

OSI=Office of Scientific Investigations

OSE= Office of Surveillance and Epidemiology

DEPI= Division of Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DRISK=Division of Risk Management

Glossary

AA	accelerated approval
AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CAV	cyclophosphamide, doxorubicin, vincristine
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CR	complete response
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CUI	clinical utility index
DHOT	Division of Hematology Oncology Toxicology
DO2	Division of Oncology 2
DOR	duration of response
DMC	data monitoring committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCTD	electronic common technical document
EFT	Ewing family of tumors
ES-SCLC	extensive-stage small cell lung cancer
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act

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GCP	good clinical practice
GCT	germ cell tumor
GRMP	good review management practice
H&N	head & neck
IA	investigator assessment
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IRC	independent review committee
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
LS-SCLC	limited-stage small cell lung cancer
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
ORR	overall response rate
PBPK	physiologically-based pharmacokinetics
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PFS	progression-free survival
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PR	partial response
PS	performance status
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SCLC	small cell lung cancer
SAP	statistical analysis plan

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SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information

1 Executive Summary

1.1. Product Introduction

Lurbinectedin is an alkylating drug that is an inhibitor of oncologic transcription. It binds covalently in GC rich DNA sequences resulting in double-strand DNA breaks, leading to cell death. Currently, lurbinectedin is not approved in the United States (US) for any indication.

In this new drug application (NDA), the proposed indication is for the treatment of adult patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy.

The recommended dosing regimen for the proposed indication is 3.2 mg/m² administered every 21 days as a 60-minute intravenous (IV) infusion until disease progression or unacceptable toxicity.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The FDA review teams recommend accelerated approval of lurbinectedin for the following indication: *Lurbinectedin is indicated for the treatment of adult patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy.*

The recommendation for accelerated approval, according to 21 CFR 314.510 Subpart H, is based on the results from a single trial, PM1183-B-005-14 (Study B-005), an ongoing, multicenter, open-label, non-randomized, multi-cohort trial evaluating the safety and efficacy of lurbinectedin as a single-agent in adult patients with advanced solid tumors. The efficacy is primarily based on results from a cohort of 105 patients with metastatic SCLC who had disease progression on or after first-line treatment with platinum-based chemotherapy. In this cohort, the confirmed investigator-assessed overall response rate (ORR), as per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v.1.1), was 35% (95% CI: 26, 45). The median duration of response (DOR) was 5.3 months (95% CI: 4.1, 6.4). This was further supported by ORR, as assessed by independent review committee (IRC) per RECIST v1.1, of 30% (95% CI: 22, 40), with a median DOR of 5.1 months (95% CI: 4.9, 6.4).

FDA considers response rate as an approval endpoint for SCLC because in the absence of therapy, tumors grow or remain stable rather than shrink. The observed response rates were clinically meaningful, and were seen across subgroups of patients with SCLC who had “sensitive” or “resistant” disease. Forty-three percent of the patients with SCLC in this study had resistant disease, defined as disease that is refractory to or progresses less than 90 days after completion of platinum-based chemotherapy. The remaining 57% of patients in this study had sensitive disease, defined as disease that progresses 90 days or later after completion of

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platinum-based chemotherapy. Patients with resistant disease had an investigator-assessed ORR of 22% (95% CI: 11, 37), and patients with sensitive disease had an investigator-assessed ORR of 45% (95% CI: 32, 58).

Furthermore, lurbinectedin has an acceptable safety profile when assessed in the context of a life-threatening disease and current available therapy. The most frequent grade 3-4 reactions ($\geq 5\%$) for patients with SCLC treated with lurbinectedin were myelosuppression, fatigue, pneumonia, decreased sodium, elevated liver enzymes, and elevated glucose.

Based on these results, and a favorable benefit-risk profile, and limited available therapy in this patient population constituting an unmet medical need, the FDA review teams recommend accelerated approval of lurbinectedin for the following indication: *treatment of adult patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy.*

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Metastatic small cell lung cancer (SCLC) is a life-threatening condition with poor prognosis. Current first-line treatment for metastatic SCLC or extensive-stage disease (ES-SCLC) is platinum-based chemotherapy with or without atezolizumab or durvalumab^{3,7,8}. Although SCLC is responsive to initial treatment, disease progression is common². Depending on the interval between completion of chemotherapy and detection of relapse, treatment options include retreatment with a platinum-based regimen (for patients with disease recurrence >6 months from last dose of platinum) or use of single-agent chemotherapy³. Topotecan is the only FDA-approved therapy for patients with SCLC whose disease has progressed at least 60 days after initiation of first-line chemotherapy (platinum-sensitive). In this setting, topotecan has shown a response rate of 24% (95% CI: 16, 32) with a median duration of response of 3.3 months¹⁵. There is no approved therapy for patients with SCLC platinum-resistant disease who have no response or have disease progression after first-line chemotherapy.

Lurbinectedin is an alkylating drug that is an inhibitor of oncologic transcription. It binds covalently in GC rich DNA sequences resulting in double strand DNA breaks, ultimately leading to cell death. Currently, lurbinectedin is not approved in the US for any indication.

This New Drug Application (NDA) for lurbinectedin is supported by results from PM1183-B-005-15 (Study B-005), an ongoing, multicenter, open-label, non-randomized, multi-cohort trial evaluating the safety and efficacy of lurbinectedin as a single-agent in adult patients with advanced solid tumors. The efficacy is primarily based on results from a cohort of 105 patients with metastatic SCLC who had disease progression on or after first-line treatment with platinum-based chemotherapy. All patients had received prior platinum-based therapy and 8% had received prior immunotherapy. About 43% of the patients with SCLC had resistant disease, defined in this study as disease that is refractory to or progresses less than 90 days after completion of platinum-based chemotherapy. The remaining 57% of patients in this cohort had sensitive disease, defined in this study as disease that progresses 90 days or later from completion of platinum-based chemotherapy.

The primary efficacy outcome measure is investigator-assessed overall response rate (ORR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v.1.1). The ORR was 35% (95% CI: 26, 45). Patients with resistant disease had an ORR of 22% (95% CI: 11, 37), and patients with sensitive disease had an ORR of 45% (95% CI: 32, 58). The median duration of response (DOR) was 5.3 months (95% CI: 4.1, 6.4). ORR as assessed by independent review committee (IRC) per RECIST v1.1, a secondary endpoint, was 30% (95% CI: 22, 40) with a median DOR of 5.1 months (95% CI: 4.9, 6.4). According to IRC, patients with resistant disease had an ORR of 13% (95% CI: 5, 27), and patients with sensitive disease had an ORR of 43% (31, 57).

The overall safety population consisted of 554 patients from two separate studies (Study B-005 and CORAIL) who had various advanced solid tumors and had received the same dose and regimen of single-agent lurbinectedin. The observed safety profile of lurbinectedin in the 105 patients SCLC cohort was similar to the overall safety population, and was acceptable when considered in the context of a life-threatening disease. In the SCLC cohort, the most frequent grade 3-4 adverse reactions ($\geq 5\%$) were myelosuppression, fatigue, pneumonia, decreased sodium, elevated liver enzymes, and elevated glucose. Rate of treatment discontinuation was 2% in the SCLC cohort, less frequent than that seen in the overall safety population (9%). The most common ($\geq 3\%$) serious adverse reactions were pneumonia, febrile neutropenia, myelosuppression (neutropenia, lymphopenia, thrombocytopenia, anemia), dyspnea, and respiratory tract infection in patients with SCLC. Six treatment-emergent deaths (1.1%) were identified in the overall safety population that were considered possibly related to lurbinectedin that include deaths due to sepsis, septic shock, pneumonia and pneumonitis. Four treatment-emergent deaths were reported in the SCLC cohort which were due to disease progression. There were no significant safety concerns identified during the review of the application requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS).

In summary, based on the results from Study B-005 and totality of information in the Application, and favorable risk-benefit profile in the context of a life-threatening disease with an unmet medical need, the review teams find that the submitted evidence meets the statutory evidentiary standard for accelerated approval of lurbinectedin for the following indication: *Treatment of adult patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy.*

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	<ul style="list-style-type: none"> • Lung cancer is the leading cause of cancer-related mortality in the US and worldwide. Approximately 15% of lung cancers diagnosed are small cell lung cancer (SCLC). The majority of patients with SCLC have disseminated disease at presentation^{1,2}. • Current first-line treatment for extensive-stage and metastatic SCLC is platinum-based chemotherapy with or without atezolizumab or durvalumab, which is associated with a median overall survival of approximately 9-13 months^{3,7,8}. • Depending on the interval between completion of chemotherapy and detection of progression or recurrence, treatment options include retreatment with a platinum-based regimen (for patients with recurrence >6 months from last dose of platinum) or use of single-agent chemotherapy³. 	SCLC is a serious and life-threatening condition with poor survival.
<u>Current Treatment Options</u>	<ul style="list-style-type: none"> • In the second-line setting, topotecan is the only FDA-approved therapy for patients with SCLC platinum-sensitive disease who have progressed at least 60 days after initiation of first-line chemotherapy. In this setting, topotecan has shown a response rate of 24% (95% CI: 16, 32) with a median duration of response of 3.3 months¹⁵. • There is no approved therapy for patients with SCLC platinum-resistant disease who have no response to or disease progression after first-line chemotherapy. 	There is an unmet medical need for patients with metastatic SCLC with progression after prior platinum-containing therapy, particularly in patients with platinum-resistant disease.
<u>Benefit</u>	<ul style="list-style-type: none"> • The efficacy of lurbinectedin as a single-agent was evaluated in PM1183-B-005-14 (Study B-005), an ongoing, multicenter, open-label, basket trial of patients with advanced solid tumors including a cohort of 105 patients with SCLC who progressed on or after receiving a prior chemotherapy-based regimen. • According to investigator assessment (IA), the overall response rate 	In Study B-005, lurbinectedin administered to patients with metastatic SCLC who progressed on or after platinum-based chemotherapy demonstrated an ORR and DOR that was clinically meaningful and was also seen across subgroups of patients who had “sensitive” or

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>(ORR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v.1.1) in patients with SCLC was 35% (95% CI: 26, 45). All responders demonstrated a partial response (PR). The median duration of response (DOR) was 5.3 months based on IA.</p> <ul style="list-style-type: none"> • The IRC-determined ORR was 30% (95% CI: 22, 40) with a median DOR of 5.1 months (95% CI: 4.9, 6.4). Patients with resistant disease had an ORR of 13% (95% CI: 5, 27), and patients with sensitive disease had an ORR of 43% (95% CI: 31, 57). • Patients with resistant disease, defined in this study as disease that is refractory to or progresses less than 90 days after completion of platinum-based chemotherapy, had an ORR of 22% (95% CI: 11, 37) according to IA. Patients with sensitive disease, defined in this study as disease that progresses 90 days or later from completion of platinum-based chemotherapy, had an ORR of 45% (95% CI: 32, 58) according to IA. • Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s). The Applicant proposes to verify the clinical benefit of lurbinectedin in the treatment of patients with SCLC who have disease progression on or after prior platinum-containing therapy, based on the results of another ongoing study, PM1183-C-003-14 (ATLANTIS). This is a randomized study assessing overall survival (OS) in patients receiving lurbinectedin and doxorubicin compared to a investigator’s choice chemotherapy (either topotecan or the combination CAV) as control in the second-line setting for SCLC. 	<p>“resistant” disease. FDA considers response rate as an approval endpoint for SCLC because such responses would not occur by chance alone (that is, in the absence of therapy, tumors grow or remain stable rather than shrink). Additional data to assess clinical benefit of lurbinectedin will be obtained from the results of Study ATLANTIS.</p> <p>With a favorable risk-benefit profile in the context of a life-threatening disease with an unmet medical need, the submitted evidence meets the statutory evidentiary standard for accelerated approval.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p><u>Risk and Risk Management</u></p>	<ul style="list-style-type: none"> • The overall safety population consists of 554 patients, including 335 patients with a variety of advanced solid tumors from Study B-005 and 219 patients with platinum-resistant ovarian cancer from PM1183-C-004-14 (CORAIL). All 554 patients received single-agent lurbinectedin at the dose of 3.2 mg/m² intravenously once every 21 days. • In the SCLC population, the most common (≥20%) adverse reactions were leukopenia, lymphopenia, fatigue, anemia, neutropenia, increased creatinine, increased alanine aminotransferase (ALT), increased glucose, thrombocytopenia, nausea, decreased appetite, musculoskeletal pain, decreased albumin, constipation, dyspnea, decreased sodium, increased aspartate aminotransferase (AST), vomiting, cough, decreased magnesium and diarrhea. The frequencies of these adverse reactions were generally consistent across the overall safety population. • Nine percent of patients in the overall safety population, and 2% in the SCLC cohort discontinued lurbinectedin due to an adverse reaction. • Serious adverse reactions occurred in 41% of all patients and 34% in the SCLC cohort. Febrile neutropenia was the most frequently reported serious adverse reaction with an overall incidence of 6%. • The observed safety profile of lurbinectedin in the 105 patients SCLC cohort was similar to the overall safety population. 	<p>The observed safety profile is acceptable when assessed in the context of the treatment of a life-threatening disease. There were no significant safety concerns identified during the review of the application requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS) to ensure safe use of the combination.</p>

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

<input type="checkbox"/>	The patient experience data that were submitted as part of the application include:	Section of review where discussed, if applicable [e.g., Section 6.1 Study endpoints]
<input type="checkbox"/>	Clinical outcome assessment (COA) data, such as	
<input type="checkbox"/>	Patient reported outcome (PRO)	
<input type="checkbox"/>	Observer reported outcome (ObsRO)	
<input type="checkbox"/>	Clinician reported outcome (ClinRO)	
<input type="checkbox"/>	Performance outcome (PerfO)	
<input type="checkbox"/>	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
<input type="checkbox"/>	Patient-focused drug development or other stakeholder meeting summary reports	
<input type="checkbox"/>	Observational survey studies designed to capture patient experience data	
<input type="checkbox"/>	Natural history studies	
<input type="checkbox"/>	Patient preference studies (e.g., submitted studies or scientific publications)	
<input type="checkbox"/>	Other: (Please specify):	
<input type="checkbox"/>	Patient experience data that were not submitted in the application, but were considered in this review:	
<input type="checkbox"/>	Input informed from participation in meetings with patient stakeholders	
<input type="checkbox"/>	Patient-focused drug development or other stakeholder meeting summary reports	
<input type="checkbox"/>	Observational survey studies designed to capture patient experience data	
<input type="checkbox"/>	Other: (Please specify):	
<input checked="" type="checkbox"/>	Patient experience data was not submitted as part of this application.	

Reviewer Note: No clinical outcome assessment or patient reported outcome data were submitted in this application.

X Adnan Jaigirdar
Cross Discipline Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

Lung cancer is the leading cause of cancer and cancer-related mortality worldwide¹ and the leading cause of cancer-related deaths in the United States (US)². Small cell lung cancer (SCLC) is an aggressive neuroendocrine tumor and accounts for approximately 15% of lung cancers and remains the seventh most common cause of cancer-related death in the US.³

At the time of diagnosis, 30% of patients will have tumors confined to the hemithorax of origin, the mediastinum, or the supraclavicular lymph nodes (limited-stage disease, LS-SCLC), but the majority of patients will have tumors that have spread beyond the supraclavicular areas, with malignant pleural or pericardial effusion or hematogenous metastasis (extensive-stage disease, ES-SCLC)⁴. Regardless of stage at the time of the diagnosis, the current prognosis for patients with ES-SCLC, which includes metastatic disease, is poor.

Patients with ES-SCLC who progress following platinum-based chemotherapy are typically categorized as having either platinum-sensitive or resistant disease. The chemotherapy-free interval (CTFI), defined as the length of time from last platinum dose to time of relapse or disease progression, distinguishes platinum-sensitive patients (progression or recurrence \geq 90 days from last platinum dose) from those who are platinum-resistant (progression or recurrence $<$ 90 days). In SCLC, the likelihood of response in the second-line is highly dependent on the CTFI. Patients who are considered chemotherapy sensitive have an approximately 25% chance of response to subsequent treatment, in contrast to patients without an initial response or those who relapse earlier and have a less than 10% chance of response^{5,6}.

2.2. Analysis of Current Treatment Options

First-Line Treatment for ES-SCLC

Until recently, treatment for newly diagnosed ES-SCLC, including metastatic SCLC, generally consisted of four to six cycles of cisplatin or carboplatin chemotherapy in combination with either etoposide or irinotecan. In 2019, FDA approved atezolizumab in combination with carboplatin and etoposide for the first-line treatment of patients with ES-SCLC⁷. Additionally more recently, FDA approved durvalumab in combination with etoposide and either carboplatin or cisplatin as first-line treatment of patients with ES-SCLC⁸.

For patients with good performance status who achieve a complete response or a very good partial response following initial therapy for ES-SCLC, prophylactic cranial irradiation⁹ and thoracic radiation (in patients with low-bulk metastatic ES-SCLC)¹⁰ have been shown to improve survival in randomized controlled trials.

Second-Line Treatment Options for ES-SCLC

For patients with disease recurrence occurring more than 6 months after completion of platinum-based chemotherapy, re-treatment with a platinum-based combination chemotherapy regimen is recommended^{11, 12, 13}.

For patients with disease progression or recurrence within 6 months following completion of platinum-based chemotherapy, treatment options include single-agent chemotherapy and palliative radiotherapy. Although several chemotherapy agents have been shown to have anti-tumor activity in SCLC, topotecan (oral administration¹⁴ and intravenous administration¹⁵) is the only agent currently approved by the FDA for the treatment of patients with SCLC with disease progression after first-line chemotherapy.

Topotecan administered intravenously is specifically approved for “patients with platinum-sensitive disease who progressed at least 60 days after initiation of first-line chemotherapy”. The approval of topotecan administered intravenously was based on the results of a randomized trial of topotecan compared to combination chemotherapy (CAV) in patients with SCLC who were considered sensitive to first-line chemotherapy (i.e., responders whose disease progressed ≥ 60 days after completion of first-line therapy); and three single-arm trials in patients with recurrent or progressive SCLC after first-line chemotherapy¹⁵. The randomized trial demonstrated similar results for topotecan as a single-agent compared to CAV for median OS, time to progression, overall response rate (ORR) and median duration of response. ORR with topotecan in the randomized trial was 24% (95% CI 16, 32). In the three single-arm trials, ORR ranged from 11% to 31% for patients with platinum-sensitive SCLC (responders whose disease subsequently progressed ≥ 90 days after completion of first-line therapy) and 2% to 7% for patients with platinum-refractory SCLC (no response to first-line chemotherapy or response followed by disease progression within 90 days of completing first-line therapy).

Several chemotherapy agents have been shown to have anti-tumor activity in relapsed SCLC and are used in clinical practice, including paclitaxel¹⁶, docetaxel¹⁷, vinorelbine¹⁸, temozolomide¹⁹ and bendamustine²⁰. ORRs have been reported to range between 10 to 29%.

Table 1 below highlights certain key trials conducted with topotecan, which is the only FDA-approved agent for treatment of patients with SCLC who have progressed after first-line chemotherapy, the indication that is being considered for this application.

Table 1: FDA Approved Second-Line Agents for SCLC

Product Name, Approval Date	Product Indication	Trial Design	Primary Endpoint	Clinical Benefit/Effect
HYCAMTIN (topotecan) for injection NOV-1998	Treatment of patients with platinum-sensitive disease who progressed at least 60 days after initiation of first-line chemotherapy	Randomized, open-label study comparing topotecan and CAV in patients with limited or extensive-stage SCLC who progressed at least 60 days after completion of first-line chemotherapy Three open-label, single-arm studies in patients with recurrent or progressive SCLC after treatment with first-line chemotherapy. Study populations include patients with platinum-sensitive SCLC (responders who subsequently progressed ≥ 90 days after completion of first-line therapy) and platinum-refractory SCLC (no response to first-line chemotherapy or response followed by progression within 90 days of completing first-line therapy).	ORR DOR ORR	Topotecan: 24% (95% CI: 16, 32) CAV: 18% (95% CI: 11, 26) Topotecan: 3.3 mo (95% CI: 3, 4.1) CAV: 3.5 (95% CI: 3, 5.3) Patients with platinum-sensitive disease: 11 – 31% Patients with platinum-refractory disease: 2 – 7%
HYCAMTIN (topotecan) oral capsules NOV-2007	Treatment of patients with relapsed SCLC	Randomized, open-label study comparing oral topotecan with best supportive care (BSC) to BSC alone in patients with relapsed SCLC who were prior responders to first-line chemotherapy	OS	HR 0.64 (95% CI: 0.45, 0.90) Median OS 6.0 mo oral topotecan with BSC vs. 3.2 mo BSC alone

Third-Line and Beyond Treatment Options for Metastatic SCLC

Nivolumab²¹ and pembrolizumab²² have both been granted accelerated approval (AA) by FDA for use as third-line therapy in patients with metastatic SCLC.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Lurbinectedin is currently not approved in any country.

3.2. Summary of Presubmission/Submission Regulatory Activity

The pre-submission key regulatory activity for lurbinectedin pertaining to the NDA is summarized in the following table:

Table 2: Pre-Submission Regulatory Activity Related to Submission

Date	Regulatory Interaction/Milestone
21-NOV-2008	Pre-IND meeting held to discuss the development strategy of PM01183 for the treatment of solid tumors.
15-DEC-2008	New IND (b) (4) submitted for Protocol PM1183-A-001-08, the first-in-human (FIH) study with lurbinectedin entitled, "Phase I, multicenter, open-label, dose-escalating, clinical and pharmacokinetic study of PM01183 in patients with advanced solid tumors." The study was allowed to proceed on 16-JAN-2009.
19-SEP-2013	Type C guidance meeting to discuss starting materials for lurbinectedin production scheduled for 26-SEP-2013. FDA issued preliminary minutes on 19-SEP-2013, which Pharma Mar considered sufficient responses; therefore, the sponsor canceled the meeting.
28-NOV-2014	The protocol and statistical analysis plan (SAP) for the QT study (PM1183-B-00514-QT) were submitted and reviewed by the Agency's QT Interdisciplinary Review Team and feedback was provided on the study design.
09-OCT-2015	New IND 127944 submitted for Protocol PM1183-C-003-14 entitled, "Phase III randomized clinical trial of lurbinectedin (PM00183) plus doxorubicin (DOX) versus topotecan as treatment in patients with small-cell lung cancer (SCLC) who failed one prior platinum-containing line (ATLANTIS trial)." On November 3, 2015, FDA placed this IND on full clinical hold due to the concern that the protocol design does not allow for isolation of the relative contribution of PM01183 when used in combination with doxorubicin and the study would not be able to meet its stated objectives.
03-DEC-2015 28-JAN-2016	In a follow-up teleconference and Type A meeting, FDA recommended an adaptive study design with single-agent doxorubicin and single-agent lurbinectedin arms with the possibility to discontinue arms for futility at interim analysis. This would allow assessment of the contribution of each drug to the regimen. Pharma Mar could also provide clinical and nonclinical data from other studies that could support contribution of the individual components to the Phase 3 study. Upon inquiry from FDA regarding assessing lurbinectedin as a single-agent, the Applicant informed that there is an

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ZEPZELCA (Lurbinectedin)

	ongoing Phase 2 trial with lurbinectedin as a single-agent to assess anti-tumor activity, but there is not enough data to support a lurbinectedin single-agent arm in Phase 3. Regarding single-agent doxorubicin as a control arm, the sponsor stated that in SCLC, investigators do not want to use doxorubicin alone in the setting of platinum failure but are willing to use the CAV regimen.
12-FEB-2016	The Applicant submitted a Response to the Full Clinical Hold letter that included a revised clinical protocol and statistical analysis plan for the ATLANTIS study. To potentially isolate the contribution of lurbinectedin to the combination regimen, Pharma Mar added CAV as an option in the control arm and added choice of treatment (CAV or topotecan) as a stratification factor. A secondary endpoint was also added comparing lurbinectedin plus doxorubicin to the CAV arm, in the CAV stratum to assess the contribution of lurbinectedin to doxorubicin, assuming that lurbinectedin will be more active than cyclophosphamide and vincristine. On 11-MAR-2016, the clinical hold on IND 127944 was removed.
01-AUG-2018	Orphan drug designation was granted to lurbinectedin for the treatment of SCLC.
11-DEC-2018	A Type B, End of Phase 2 meeting was held to discuss results from the SCLC cohort of Study B-005 to support an application for AA of lurbinectedin for the treatment of patients with advanced SCLC with disease progression on or after one prior line of chemotherapy and for the ongoing ATLANTIS trial to serve as the confirmatory study to verify clinical benefit.
10-JUN-2019	Type C, Written Response Only meeting minutes issued to address Pharma Mar regarding data standardization strategy for non-clinical and clinical studies, as well as integrated analyses to be included in the planned NDA submission.
19-JUN-2019	A Type B, pre-NDA, CMC-only meeting was held to reach agreement on key issues relevant to the CMC component of the NDA.
07-AUG-2019	A Type B, pre-NDA meeting was held to discuss the data intended to support the application for lurbinectedin for the proposed indication of the treatment (b) (4) , as well as the filing and format of the planned NDA. The Applicant indicated their plan to submit under accelerated approval regulations with the ongoing ATLANTIS study serving as confirmatory for full approval.
30-SEP-2019	FDA issued Type C, Written Response Only meeting minutes to provide feedback on Pharma Mar's proposed approach to characterize the safety of lurbinectedin in the NDA.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

An OSI audit was conducted for this NDA. See Clinical Inspection Summary by Michele Fedowitz, M.D., Good Clinical Practice Assessment Branch, Division of Clinical Compliance Evaluation, OSI.

The review division (DO2) and OSI selected two investigator sites, the study sponsor, and the contract research organization (CRO) (b) (4) for clinical inspection. Pharma Mar and the CRO responsible for clinical trial monitoring and management of this study were chosen for clinical inspection given this is a new molecular entity application. The two investigators were Dr. Jose Manuel Trigo (Site ES022), who had the highest enrollment and a relatively higher number of treatment responders, and Dr. Sant Chawla (Site US013), who was selected for audit on the basis of having one of the highest ranked domestic sites, which included only two patients.

The inspections of Dr. Trigo and the CRO demonstrated that the Applicant's submitted clinical data were verifiable, with no evidence of underreporting of adverse events or insufficient protection of study subjects. The scheduled inspections of Dr. Chawla and the study sponsor, Pharma Mar Inc., were cancelled because of the COVID-19 pandemic related travel restrictions which significantly limited OSI's ability to conduct onsite Good Clinical Practice (GCP) inspections. Based on the results of the completed inspections, the conduct of this study was adequately monitored, and the clinical data generated from Dr. Trigo's site appear to be reliable in support of this NDA.

4.2. Product Quality

Please see FDA CMC review for further details. Per the CMC review team, recommends approval for this application.

4.3. Clinical Microbiology

Please see FDA product quality microbiology review for further details. The review team recommends approval for this application.

4.4. Devices and Companion Diagnostic Issues

Not applicable (no companion device or diagnostic is included in this application).

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Lurbinectedin is small molecule with an established pharmacological class (EPC) of alkylating drug. It consists of two fused tetrahydroisoquinoline rings linked to an additional tetrahydro- β -carboline ring. The drug binds covalently to the exocyclic amino group of guanines in the minor groove of GC rich DNA sequences. Binding results in adduct formation and bends DNA. The formation of adducts results in eventual double strand breaks, ultimately leading to cell death. The Applicant presented additional data showing an association between lurbinectedin adducts and degradation of phosphorylated RNA polymerase II, leading to decreased transcription. Consistent with its mechanism of action, lurbinectedin had antiproliferative and cytotoxic activity in multiple tumor cell lines with IC_{50} s in the low nanomolar range and this activity was enhanced in cell lines with defects in DNA mismatch repair machinery. Incubation with lurbinectedin also resulted in increased cell death of human monocytes and, at lower concentrations, decreased migration and chemokine production.

In in vivo studies, administration of lurbinectedin to athymic mice implanted with various human tumor cell line inhibited tumor growth in an array of human tumor models including, small cell lung cancer (SCLC). Investigators also showed enhanced anti-tumor activity in an in vivo SCLC implantation model following treatment with the combination of lurbinectedin and doxorubicin compared to either drug alone. In other models, administration of lurbinectedin to mice implanted with several tumor cell lines resulted in reductions in blood and tumor infiltrating macrophages as well.

The Sprague Dawley rat, Beagle dog and Cynomolgus monkey were the main species used for toxicological assessment of lurbinectedin. Despite using dogs in the initial 4-week toxicology studies, the Applicant utilized the monkey in the 13-week non-rodent toxicology study due to metabolic data suggesting that monkey metabolism was more similar to human than other tested non-rodent species. There were no unique human metabolites for lurbinectedin versus animals. Two metabolites, M1 and PM030047, were present in humans at approximately 14% and 10% of the parent exposure, respectively. PM030047 was present in rat, but exposure levels were uncertain. In vivo exposure levels in monkeys appeared to be lower for both metabolites and, as animals tolerated lower lurbinectedin doses than the 3.2 mg/m² human dose, there is not full toxicological coverage of these metabolites; however given that each of these main metabolites represent less than 15% of the parent compound and toxicity profiles in humans are similar to those in animals, the disparity in metabolite exposure does not represent a significant safety concern for the intended patient population. There were no clear acute effects on cardiovascular, CNS, or respiratory parameters in any species.

The major toxicological findings in all three tested species were injection site findings including hemorrhage, edema, inflammation, thrombosis, and necrosis and bone marrow effects leading to transient leukopenia and mild anemia with decreased cellularity in the bone marrow.

Decreases in reticulocytes of at least 90% occurred after dosing at the high dose levels in all 3 species. Gastrointestinal tract toxicity was also common at high dose levels, with soft/liquid feces in all species and vomiting in non-rodent species; transient inappetence and weight loss following dosing also occurred in rats and monkeys. In the 8-cycle study in rats there were also signs of male reproductive toxicity (testicular atrophy and hypospermia) at the high dose of 0.06 mg/kg (0.36 mg/m²; exposure approximately 24 times lower than the human AUC of 551 ng*hr/mL at the 3.2 mg/m² dose). Dogs showed signs of testicular tubular cell degeneration at doses ≥ 0.01 mg/kg (0.2 mg/m²; exposure approximately 90 times lower than the human AUC at the 3.2 mg/m² dose). Finally, in the 4-week rat study, there were signs of liver toxicity at the high dose in both sexes (0.18 mg/kg in males/0.09 mg/kg in females) characterized by large increases in liver enzymes and bilirubin as well as hepatocyte necrosis, hemorrhage and thrombi. Bone marrow suppression, GI, and liver toxicity are common clinical findings as well. The highest doses used in the rat and monkey 8-cycle studies resulted in exposures approximately 8 times lower than the human exposure at the recommended dose of 3.2 mg/m² once every 3 weeks.

Lurbinectedin was negative in the in vitro Ames assay but induced mutations in the mouse TK lymphoma assay, confirming that, as expected based on its mechanism of action, lurbinectedin is genotoxic. Consistent with the principles discussed in the ICH S9 guidance for industry, the Applicant did not conduct fertility or pre- and post-natal development studies to support the the submission of an NDA for a drug intended for the treatment of patients with advanced cancer. Given its mechanism of action as a genotoxic agent targeting rapidly dividing cells, FDA would not generally request an embryofetal development study, however, the Applicant did conduct a preliminary single dose, single-dose level embryo-fetal development study in rats. Six pregnant rats received a single lurbinectedin dose of 0.1 mg/kg (0.6 mg/m²) or vehicle control on Day 10. There were no viable fetuses in lurbinectedin-treated dams. A warning for embryo-fetal toxicity is included in the label and the nonclinical team recommends 6 and 4 months of effective contraception for females and males, respectively, consistent with principles for a genotoxic agent with teratogenic effects as discussed in the FDA Oncology Reproductive Toxicity Testing and Labeling Recommendations guidance and considering the elimination half life of 51 hours. Similarly, while there were no studies investigating the presence of lurbinectedin in breast milk, based on its 51-hour half life, the label includes a recommendation not to breastfeed during treatment with lurbinectedin and for 2 weeks after the final dose. The Applicant did not conduct carcinogenicity studies based on the proposed patient population. Lurbinectedin did not demonstrate the potential for phototoxicity in an in vitro study. The nonclinical studies were sufficient to assess the toxicity of lurbinectedin and there are no outstanding issues from a pharmacology/toxicology perspective that would prevent its approval for the treatment of patients with metastatic SCLC (b) (4)

5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

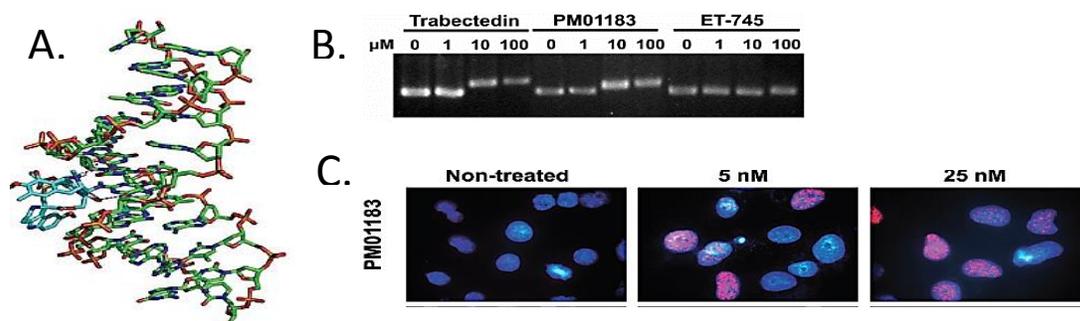
Primary pharmacology

A. In Vitro Studies

The Applicant screened a number of compounds for activity against 36 tumor cell lines and identified PM01183 as a lead compound with high potency over a range of concentrations (average $IC_{50} < 1$ nM)(Study #P62A). PM01183 showed cytotoxic activity against several different leukemia and lymphoma derived cell lines with IC_{50} values in the low nanomolar range (Study #PMAR10-CB017). PM01183 also showed antiproliferative activity against a panel of SCLC cell lines with an average IC_{50} of 0.65 nM compared to an average IC_{50} of 191 nM for doxorubicin in the same panel (Study PHAR19-CB004).

The Applicant submitted several of their own publications exploring the mechanism of action of lurbinectedin (PM01183). Investigators showed that PM01183 and the related compound trabectedin bound stably to DNA as measured by mobility shifts in agarose gels, though a negative control compound, ET-745 did not (Figure 1B) (Leal et.al., 2010). Molecular modeling of lurbinectedin binding showed covalent binding of the drug to central guanines in GC rich DNA sequences. Binding occurred in the minor groove leading to widening of the minor groove and slightly bent DNA (Figure 1A). Consistent with this predicted adduct formation, incubation of A549 tumor cells for 6 hours with increasing concentrations of PM01183 resulted in an increased incidence of cells that stained positive for γ -H2AX, suggesting the presence of DNA double strand breaks (Figure 1C).

Figure 1: Lurbinectedin Binding to DNA



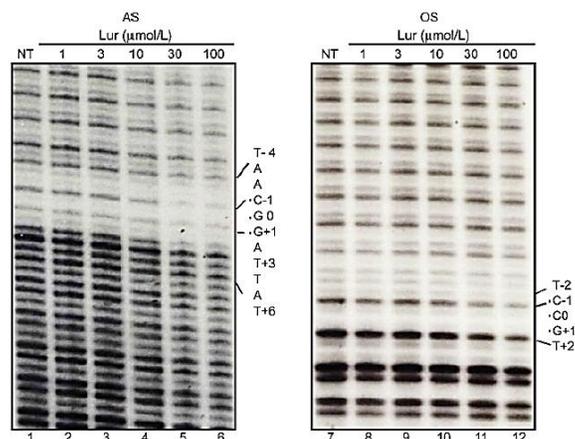
A. Model of lurbinectedin covalent binding to guanine 7 of a model CGG-containing oligonucleotide. B. C. A549 cells were treated with either PM01183 or trabectedin at the indicated concentrations during 6 h, followed by additional 18 h of incubation without the drug. After fixation, cells were immunostained for γ -H2AX and nuclei were visualized with Hoechst 33342.

(Adapted from Leal et al., 2010)

In a second publication, Santamaria Nunez et al (Santamaria Nunez et al. 2016) designed a DNA strand with a single predicted high affinity binding site (CGG triplet) for lurbinectedin then incubated the DNA with the drug for 30 minutes at room temperature before digestion with DNase I for 45 seconds and resolution on an 8% denaturing urea-polyacrylamide gel.

Incubation with lurbinectedin resulted in concentration-dependent protection from digestion around the CGG site in both the target strand (AS) and, to a lesser extent, the opposite strand (OS) (Figure 2). Santamaria Nunez presented additional data suggesting that the lurbinectedin adducts were associated *phosphorylated* RNA polymerase II-dependent double strand breaks and with degradation of phosphorylated RNA polymerase II at active sites of transcription (data not shown).

Figure 2: Lurbinectedin-mediated Protection of DNA from DNaseI Digestion



DNase I footprinting on DNA template containing a unique drug-binding site. The AS/CGG (AS, left part) and OS/CCG (OS, right part) were incubated with increasing Lurbinectedin (Lur) concentrations and treated with DNase I. The positions of the protected nucleotides are indicated (G0 is the guanine that is covalently bound to the drug)

(Taken from Santamari Nunez et al., 2016)

Finally, in Study PMAR10-CB027, the Applicant presented data showing a difference in the sensitivity to PM01183-mediated cytotoxicity of a cell line with DNA mismatch repair defects (HCT-116 line) compared to the same cell line that was DNA mismatch repair proficient (HCT-166Chr3). This data suggests that lurbinectedin may have increased activity in cell lines with defects in DNA mismatch repair machinery.

Table 3: DNA MMR Pathway Status Confers Differences in Lurbinectedin Sensitivity

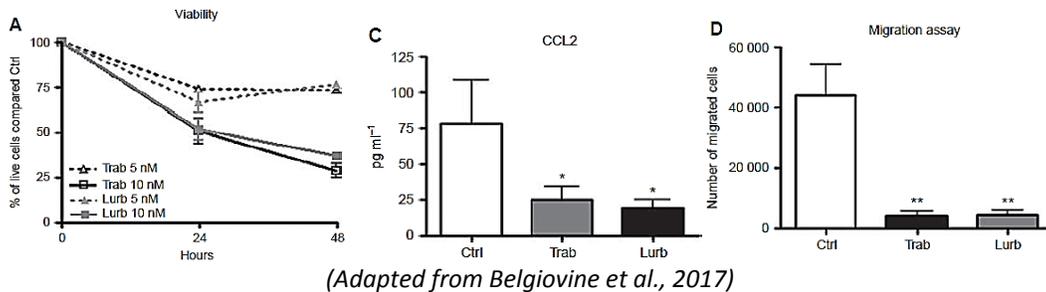
Compound	Cell line	IC50 [M]	St. Dev. [M]	RI (Chr3/wt)
Yondelis	HCT-116	1.20E-08	9.48E-09	1.7
	HCT-116-Chr3	2.04E-08	1.59E-08	
PM01183	HCT-116	4.33E-09	3.46E-09	10.9
	HCT-116-Chr3	4.71E-08	1.21E-08	

(Applicant Figure from Study #PMAR10-CB027)

The Applicant also conducted studies described in Belgiovine et al. 2017, investigating the effects of lurbinectedin on monocytes. Incubation of lurbinectedin with human monocytes resulted in increased apoptosis at concentrations as low as 5 nM (Figure 3); short incubation with the same concentration resulted in decreased chemokine production by LPS-treated

human monocytes with similar findings in a human myxoid liposarcoma cell line (not shown). Trabectedin had similar activity.

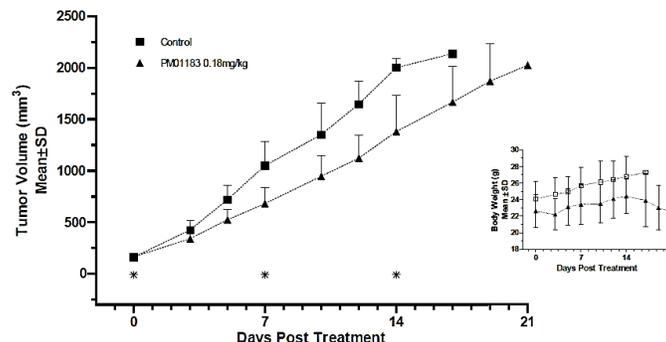
Figure 3: Lurbinectedin Effects on Human Monocytes



B. In Vivo Studies

The Applicant conducted multiple in vivo studies investigating the activity of PM01183 alone or, more frequently, in combination with other cytotoxic or targeted anti-cancer therapeutic using cell lines derived from a wide array of tumor types and demonstrated potential PM01183 activity against multiple cell types. In Study #PMAR19-NC005, investigators subcutaneously implanted female athymic mice (10/group) with small cell lung cancer (SCLC) NCI-H82 or NCI-H526 tumors. After tumors reached a volume of 150 mm³ animals received intravenous administration of PM01183 at a dose of 0.18 mg/kg once a week for 2-3 weeks; treated animals implanted with either cell line showed a reduction in tumor volume compared to placebo-treated animals on Days 4 to 14 of the experiment with little evidence of severe toxicity based on body weight changes (Figure 4).

Figure 4: In vivo Effects of Lurbinectedin on H82 (SCLC) Implanted Tumors



*Dosing days 0, 7 & 14.

(Applicant Figure excerpted from Study #PMAR19-NC005)

In additional in vivo studies using the same SCLC tumor cell lines (PMAR19-NC003 and PMAR-NC004), the Applicant investigated the activity of PM01183 in combination with doxorubicin. Treatment of implanted mice with lurbinectedin at doses ranges from 0.18 mg/kg (MTD) to 0.045 mg/kg or doxorubicin at dose of 8 to 2 mg/kg showed dose-dependent decreases in tumor volume. At the highest doses of both drugs, the combination of lurbinectedin with doxorubicin enhanced this anti-tumor activity compared to either drug alone (Figure 5) and resulted in longer survival times (Table 4).

Figure 5: Enhanced Anti-tumor Activity of Lurbinectedin in Combination with Dox

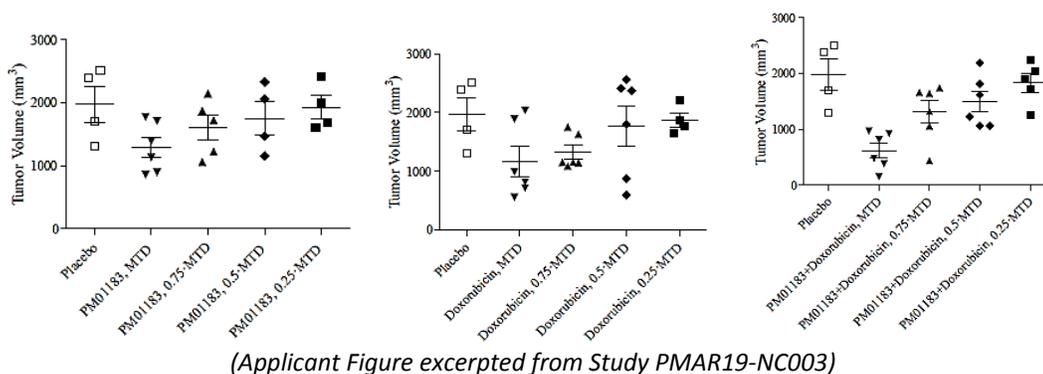


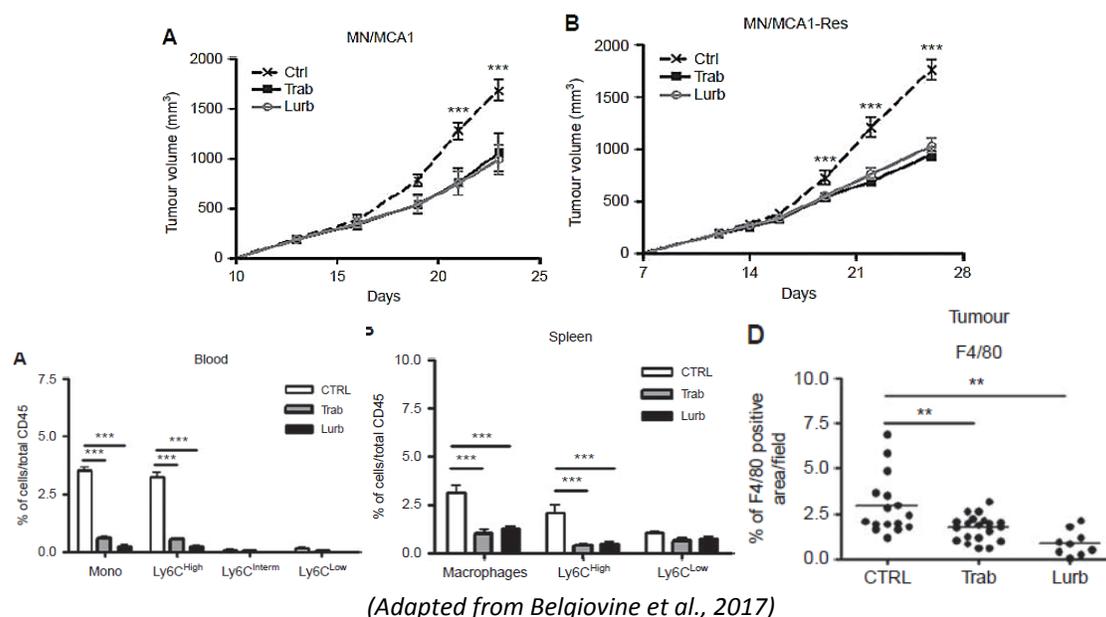
Table 4: Increased Survival in H82 Implanted Mice Administered Lurbinectedin +Dox

Group	Compound	Median survival time (days)
01	Placebo	12
02	PM01183	17
03	Doxorubicin	21
04	PM01183 + Doxorubicin	36.5

(Applicant Table excerpted from Study PMAR19-NC003)

Finally, in Belgiovine et al. 2017, investigators implanted C57BL/6 mice with the wild type or lurbinectedin resistant (based on in vitro data) murine fibrosarcoma cell line MN/MCA1 before initiating treatment with lurbinectedin or trabectedin once weekly for 3 weeks at doses of 0.1 or 0.13 mg/kg (0.2 or 0.15 mg/kg in the resistant model), respectively, once tumors were palpable. Lurbinectedin had similar activity in both models and resulted in decreases in the percentage of monocytes in the blood and macrophages in the spleen as well as reductions in percentage of spleen-derived (F4/80+) macrophages in the tumors (Figure 6).

Figure 6: Lurbinectedin Effects on Monocytes/Macrophages in Tumor-Implanted Mice



Secondary Pharmacology

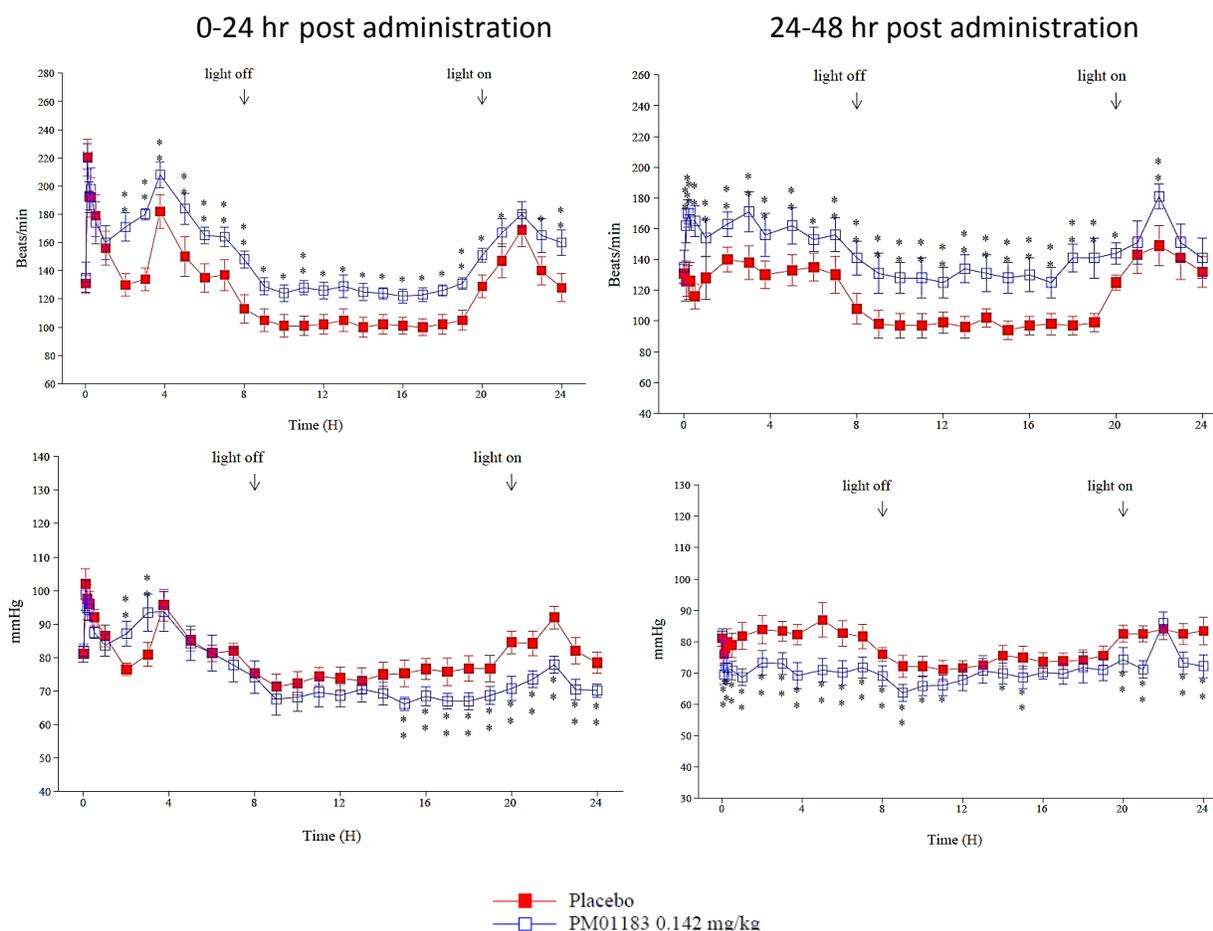
The Applicant conducted a screening assay to investigate off target activity of lurbinectedin against a panel of enzymes and receptors. At a concentration of 200 nM, lurbinectedin showed no significant activity against any tested receptor (Study #FR095-0003616).

Safety Pharmacology

The Applicant assessed the cardiac safety of lurbinectedin using both in vitro and in vivo assays. PM01183 inhibited hERG tail current recorded from stably transfected HEK293 cells in a concentration-dependent manner up to 10 μ M, with estimated IC₂₅ and IC₅₀ values for PM01183 of 3.7 and 8.8 μ M, respectively, indicating a low risk for QTc prolongation by this mechanism at clinically relevant concentrations (Study # ZNA14886.002).

In GLP-compliant study #20160140PCCYP, intravenous administration of PM01183 to conscious cynomolgus monkeys (4 males and 2 females) at a dose of 0.142 mg/kg over 30 seconds induced effects on blood pressure (mean, systolic and diastolic blood pressure) and heart rate (up to ~16% increases associated with changes in autonomic balance, signs of nausea, arrhythmias concomitant with nausea phases (mainly during the first 24 hours post-dosing period), and impairment of the nycthemeral cycle of body temperature during the night period for 48 hours postdosing. Delayed mild decreases in blood pressure and increases in heart rate were long lasting (around 36-46 hours post-dosing).

Figure 7: HR (top) and MAP (bottom) in Monkeys



In a second GLP-compliant in vivo cardiovascular safety study, Study # ZNA14886.005, single dose intravenous administration of 0.03 mg/kg PM01183 caused vomiting in conscious, telemetered Beagle dogs. Administration of 0.003 or 0.01 mg/kg PM01183 had no effect on heart rate, but the high dose of 0.03 mg/kg PM01183 resulted in increased heart rate by approximately $89 \pm 26\%$ compared to approximately $22 \pm 19\%$ with vehicle immediately after dosing. Heart rate returned to pre-dose base values by 30 minutes post-dose. There was no marked effect on arterial blood pressure (systolic, diastolic and mean) following administration of PM01183 at any dose level. While the high dose levels in each species were lower than the 3.2 mg/m^2 clinical dose, these studies do not suggest a clear acute cardiovascular risk with PM01183.

In GLP-compliant Study # ZNA14886.003, the Applicant assessed the potential for acute CNS effects following intravenous administration of PM01183 to rats at doses up to 0.165 mg/kg (males) or 0.081 mg/kg (females). PM01183 did not induce gross behavioral or physiological changes (Irwin test) up to 24 hours post-dose; 2 mg/kg chlorpromazine (positive control) resulted in expected effects.

The Applicant assessed potential respiratory effects of PM01183 in rats (8/sex/group) in GLP-compliant Study #ZNA14886.004 by measuring respiration rate and tidal volume at 15, 60, and 1440 (24 hours) minutes post intravenous dose administration of PM01183 at doses of 0.016 and 0.051 and 0.165 mg/kg (males) or 0.008, 0.025 and 0.081 mg/kg (females). PM01183 did not significantly affect the respiration rate or tidal volume of conscious rats at doses up to 0.081 mg/kg when compared to vehicle treated animals. A small but statistically significant decrease in tidal volume occurred in male rats at the 0.165 mg/kg high dose level only at 24 hours post-dose when compared to vehicle group data. Administration of 10 mg/kg morphine resulted in the expected transitory decreases in both respiration rate and tidal volume, demonstrating the sensitivity of the testing conditions; the morphine-mediated decreases had returned to baseline by 24 hours post-dose.

5.4. ADME/PK

Type of Study	Major Findings																																																														
Absorption																																																															
	N/A; lurbinectedin is an IV drug																																																														
Distribution																																																															
Determination of PM01183 Plasma Protein Binding Properties (PUSA00643)	PM01183 showed similar protein binding (~95%) at 80 and 800 µM concentrations in plasma from mouse, rat, guinea pig, rabbit, dog, and human.																																																														
Determination of In Vitro Blood Cell Partitioning in Rat, Dog, Monkey and Human Blood (VNG3495-2016)	The associations of [¹⁴ C]PM01183 with blood cells were 23.6 to 23.2% in male rats, 29.7 to 29.8% in male monkeys, 26.2 to 25.1% in male dogs and 9.47 to 10.6% in human males at concentrations of 200 and 500 nM respectively. Blood to plasma ratios were 0.773 and 0.775 in the male rat, 0.797 and 0.798 in male monkey, 0.759 and 0.747 in male dog and 0.651 and 0.643 in human males at 200 and 500 nM respectively.																																																														
Tissue Distribution in the Rat Following Single Intravenous Administration (VGN3665-2015)	<p>Mean tissue concentrations of Radioactivity in Male (0.2 mg/kg, i.v.) and female (0.1 mg/kg, i.v.) Sprague-Dawley Rats at 72 Hours Post-dose</p> <table border="1"> <thead> <tr> <th rowspan="2">Tissue</th> <th colspan="3">Male</th> <th colspan="3">Female</th> </tr> <tr> <th>AUC_{0-t} (h·ng-eq/g)</th> <th>C_{max} (ng-eq/g)</th> <th>T_{max} (h)</th> <th>AUC_{0-t} (h·ng-eq/g)</th> <th>C_{max} (ng-eq/g)</th> <th>T_{max} (h)</th> </tr> </thead> <tbody> <tr> <td>Kidney</td> <td>7890</td> <td>698</td> <td>0.25</td> <td>5813</td> <td>342</td> <td>0.25</td> </tr> <tr> <td>Liver</td> <td>13201</td> <td>1111</td> <td>0.25</td> <td>8280</td> <td>531</td> <td>0.25</td> </tr> <tr> <td>Lung</td> <td>9268</td> <td>935</td> <td>0.25</td> <td>7760</td> <td>490</td> <td>0.25</td> </tr> <tr> <td>Lymphnodes</td> <td>11695</td> <td>288</td> <td>2.00</td> <td>9872</td> <td>179</td> <td>8.00</td> </tr> <tr> <td>Small Intestine</td> <td>7177</td> <td>601</td> <td>2.00</td> <td>5819</td> <td>347</td> <td>2.00</td> </tr> <tr> <td>Spleen</td> <td>21072</td> <td>686</td> <td>0.25</td> <td>19226</td> <td>519</td> <td>8.00</td> </tr> <tr> <td>Thyroid</td> <td>9602</td> <td>478</td> <td>0.25</td> <td>7594</td> <td>270</td> <td>0.25</td> </tr> </tbody> </table> <p>Tissue radioactivity exposure, as measured by means of AUC_{0-t}, was comparable between males and females, though females received half the dose administered to males, indicating a possible increased uptake of the [¹⁴C]PM01183-derived total radioactivity in female tissues. The lowest radioactivity concentrations were detected in the brain (<5 and <2.3 ng-eq/g for male and female rats, respectively) and testes (<12 ng-eq/g). The highest values of total activity were in spleen, followed by lymph nodes, liver, thyroid glands, kidney, lung and skin.</p>	Tissue	Male			Female			AUC _{0-t} (h·ng-eq/g)	C _{max} (ng-eq/g)	T _{max} (h)	AUC _{0-t} (h·ng-eq/g)	C _{max} (ng-eq/g)	T _{max} (h)	Kidney	7890	698	0.25	5813	342	0.25	Liver	13201	1111	0.25	8280	531	0.25	Lung	9268	935	0.25	7760	490	0.25	Lymphnodes	11695	288	2.00	9872	179	8.00	Small Intestine	7177	601	2.00	5819	347	2.00	Spleen	21072	686	0.25	19226	519	8.00	Thyroid	9602	478	0.25	7594	270	0.25
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Type of Study	Major Findings																																																																																																																								
Metabolism																																																																																																																									
PMAR14-NC032: The in vitro metabolism of PM00183 in liver microsomes of mouse, rat, dog, NHP (cynomolgus), mini-pig and human	<p>The Applicant measured ¹⁴C-lurbinectedin metabolites in liver microsomes from multiple species in the presence of activation by NADPH. The NHP had a metabolic profile most similar to humans in this in vitro assay. The NHP was, therefore, used as the species for toxicological assessment in the long-term non-rodent toxicology study.</p> <table border="1"> <thead> <tr> <th rowspan="2">Compound</th> <th>Human</th> <th colspan="2">NHP</th> <th colspan="2">Dog</th> <th>Mini-pig</th> <th colspan="2">Rat</th> <th colspan="2">Mouse</th> </tr> <tr> <th>M/F</th> <th>M</th> <th>F</th> <th>M</th> <th>F</th> <th>M</th> <th>M</th> <th>F</th> <th>M</th> <th>F</th> </tr> </thead> <tbody> <tr> <td>¹⁴C-PM01183</td> <td>17.8</td> <td>5.9</td> <td>5.2</td> <td>31.4</td> <td>56.9</td> <td>14.8</td> <td>65.1</td> <td>76.9</td> <td>9.9</td> <td>8.9</td> </tr> <tr> <td>PM030047</td> <td>19.1</td> <td>11.1</td> <td>12.2</td> <td>43.9</td> <td>39.0</td> <td>54.4</td> <td>10.3</td> <td>16.6</td> <td>38.1</td> <td>33.7</td> </tr> <tr> <td>PM01158</td> <td>3.8</td> <td>4.1</td> <td>4.7</td> <td>-</td> <td>-</td> <td>1.0</td> <td>-</td> <td>-</td> <td>1.3</td> <td>0.9</td> </tr> <tr> <td>PM030036</td> <td>8.2</td> <td>4.3</td> <td>4.8</td> <td>-</td> <td>-</td> <td>-</td> <td>-</td> <td>-</td> <td>2.5</td> <td>1.9</td> </tr> <tr> <td>M1</td> <td>16.3</td> <td>28.3</td> <td>25.1</td> <td>1.9</td> <td>-</td> <td>6.8</td> <td>3.3</td> <td>1.9</td> <td>6.9</td> <td>5.3</td> </tr> <tr> <td>M2a^a</td> <td>6.1</td> <td>9.2</td> <td>9.4</td> <td>4.2</td> <td>-</td> <td>10.5</td> <td>4.5</td> <td>-</td> <td>13.5</td> <td>12.7</td> </tr> <tr> <td>M2b^b</td> <td>7.1</td> <td>3.5</td> <td>3.2</td> <td>8.2</td> <td>3.3</td> <td>6.9</td> <td>7.8</td> <td>3.5</td> <td>12.7</td> <td>6.8</td> </tr> <tr> <td>M3^a</td> <td>4.9</td> <td>5.7</td> <td>7.6</td> <td>-</td> <td>-</td> <td>5.3</td> <td>-</td> <td>-</td> <td>2.8</td> <td>2.2</td> </tr> <tr> <td>Total</td> <td>83.3</td> <td>72.1</td> <td>72.2</td> <td>89.6</td> <td>99.2</td> <td>99.8</td> <td>91.0</td> <td>98.8</td> <td>87.9</td> <td>72.3</td> </tr> </tbody> </table>	Compound	Human	NHP		Dog		Mini-pig	Rat		Mouse		M/F	M	F	M	F	M	M	F	M	F	¹⁴ C-PM01183	17.8	5.9	5.2	31.4	56.9	14.8	65.1	76.9	9.9	8.9	PM030047	19.1	11.1	12.2	43.9	39.0	54.4	10.3	16.6	38.1	33.7	PM01158	3.8	4.1	4.7	-	-	1.0	-	-	1.3	0.9	PM030036	8.2	4.3	4.8	-	-	-	-	-	2.5	1.9	M1	16.3	28.3	25.1	1.9	-	6.8	3.3	1.9	6.9	5.3	M2a ^a	6.1	9.2	9.4	4.2	-	10.5	4.5	-	13.5	12.7	M2b ^b	7.1	3.5	3.2	8.2	3.3	6.9	7.8	3.5	12.7	6.8	M3 ^a	4.9	5.7	7.6	-	-	5.3	-	-	2.8	2.2	Total	83.3	72.1	72.2	89.6	99.2	99.8	91.0	98.8	87.9	72.3
Compound	Human		NHP		Dog		Mini-pig	Rat		Mouse																																																																																																															
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PMAR17-NC008; PMAR17-NC018:	<p>In humans, detectable metabolites in plasma at ≥1% were M1 (~14%) and PM030047 (~10%).</p>																																																																																																																								
Determination of PM01183 metabolites (M1, PM01158, and PM030036) following 4/8 cycles of administration by intravenous route to non-human primates	<p>The Applicant measured concentrations of three metabolites of PM01183 (M1, PM01158 and PM030036) in plasma samples after administration of lurbinectedin in both 4 cycle and 8-cycle repeat dose studies. In the 4-week study the Applicant also analyzed levels of PM030047. Similar to findings in humans in whom levels were < 1%, the concentrations of PM01158 and PM030036 were in all samples below the limit of quantification (LOQ 0.1 ng/mL). M1 was present in plasma samples with mean AUC_{0-tlast} percentage of between 2 and 7.5% over the course of 8 cycles. In the 4 cycle studies PM030047 was detectable at AUC levels between 0.4 and 2.3% of parent. Animals tolerated lower doses of lurbinectedin than the 5.4 mg/m² human dose, so there is not full coverage of the main lurbinectedin metabolites in animals. There is, however, partial coverage for each of these metabolites and there are no unique human metabolites.</p>																																																																																																																								

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Type of Study	Major Findings																																																					
Excretion																																																						
[14C] PM01183: Pharmacokinetics and Disposition in the Rat following Single Intravenous Administration (Study Number VPT2836)	<p>The primary route of excretion in Sprague Dawley rats, after IV administration, was via the feces with a mean fecal cumulative excretion of approximately 91% of the administered dose up to 168 h post-dose. Urine represented a very minor route of excretion with a mean cumulative recovery of 3% of the administered dose, excreted within 168 h post-dose. Only 3% and 6% of the radioactivity dose was still present in the carcass of male and female rats, respectively, at 168 h post-dose. At the end of the collection period (168 h post-dose), the mean total recovery of the dosed radioactivity was greater than 98% in both sexes.</p> <p>Pharmacokinetic Parameters of Total Radioactivity in Blood and Plasma Following a Single IV Bolus of [¹⁴C]PM01183 to Male (0.2 mg/kg) and Female (0.1 mg/kg) Rats</p> <table border="1"> <thead> <tr> <th>Matrix</th> <th>Sex</th> <th>T_{max} (h)</th> <th>C_{max} (ng-eq/g)</th> <th>C₀^a (ng-eq/g)</th> <th>AUC_{0-t}^d (h·ng-eq/g)</th> <th>AUC_{0-∞} (h·ng-eq/g)</th> <th>t_{1/2} (h)</th> </tr> </thead> <tbody> <tr> <td rowspan="2">Blood</td> <td>Male</td> <td>0.25</td> <td>64.2</td> <td>94.8</td> <td>340</td> <td>519^b</td> <td>62.46^c</td> </tr> <tr> <td>Female</td> <td>0.25</td> <td>33.0</td> <td>46.1</td> <td>235</td> <td>328^b</td> <td>33.25^c</td> </tr> <tr> <td rowspan="2">Plasma</td> <td>Male</td> <td>0.25</td> <td>66.0</td> <td>101</td> <td>251</td> <td>285</td> <td>27.70</td> </tr> <tr> <td>Female</td> <td>0.25</td> <td>27.9</td> <td>35.7</td> <td>167</td> <td>225^b</td> <td>29.33^c</td> </tr> </tbody> </table> <p>a. C₀ was back-extrapolated from PK elaboration. b. Potentially unreliable estimate since %AUC extrapolated >20%. c. Potentially unreliable estimate since λ period [(λ_{z_upper} - λ_{z_lower})/t_{1/2}] was <2 and/or r₂ was <0.9. d. AUC_{0-t} = area under the plasma concentration-time curve (AUC) from the start of dosing (0) to the last quantifiable time point (t), which was always 72 h post-dose.</p> <p>The primary route of excretion after IV administration of 0.142 mg/kg [14C]-PM01183 to male monkeys was via feces with a mean cumulative excretion (0 to 168 h post dose) of 75.9±0.9% of the administered dose. Urine represented a very minor route of excretion with a mean cumulative excretion of 4.0±1.1% of the dose over the entire collection period. Mean recovery of dose radioactivity in the cage rinse at 168 h post-dose was 2.1±0.6%. At the end of the collection period (168 h post-dose), the mean total radioactivity recovery accounted for 82.0±1.6% of the administered dose.</p> <p>Pharmacokinetics in Blood and Plasma</p> <table border="1"> <thead> <tr> <th>Matrix</th> <th>C_{max} (ng/mL)</th> <th>AUC_{0-inf} (h.ng/mL)</th> <th>T_{1/2} (h)</th> <th>Cl (mL/h/kg)</th> </tr> </thead> <tbody> <tr> <td>Blood</td> <td>156±47.2</td> <td>956±17.2</td> <td>76.93±10.62</td> <td>152±19.0</td> </tr> <tr> <td>Plasma</td> <td>159±45.2</td> <td>888±15.0</td> <td>93.70±2.50</td> <td>163±16.2</td> </tr> </tbody> </table>	Matrix	Sex	T _{max} (h)	C _{max} (ng-eq/g)	C ₀ ^a (ng-eq/g)	AUC _{0-t} ^d (h·ng-eq/g)	AUC _{0-∞} (h·ng-eq/g)	t _{1/2} (h)	Blood	Male	0.25	64.2	94.8	340	519 ^b	62.46 ^c	Female	0.25	33.0	46.1	235	328 ^b	33.25 ^c	Plasma	Male	0.25	66.0	101	251	285	27.70	Female	0.25	27.9	35.7	167	225 ^b	29.33 ^c	Matrix	C _{max} (ng/mL)	AUC _{0-inf} (h.ng/mL)	T _{1/2} (h)	Cl (mL/h/kg)	Blood	156±47.2	956±17.2	76.93±10.62	152±19.0	Plasma	159±45.2	888±15.0	93.70±2.50	163±16.2
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[14C]=PM01183: Pharmacokinetics and Disposition in the Monkey Following Single Intravenous Bolus Administration (Study No. VNG5331)																																																						

5.5. Toxicology

5.5.1. General Toxicology

Study title/ number: Multiple-Cycle Toxicity Study Following 8 Cycles of Administration by Intravenous Route to Rats (With A 3 Week Treatment-Free Period) /

(b) (4) Study No. A2649.

Key Study Findings

- Intravenous administration of PM01183 up to 0.06 mg/kg in males and up to 0.03 mg/kg in female rats every 3 weeks for 8 cycles caused mortalities in a dose unrelated manner.
- Hemopoietic system (bone marrow, spleen and thymus) and injection sites were main targets of toxicity.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: Males – 0.01, 0.03, or 0.06 mg/kg every 3 week for 8 cycles.
Females – 0.005, 0.01, or 0.03 mg/kg every 3 week for 8 cycles.

Route of administration: Intravenous
Formulation/Vehicle: Lactate
Species/Strain: Sprague Dawley SD rats
Number/Sex/Group: Toxicity – 20 animals/group
Toxicokinetics – 12 animals/group

Age: 10-11 week
Satellite groups/ unique design: Toxicokinetic groups
Deviation from study protocol affecting interpretation of results: No

Observations and Results: changes from control

Parameters	Major findings
Mortality	<ul style="list-style-type: none">• Control – 2 males found dead on Days 25 & 130), and one female on Day 67 (attributed to errors with retro-orbital bleeding procedures or water gavage error in one male)

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Parameters	Major findings																																																																																																											
	<ul style="list-style-type: none"> Low dose males (0.01 mg/kg) – one male sacrificed on Day 107 for humane reasons— damaged eyes Mid dose females (0.01 mg/kg) – one female sacrificed on Day 100 for humane reasons-damaged eyes 																																																																																																											
Clinical Signs	Damaged eye, swollen eye and corneal opacity were noted in several control and treated animals (blood samples were taken from retro-orbital sinus under anesthesia). High dose – damaged tail, ulceration and scabs in males and females; the tail vein was the injection site.																																																																																																											
Body Weights	Males at the 0.06 mg/kg dose level showed mild ($\leq 8\%$) body weight loss after each injection beginning Cycle 4 (Day 64) accompanied by transient mild decreases in food consumption																																																																																																											
Ophthalmoscopy	No treatment-related ocular abnormalities in Weeks 21 and 24 of the study.																																																																																																											
Hematology	MD and HD - prolonged reticulocytopenia and leucopenia were observed in both sexes during the dosing period and showed recovery at final sacrifice.																																																																																																											
Clinical Chemistry	Bilirubin and blood urea nitrogen increased, and triglycerides decreased, but changes were minor ($\leq 20\%$). Complete recovery at the end of the study.																																																																																																											
Urinalysis	No relevant changes																																																																																																											
Gross Pathology	Three days after the last treatment – Dark abrasion scabs at the injection site and reduced size of the thymus in high dose males. Three weeks after the last treatment – Treatment related changes were still present at post mortem examination in the injection site of high dose males.																																																																																																											
Organ Weights	High dose- Reduced thymus weight (males) and spleen (females)																																																																																																											
Histopathology Adequate battery: Yes	High dose – hemopoietic system (bone marrow, spleen and thymus), injection site (mild to severe necrosis) and stomach (only in males) at interim sacrifice. Showed recovery at final sacrifice. <table border="1" data-bbox="565 1346 1281 1703"> <thead> <tr> <th rowspan="2">Sex Group</th> <th colspan="4">Males</th> <th colspan="4">Females</th> </tr> <tr> <th>1</th> <th>2</th> <th>3</th> <th>4</th> <th>1</th> <th>2</th> <th>3</th> <th>4</th> </tr> </thead> <tbody> <tr> <td>Bone marrow, decreased hematopoietic cells</td> <td>0</td> <td>0</td> <td>0</td> <td>10</td> <td>0</td> <td>0</td> <td>0</td> <td>10</td> </tr> <tr> <td>Epididymides, hypospermia</td> <td>0</td> <td>0</td> <td>0</td> <td>1</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Kidney, nephropathy</td> <td>0</td> <td>0</td> <td>0</td> <td>0</td> <td>3</td> <td>0</td> <td>0</td> <td>7</td> </tr> <tr> <td>Prostate gland, inflammatory cell foci</td> <td>0</td> <td>0</td> <td>0</td> <td>2</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Spleen, lymphoid depletion</td> <td>0</td> <td>0</td> <td>0</td> <td>5</td> <td>0</td> <td>0</td> <td>0</td> <td>6</td> </tr> <tr> <td>pigmentation</td> <td>1</td> <td>0</td> <td>0</td> <td>5</td> <td>6</td> <td>0</td> <td>5</td> <td>7</td> </tr> <tr> <td>Stomach, epithelial hyperplasia</td> <td>0</td> <td>0</td> <td>0</td> <td>5</td> <td>0</td> <td>0</td> <td>0</td> <td>0</td> </tr> <tr> <td>Testes, atrophy</td> <td>0</td> <td>0</td> <td>0</td> <td>1</td> <td>-</td> <td>-</td> <td>-</td> <td>-</td> </tr> <tr> <td>Thymus, lymphoid depletion</td> <td>3</td> <td>5</td> <td>8</td> <td>9</td> <td>0</td> <td>0</td> <td>0</td> <td>0</td> </tr> <tr> <td>Tail necrosis</td> <td>0</td> <td>0</td> <td>0</td> <td>5</td> <td>0</td> <td>0</td> <td>0</td> <td>5</td> </tr> </tbody> </table>	Sex Group	Males				Females				1	2	3	4	1	2	3	4	Bone marrow, decreased hematopoietic cells	0	0	0	10	0	0	0	10	Epididymides, hypospermia	0	0	0	1					Kidney, nephropathy	0	0	0	0	3	0	0	7	Prostate gland, inflammatory cell foci	0	0	0	2					Spleen, lymphoid depletion	0	0	0	5	0	0	0	6	pigmentation	1	0	0	5	6	0	5	7	Stomach, epithelial hyperplasia	0	0	0	5	0	0	0	0	Testes, atrophy	0	0	0	1	-	-	-	-	Thymus, lymphoid depletion	3	5	8	9	0	0	0	0	Tail necrosis	0	0	0	5	0	0	0	5
Sex Group	Males				Females																																																																																																							
	1	2	3	4	1	2	3	4																																																																																																				
Bone marrow, decreased hematopoietic cells	0	0	0	10	0	0	0	10																																																																																																				
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Spleen, lymphoid depletion	0	0	0	5	0	0	0	6																																																																																																				
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Toxicokinetics	There were no gender differences in terms of Cmax and exposure after dose normalization and no accumulation after repeated administrations.																																																																																																											

Parameters	Major findings			
	Males			
	Day 1	C _{max}	AUC _{0-inf}	t _{1/2}
	mg/kg	(ng/mL)	(ng/mL*h)	(h)
	0.01	1.84	2.07	0.95
	0.03	7.61	11.23	2.31
	0.06	12.85	18.86	1.97
	Day 148			
	0.01	2.21	3.09	1.05
	0.03	8.45	13.03	2.81
	0.06	17.11	23.01	2.35
	Females			
	Day 1	C _{max}	AUC _{0-inf}	t _{1/2}
	mg/kg	(ng/mL)	(ng/mL*h)	(h)
	0.005	0.70	0.95	0.70
	0.01	1.85	2.89	1.25
	0.03	5.18	10.14	1.83
	Day 148			
	0.005	1.59	1.35	0.40
	0.01	2.15	2.95	1.08
	0.03	7.12	10.94	2.07

**Study title/ number: 8-Cycle Intravenous Toxicity Study in Cynomolgus Monkeys
Followed by A 3 Week Treatment Free Period. (b) (4) Study
Number A2596.**

- Intravenous administration of PM01183 at the dose of 0.125 mg/kg every 3 weeks for 8-cycles was not tolerated by Cynomolgus monkeys
- Bone marrow and thymus were the target organs of toxicity of PM01183.
- There was no accumulation on Days 64 and 148 compared with Day 1

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 0.083, 0.104, or 0.125 mg/kg/dose, every 3 weeks for 8 cycles

Route of administration: Bolus intravenous

Formulation/Vehicle: Lactate

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Species/Strain: Cynomolgus monkey (Macaca fascicularis)
 Number/Sex/Group: 6/sex/group (4 main, 2 for recovery)
 Age: 28 to 37 months
 Satellite groups/ unique design: None
 Deviation from study protocol affecting interpretation of results: No

Observations and Results: changes from control

Parameters	Major findings
Mortality	<p>Low dose (0.083 mg/kg) – one male sacrificed for humane reasons on Day 17 High dose (0.125 mg/kg) – 2 females sacrificed for humane reasons on Day 56 & 98</p> <p>All early death animals had poor clinical condition. The females at the high dose had clear bone marrow hypocellularity and myelosuppression with bleeding/clotting as well as GI toxicity and blackened injection sites.</p> <p>Low and high dosed animals sacrificed – liquid feces, reduced body weight and food consumption, tremors, emesis, leukocytosis, (neutrophilia), anemia, increased creatinine and urea glucose, lymphoid depletion, tubular dilation in the kidney cardiomyocyte necrosis/degeneration in the heart, hypocellularity in the bone marrow</p>
Clinical Signs	Scheduled sacrifice animals - Dose-related increases in swelling/scabbing/wounds at treatment sites; liquid feces and occasional emesis at all dose levels; increased alopecia at the high dose
Body Weights	Slight reduction (~ 9%) in treated females after dosing days. Body weights returned to values similar to pre-dose within 21 days during each cycle. No noticeable changes in food uptake in treated males.
Ophthalmoscopy	No treatment-related effects
ECG	No treatment-related effect on electrocardiographic findings

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ZEPZELCA (Lurbinectedin)

Parameters	Major findings
Hematology	Leukopenia and slight to moderate anemia 7 days after each cycle and subsequent recovery 21 days after each cycle Dose-dependent decreases in reticulocytes (up to 90% at the high dose) during the first 7 days after dosing followed by increases compared to control during each dosing cycle
Clinical Chemistry	No effect
Urinalysis	No change of toxicological importance
Gross Pathology	High dose males – reduced size of the thymus
Organ Weights	High dose females – decreased spleen and thymus weights (~50% reduction in absolute weight) on Day 154 (7 days after last cycle of treatment)
Histopathology Adequate battery: Yes	Day 154 (7 days after last cycle of treatment) – Treatment related changes in the hematopoietic system (bone marrow atrophy and lymphoid depletion in the thymus) and in the injection site were seen in mid- and high dose animals. Day 169 (21 days after the last cycle of treatment) – treatment related changes in the hematopoietic system (bone marrow, thymus) and in the injection site were reversible or were undergoing reversal.
Toxicokinetics	There were no gender differences in terms of C _{max} and exposure. Exposures were overlapping and low dose multiples make dose proportionality uncertain; there was no evidence of accumulation using the once every 3-week cycle.

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213702
ZEPZELCA (Lurbinectedin)

Parameters		Major findings				
Toxicokinetics on Day 1						
Group/sex	C _{max} (ng/mL) Mean±SD	AUC _(0-tlast) (ng/mL*h) Mean±SD	AUC _(0-inf) (ng/mL*h) Mean±SD	Vz (L/kg) Mean±SD	Cl (L/h/kg) Mean±SD	t _{1/2} (h) Mean±SD
2/M	36.2±12.0	47.5±10.8	53.1±10.3	23.3±7.5	1.6±0.3	9.9±2.2
3/M	36.7±13.1	50.7±9.0	55.5±9.3	24.7±5.6	1.9±0.3	8.9±0.9
4/M	41.5±23.5	63.2±20.4	69.5±22.6	24.7±5.6	1.9±0.5	8.9±0.7
2/F	32.4±18.0	47.3±17.9	51.3±19.1	22.1±7.8	1.8±0.6	8.5±0.5
3/F	57.0±16.3	72.8±13.5	80.3±16.0	17.9±2.1	1.3±0.2	9.4±0.9
4/F	31.8±13.7	52.5±10.0	52.8±2.3	26.0±4.4	2.3±0.3	8.0±0.6
Toxicokinetics on Day 148						
Group/sex	C _{max} (ng/mL) Mean ± SD	AUC _(0-tlast) (ng/mL*h) Mean ± SD	AUC _(0-inf) (ng/mL*h) Mean ± SD	Vz (L/kg) Mean ± SD	Cl (L/h/kg) Mean ± SD	t _{1/2} (h) Mean ± SD
2M	25.5±7.3	38.3±4.3	42.3±4.0	25.0±4.9	2.0±0.2	8.7±1.3
3M	27.4±10.0	42.7±8.8	48.5±11.7	29.2±6.1	2.2±0.5	9.2±1.8
4M	38.9±16.4	60.9±21.1	66.1±23.1	22.6±5.6	2.1±0.7	7.8±1.3
2F	28.5±7.9	38.1±9.6	42.3±10.3	27.7±7.2	2.1±0.5	9.3±1.3
3F	59.8±28.5	66.6±21.7	72.7±24.1	20.1±5.8	1.6±0.5	9.0±0.7
4F	33.2±12.7	53.7±8.7	59.3±9.4	27.1±5.7	2.2±0.4	8.8±1.2

(Applicant Figure reproduced from Study A2596)

General toxicology; additional studies

The Applicant also conducted 4-cycle (dosing once every 3 week) toxicology studies with 3-week recovery periods in rats and dogs. These studies were submitted to FDA and reviewed by Dr. Brenda J. Gehrke under the original IND to support clinical dosing. The higher lurbinectedin doses in the 4-week studies were still below the 3.2 mg/m² clinical dose. In rats, the mid dose levels from the 4-week study (and 0.03 mg/kg in females) were the same as the high dose levels in the 8-cycle study, and findings were similar between studies. At the high dose level in the rat study additional findings included mild platelet decreases and significant liver toxicity with large increases in liver enzymes (2-17x) and bilirubin (140%) as well as hepatocyte necrosis and hemorrhage. The GI tract was also a clearer target at the 0.18/0.09 (M/F) high dose with mucosal atrophy in duodenum, jejunum, and cecum. Findings were reversible.

In the 4-week dog study, overall target organs were similar to those in rats including mild transient leukopenia and anemia at the high dose (0.03 mg/kg or 0.6 mg/m²), mild liver findings (primarily increased liver weights of ≤34%, that occurred in low and high dose groups), clinical observations of GI toxicity (inappetence, liquid feces, emesis), and injection site findings.

Study title/ number: Multiple-Cycle Toxicity Study Following 4 Cycles of Administration by Intravenous Route to Rats (With A 3 Week Treatment-Free Period) / (b) (4) Study no.: 72730.

Reviewed by Dr. Brenda J. Gehrke, IND (b) (4).

Study Title	Experimental conditions	Results
4 Cycle toxicity	• Dosing: Once every 3 weeks	• Mortality: Two males treated with the low dose (0.12 mg/m ²) died due to causes that were

Study Title	Experimental conditions	Results
study in rats Study #: (b) (4) 72730	for 4 cycles • Doses: Males: 0.02, 0.06, and 0.18 mg/kg (0.12, 0.36, and 1.08 mg/m ²) Females: 0.01, 0.03, and 0.09 mg/kg (0.06, 0.18, and 0.54 mg/m ²) • Route: IV bolus	not test-article related. One died from apparent complications of blood collection, possibly an accident, and the other died due to a urinary tract infection. Two males treated with the high dose (1.08 mg/m ²) were found dead during the study. Additionally, two high dose females (0.54 mg/m ²) were euthanized and one high dose female died. • Hematology changes included decreases in reticulocytes, platelets, and WBC parameters. • Clinical chemistry changes included increases in liver enzymes (AST, ALT, and GDH) and bilirubin. • Target organs of toxicity: Liver, bone marrow, GI-tract, injection site, spleen, and thymus • Increased liver enzymes following the recovery period indicated liver toxicity was not fully recovered following the 3-week recovery period, especially in females.

Study title/ number: Multiple-Cycle Toxicity Study Following 4 Cycles of Administration by Intravenous Route to Dogs (With A 3 Week Treatment-Free Period) / (b) (4) Study no.: 73520.
Reviewed by Dr. Brenda J. Gehrke, IND (b) (4).

Study Title	Experimental conditions	Results
4 Cycle toxicity study in dogs Study #: (b) (4) 73520	• Dosing: Once every 3 weeks for 4 cycles • Doses: 0.003, 0.01, and 0.03 mg/kg (0.06, 0.2, and 0.6 mg/m ²) • Route: IV bolus	• Hematology changes included decreases in reticulocytes, and WBC parameters • Target organs of toxicity: Liver, injection site, heart, GI-tract, kidneys, and testes • While most toxicities were recoverable, histopathology findings in the liver and injection site were not fully recovered following the 3-week recovery period.

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/ number: Bacterial Mutation Assay (*S. typhimurium* and *E. coli*) / (b) (4) Study Number 73030

Key Study Findings:

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- PM01183 did not induce reverse mutations in Salmonella typhimurium or Escherichia coli in the presence or absence of S9 metabolism.

GLP compliance: Yes

Test system: Ames test

Study is valid: Yes, PM01183 did not induce two-fold increase in the number of revertant colonies at any dose level, in any tester strain (TA1535, TA1537, TA98, TA100 and WP2uvrA) in the absence or presence of S9 metabolism.

In Vitro Assays in Mammalian Cells

Study title/ number: Mutation in L5178Y TK+/- Mouse Lymphoma Cells (Fluctuation Method) / (b) (4) Study Number 73040.

Key Study Findings:

- PM01183 induced mutation in mouse lymphoma L5178Y cells after in vitro treatment in the presence and absence of S9 metabolic activation.

GLP compliance: Yes

Test system: Mouse lymphoma L5178Y cells in the presence and absence of S9 metabolic activation using a fluctuation method.

Study is valid: Yes, all acceptance criteria were met.

A significant dose-relationship was indicated by the linear trend analysis and statistically significant increase in mutation frequencies were observed in the presence and absence of S9 metabolic activation.

Table 5: Mouse Lymphoma TK Mutation after 3-hour incubation in the absence (top) or presence (bottom) of S9

Dose level (ng/ml)	RS	RTG	MF §	P	IMF §	Proportion small colony mutants	Precipitation
0.00	100%	100%	51.3	-	-	0.51	-
0.00293	120%	103%	58.3	\$	6.98	-	-
0.00586	131%	103%	64.5	NS	13.18	-	-
0.0117	158%	104%	72.7	NS	21.31	-	-
0.0234	143%	95%	89.3	NS	37.92	-	-
0.0469	130%	101%	106.8	**	55.49	-	-
0.0938	129%	90%	121.6	**	70.22	-	-
0.188	109%	105%	209.8	**	158.4@	0.53	-
0.375	94%	63%	791.4	**	740.1@	0.52	-
0.750	43%	35%	1299.5	**	1248.2@	0.50	-
1.50	18%	7%	2840.9	**	2789.6@	0.66	-
MMS 10.0 ug/ml	142%	85%	255.1	-	203.7@	0.56	-
Linear trend				***			

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ZEPZELCA (Lurbinectedin)

Dose level (ng/ml)	RS	RTG	MF §	P	IMF §	Proportion small colony mutans	Precipitation
0.00	100%	100%	66.1	-	-	0.27	-
0.0234	101%	99%	66.5	\$	0.35	-	-
0.0469	103%	97%	75.2	NS	9.03	-	-
0.0938	110%	111%	75.0	NS	8.89	-	-
0.188	121%	131%	72.8	NS	6.64	-	-
0.375	110%	110%	83.4	NS	17.22	-	-
0.750	94%	101%	111.3	NS	45.19	-	-
1.50	86%	93%	217.4	**	151.3@	0.46	-
3.00	74%	75%	628.8	**	562.7@	0.51	-
6.00	42%	37%	1428.7	**	1362.5@	0.64	-
9.00	14%	13%	1789.7	**	1723.5@	0.60	-
B(a)P 2.00 $\mu\text{g/ml}$	12%	11%	896.0	-	829.9@	0.59	-
Linear trend				***			

§ = per 10⁶ viable cells
 NS = Not statistically significant
 * = Statistically significant at p < 5 %
 ** = Statistically significant at p < 1%
 *** = Statistically significant at p < 0.1%
 \$ = Treatment excluded from test statistics
 @ = Induced mutant frequency (IMF) > global evaluation factor (GEF = 126 x 10⁻⁶)

(Applicant Tables excerpted from Study #73040)

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

No studies were submitted. Because lurbinectedin was positive in the in vitro mouse TK lymphoma assay and based on its mechanism of action as an agent that alkylates DNA and causes double strand breaks, no additional in vivo studies are necessary to assess the potential for lurbinectedin to cause genotoxicity.

Other Genetic Toxicity Studies: None submitted

5.5.3. **Carcinogenicity**

None submitted or required for the proposed indication.

5.5.4. **Reproductive and Developmental Toxicology**

Fertility and Early Embryonic Development

Not submitted or required to support the treatment of patients with advanced cancer.

Embryo-Fetal Development

**Study title/ number: Investigative Intravenous Embryo-Fetal Development Study in Rats / (b) (4)
 STUDY Number X0880**

Key Study Findings

- Intravenous administration of PM01183 at 0.1 mg/kg on Day 10 post coitum induced maternal toxicity in SD rats.
- No viable fetuses in females treated with PM01183 (100% embryotoxicity/fetotoxicity).

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213702
ZEPZELCA (Lurbinectedin)

Conducting laboratory and location: [redacted] (b) (4)
[redacted]
[redacted]

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0.1 mg/kg, single dose
Route of administration: Intravenous
Formulation/Vehicle: Lactate, (b) (4) number 14938
Species/Strain: Sprague Dawley rat
Number/Sex/Group: 6 females
Satellite groups: None
Study design: Animals were administered PM01183 or placebo on Day 10 and sacrificed on Day 20 post coitum.
Deviation from study protocol affecting interpretation of results: No

Observations and Results

Parameters	Major findings																																																										
Mortality	None in both groups {control (1) & test (2)}.																																																										
Clinical Signs	Piloerection in PM01183 treated animals (five out of six females between Days 12 and 15)																																																										
Body Weights	<p>Test animals - Severe reductions in body weight (18 to 32%)</p> <table border="1"> <thead> <tr> <th rowspan="2">Group</th> <th rowspan="2"></th> <th colspan="6">Day of Phase</th> </tr> <tr> <th>0!</th> <th>6"</th> <th>10^</th> <th>14</th> <th>18</th> <th>20</th> </tr> </thead> <tbody> <tr> <td rowspan="3">1</td> <td>Mean</td> <td>226.20</td> <td>250.97</td> <td>270.99</td> <td>290.36</td> <td>339.42</td> <td>375.40</td> </tr> <tr> <td>SD</td> <td>12.40</td> <td>17.76</td> <td>16.53</td> <td>16.06</td> <td>20.96</td> <td>25.77</td> </tr> <tr> <td>N</td> <td>6</td> <td>6</td> <td>6</td> <td>6</td> <td>6</td> <td>6</td> </tr> <tr> <td rowspan="3">2</td> <td>Mean</td> <td>224.55</td> <td>246.00</td> <td>261.34</td> <td>239.21**</td> <td>256.63**</td> <td>255.54**</td> </tr> <tr> <td>SD</td> <td>8.10</td> <td>11.51</td> <td>12.32</td> <td>20.88</td> <td>24.60</td> <td>31.74</td> </tr> <tr> <td>N</td> <td>6</td> <td>6</td> <td>6</td> <td>6</td> <td>6</td> <td>6</td> </tr> </tbody> </table> <p>Note: ! = Gestation phase; " = Dosing/Gestation phase * = mean value of group is significantly different from control at p < 0.05 ** = mean value of group is significantly different from control at p < 0.01 Statistical analysis: Dunnett's test if group variances are homogeneous Modified t test if group variances are inhomogeneous (\$) ^ = Day of dosing</p>	Group		Day of Phase						0!	6"	10^	14	18	20	1	Mean	226.20	250.97	270.99	290.36	339.42	375.40	SD	12.40	17.76	16.53	16.06	20.96	25.77	N	6	6	6	6	6	6	2	Mean	224.55	246.00	261.34	239.21**	256.63**	255.54**	SD	8.10	11.51	12.32	20.88	24.60	31.74	N	6	6	6	6	6	6
Group				Day of Phase																																																							
		0!	6"	10^	14	18	20																																																				
1	Mean	226.20	250.97	270.99	290.36	339.42	375.40																																																				
	SD	12.40	17.76	16.53	16.06	20.96	25.77																																																				
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	SD	8.10	11.51	12.32	20.88	24.60	31.74																																																				
	N	6	6	6	6	6	6																																																				
Necropsy findings Cesarean Section Data	All females were pregnant at necropsy. Control: Live fetuses Test: No viable fetuses (100% post-implantation loss)																																																										
Necropsy findings Offspring [malformations, variations, etc.]	Control: No abnormalities in fetuses detected Test: No viable fetuses (100% post-implantation loss)																																																										

LD: low dose; MD: mid dose; HD: high dose

Prenatal and Postnatal Development

Not submitted or required to support the treatment of patients with advanced cancer.

5.5.5. **Other Toxicology Studies**

Study title/ number: Single Dose Intravenous and Paravenous Tolerance Study in Rabbits / (b) (4) Study no.: 73760

- Single intravenous administration of 0.5 mL lurbinectedin at concentrations of 3 and 30 µg/mL did not cause toxicity in New Zealand White rabbits.
- Diffuse edema associated with acute inflammatory reaction and necrosis were observed when PM01183 was injected at the same dose volume and concentrations by the paravenous route.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 1.5 and 15 µg/animal, single dose
Route of administration: Intravenous and paravenous
Species/Strain: New Zealand White rabbits (Hsdif:NZW)
Number/Sex/Group: 3 male rabbits
Age: 11-13-11 weeks
Satellite groups/ unique design: No
Deviation from study protocol affecting interpretation of results: No

Observations and Results: changes from control

Parameters	Major findings
Mortality	None
Clinical Signs	Intravenous treatment – Control – very slight erythema in 2 animals 3 µg/mL – very slight erythema in 2 animals 30 µg/mL – very slight erythema in one animal Paravenous treatment – Control – very slight/well defined erythema in 2 animals. Complete recovery at 72 hours observation

Parameters	Major findings
	<p>3 µg/mL – Very slight erythema in 3 animals and edema in one animal on Day 1. Well defined erythema and very slight edema were seen in 3 animals at 72 hours post dose.</p> <p>30 µg/mL - Very slight erythema in 3 animals and edema in one animal on Day 1. Moderate to severe erythema and severe edema were seen at 48- and 72-hour examination.</p>
Body Weights	No effect
Gross Pathology	Paravenous treatment – increased incidence of dark coloration as compared to control and intravenous animals.
Organ Weights	
Histopathology	Histopathological examination was restricted to the left and right ears. Diffuse edema associated with acute inflammatory reaction and necrosis were seen in animals receiving PM01183 at the low and high dosage by paravenous administration

Study title/ number: Balb/C 3T3 Cell Phototoxicity Assay (Neutral Red Uptake) / (b) (4)
Study Number: 97070

- The IC₅₀ values in the presence and absence of UVA light were 20.6 and 20.3 ng/mL, respectively, with Photo Irritation Factor (PIF) 0.983.
- The positive control Chlorpromazine induced an acceptable positive response with a PIF of 31.9.
- PM01183 did not show any phototoxicity (PIF <2).

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Balb/c 3T3 cells were treated with increasing concentrations of test compound and positive control in the absence and present of UV irradiation. Neutral red uptake was measured by a spectrophotometer (530 nm).

Compound (concentration tested)	IC50 (ng/mL)		PIF
	-UVA	+UVA	
PM01183 (2.5, 5.0, 10, 20, 40, 80, 160,320 ng/mL)	20.3	20.6	0.983
Chlorpromazine	9.98	0.316	31.9

IC50 – Median inhibitory dose

PIF – Photo irritation factor

X Anwar Goheer
Primary Reviewer

X Whitney Helms
Team Leader

6 Clinical Pharmacology

6.1. Executive Summary

Lurbinectedin is an inhibitor of oncologic transcription, and the proposed indication is the treatment of adult patients with metastatic small cell lung cancer (SCLC) with disease progression after platinum-based chemotherapy. The proposed dosing regimen is 3.2 mg/m² administered every 3 weeks (Q3W) as a 60-minute IV infusion.

The primary evidence of efficacy at the proposed dosage regimen was obtained from the single-arm trial B-005 that included 105 patients with SCLC. The objective response rate (ORR) (95% CI) in the overall population (sensitive and resistant disease combined) was 35% (95% CI: 26%; 45%) with a median duration of response (mDoR) of 5.3 months. The most frequent Grade 3/4 adverse events (AEs) included neutropenia (46%) and thrombocytopenia (7%). Of note, sequential dose reductions to 2.6 mg/m² then 2.0 mg/m² were allowed based on neutrophil and platelet counts.

The clinical pharmacology characteristics of lurbinectedin were studied in the first-in-human study (A-001), mass balance study (A-005), safety and efficacy study supporting the proposed indication (B-005), and supportive study in patients with ovarian cancer (C-004). Population pharmacokinetics (PK) analysis was conducted to identify the effect of intrinsic factors (age, body weight, sex, renal function, and hepatic function) and extrinsic factors (concomitant medications) on the PK of lurbinectedin. Exposure-response analyses for safety and efficacy to support the proposed dosage regimen as well as the potential for lurbinectedin to prolong the QTc interval were also included in this NDA submission.

Lurbinectedin is metabolized by CYP3A4. No dedicated clinical drug-interaction studies with modulators of CYP3A4 were conducted. The coadministration of drugs that are known to be strong or moderate CYP3A4 inhibitors and strong or moderate CYP3A4 inducers with lurbinectedin should be avoided. If the coadministration of moderate CYP3A4 inhibitors cannot be avoided, dose reductions should be implemented based on adverse events (neutropenia, thrombocytopenia, and hepatotoxicity) as clinically indicated. This recommendation is supported by the safety analysis of 39 patients who received concomitant medications that are known to be moderate CYP3A4 inhibitors which suggested similar frequency and severity of AEs in comparison to the overall patient population.

Mass balance study with radioactive lurbinectedin demonstrated that lurbinectedin is primarily eliminated in the feces (89% of radioactivity), mainly as metabolites. Population PK analysis did not identify a clinically meaningful change in lurbinectedin exposure in patients with mild hepatic impairment (total bilirubin > 1.0 x ULN to 1.5 x ULN) compared to patients with normal liver function, and no dose adjustment is necessary for this population. The effects of moderate or severe hepatic impairment on lurbinectedin exposure have not been studied and no dosing

recommendation can be made; a post-marketing requirement (PMR) is to be issued to characterize the PK of lurbinectedin in patients with varying degrees of hepatic impairment.

Renal excretion represents 6% of lurbinectedin elimination (1% as unchanged lurbinectedin). Population PK analysis did not identify a clinically meaningful difference in lurbinectedin exposure in patients with mild or moderate renal impairment compared to patients with normal renal function. The effects of severe renal impairment on lurbinectedin exposure have not been studied. No dose adjustment based on renal function is recommended.

The exposure-response analyses identified a positive relationship for efficacy with higher probability of ORR at higher lurbinectedin exposure. Similarly, the higher exposure correlated with higher probability of AEs (Grade 4 neutropenia and Grade 3/4 thrombocytopenia). Clinical utility index (CUI), which compared the probability of achieving response relative to the probability of AEs, indicated that the proposed dosing regimen of 3.2 mg/m² Q3W achieves an acceptable balance of safety and efficacy.

Recommendations

The Office of Clinical Pharmacology recommends the approval of NDA 213702 from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The primary evidence of effectiveness was obtained from study B-005. The ORR was 35% (95% CI: 26%; 45%) with a mDoR of 5.3 months (4.1; 6.4) in patients with SCLC who progressed after prior platinum containing chemotherapy.
General dosing instructions	3.2 mg/m ² as a 60-minute IV infusion Q3W. Sequential dose reductions to 2.6 mg/m ² then 2.0 mg/m ² are allowed based on adverse reactions (neutropenia, thrombocytopenia, and hepatotoxicity).
Dosing patient subgroups (intrinsic and extrinsic factors)	<ul style="list-style-type: none">• No dose adjustment is recommended for patients with mild hepatic impairment. The effect of moderate or severe hepatic impairment on lurbinectedin exposure has not been studied. A PMR is to be issued for conducting a study in patients with varying degrees of hepatic impairment to determine appropriate starting doses for these specific populations.• No dose adjustment is recommended for patients with renal impairment as renal excretion of lurbinectedin is negligible.• The coadministration of drugs that are known to be strong or moderate CYP3A4 inhibitors should be avoided. If coadministration of moderate CYP3A4 inhibitors cannot be

	<p>avoided, dose reductions may be implemented as clinically indicated. A</p> <ul style="list-style-type: none"> • is to be issued to characterize the effect of concomitant administration of itroconazole (a strong CYP3A4 inhibitor) on lurbinectedin exposure. A PMR is to be issued to assess the effect of the concomitant administration of moderate CYP3A4 inhibitor on lurbinectedin exposure using a physiologically-based PK (PBPK) modeling approach. • The coadministration of drugs that are known to be strong or moderate CYP3A4 inducers should be avoided. A PMC will be issued to characterize the effect of moderate CYP3A4 inducers on lurbinectedin exposure.
Labeling	The review team has made substantial revisions to the proposed labeling in Section 2 Dosage and Administration, Section 7 Drug Interactions, Section 8.6 (b) (4) Hepatic Impairment, and Section 12 Clinical Pharmacology.

Post-Marketing Requirements and Commitments

PMR or PMC	Key issues to be addressed	Rationale	Key considerations for design features
PMR	Identify lurbinectedin starting doses in patients with varying degrees of hepatic impairment	The primary elimination pathway of lurbinectedin is hepatic metabolism. No PK data is available to determine appropriate starting doses for patients with varying degrees of hepatic impairment.	Complete the planned PK trial to determine an appropriate starting dose of lurbinectedin in patients with moderate or severe hepatic impairment.
PMR	Determine a lurbinectedin dose in patients receiving concomitant medications that are known to be strong CYP3A4 inhibitors	Lurbinectedin is metabolized by CYP3A4. The effect of CYP3A4 inhibitors on lurbinectedin exposure has not been characterized. The purpose of this study is to inform dose adjustment with strong CYP3A4 inhibitors.	Complete the planned PK study to determine an appropriate dose of lurbinectedin in patients who require concomitant use of strong CYP3A4 inhibitors.
PMR	Determine a lurbinectedin dose in patients receiving concomitant drugs that are known to be moderate CYP3A4	PBPK modeling will leverage information gained from the clinical study with a strong CYP3A4 inhibitor to predict lurbinectedin exposure when administered concomitantly	Use clinical data from the PK study with strong CYP3A4 inhibitors to establish a PBPK model and predict the effect of a moderate CYP3A4

	inhibitors using PBPK approach	with moderate CYP3A4 inhibitors to inform dosing recommendations.	inhibitor on lurbinectedin exposure.
PMC	Determine the effect of the coadministration of a moderate CYP3A4 inducer on lurbinectedin PK	The purpose of this study is to determine the feasibility of a dose adjustment recommendation in patients who are receiving concomitant medications that are known to be moderate CYP3A4 inducers.	Complete the planned PK study to characterize the effect of a moderate CYP3A4 inducer on lurbinectin exposure.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The systemic exposure of lurbinectedin is dose-proportional over the dose range of 0.02 to 6.9 mg/m². Following the administration of the approved recommended dose of 3.2 mg/m², the geometric mean (CV%) of maximum concentration in plasma (C_{max}) is 107 µg/L (79%) and the geometric mean of the area under the concentration-time curve extrapolated to infinity (AUC_{inf}) is 551 µg*h/L (94%). No accumulation of lurbinectedin in plasma was observed after repeated administrations every 3 weeks (Q3W).

Distribution

The volume of distribution of lurbinectedin at steady-state is approximately 504 L (62%). Plasma protein binding is 99%. The mean blood-to-plasma ratio is 0.7.

Elimination

The terminal half-life of lurbinectedin is 51 hours and total plasma clearance is 11 L/h (50%).

Metabolism

Lurbinectin is primarily metabolized by CYP3A4. Lurbinectedin is the major species in plasma with the two major metabolites M1 and M4 accounting for 14% and 10% of the parent exposure.

Excretion

Following a 60-min IV infusion of lurbinectedin, 89% of the dose is excreted in the feces (less than 1% unchanged) and 6% is recovered in the urine (1% unchanged)

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dosing regimen is 3.2 mg/m² administered every 3 weeks as an intravenous infusion over 60 minutes.

Therapeutic Individualization

Hepatic Impairment

No dose adjustment is needed for patients with mild hepatic impairment. In the population PK analysis, there was no clinically significant effect of mild hepatic impairment (total bilirubin between 1 to 1.5 x ULN or AST greater than ULN, n=125) on lurbinectedin clearance compared to patients with normal hepatic function (total bilirubin and AST less than or equal ULN, n=625). The effect of moderate or severe hepatic impairment is unknown; therefore, no dosing recommendations can be made for these populations.

Renal Impairment

No dose adjustment is needed for patients with mild or moderate renal impairment. In the population PK analysis, mild impairment (CLcr of 60 to 89 mL/min calculated by Cockcroft-Gault equation, n=165) and moderate impairment (CLcr of 30 to 59 mL/min) did not affect lurbinectedin clearance. The effect of severe renal impairment and end-stage renal disease on the clearance of lurbinectedin is unknown; however, renal excretion of lurbinectedin is negligible. Thus, no PMR study is required and no dosing adjustment is recommended for these specific populations.

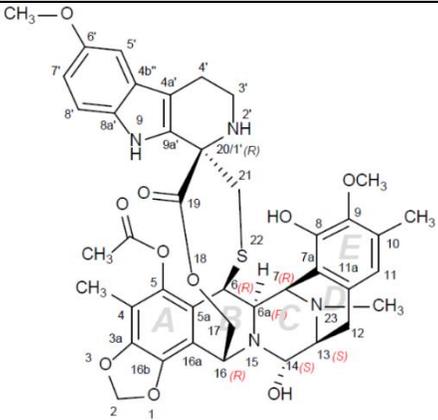
Outstanding Issues

The outstanding issues from a clinical pharmacology perspective will be addressed by the PMRs or PMCs as follows:

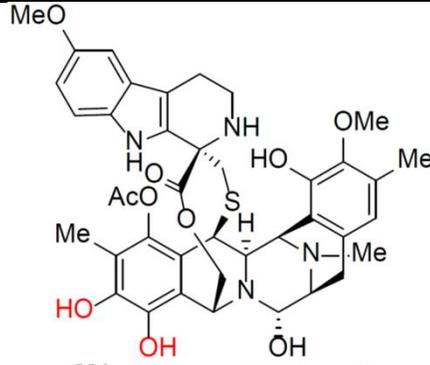
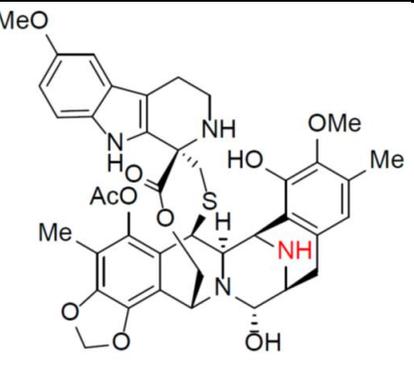
- PMR to assess the effect of moderate and severe hepatic impairment on lurbinectedin exposure
- PMR to assess the effect of concomitant administration of drugs that are known to be strong CYP3A4 inhibitors on lurbinectedin exposure
- PMR to assess the effect of concomitant administration of drugs that are known to be moderate CYP3A4 inhibitors on lurbinectedin exposure using PBPK approach
- PMC to assess the effect of concomitant administration of drugs that are known to be moderate CYP3A4 inducers on lurbinectedin exposure

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

CHEMICAL STRUCTURE AND FORMULA				
Chemical Structure and Formula	 <p>Molecular formula: C₄₁H₄₄N₄O₁₀S Molecular weight: 784.87 g/mol</p>			
PHARMACOLOGY				
Mechanism of Action	Lurbinectedin inhibits the oncogenic transcription process through binding to CG-rich sequences of DNA located around promoter regions, the eviction of oncogenic transcription factors from their binding sites, and stalling the elongating RNA polymerase II on promoters.			
Active Moiety	Lurbinectedin is the active moiety.			
QT Prolongation	The effect of a 3.2 mg/m ² lurbinectedin dose on the QTc interval was evaluated in 39 patients. The maximum mean QTcF change from baseline was 5.4 ms (two-sided upper bound 90% CI: 9.6 ms). Lurbinectedin does not increase the QT interval to any clinically significant extent.			
GENERAL INFORMATION				
Bioanalysis	Lurbinectedin concentrations in the plasma and urine samples were measured using validated LC-MS/MS methods. The bioanalytical methods are summarized in section 19.4.4.			
Healthy Volunteers vs. Patients	The pharmacokinetics of lurbinectedin could not be determined in healthy subjects due to its mutagenicity. All studies of lurbinectedin were conducted in patients who could potentially obtain therapeutic benefit.			
Drug Exposure at the Therapeutic Dosing Regimen	The geometric mean (CV%) of plasma PK parameters for lurbinectedin on Day 1 of Cycle 1 and Cycle 2 in the SCLC cohort in study B005 at the 3.2 mg/m ² dose:			
		N	C _{max} (ng/mL)	AUC _{inf} (h*ng/mL)
	Cycle 1 Day 1	101	96 (80)	488 (58)

	Cycle 2 Day 1	87	94 (106)	675 (67)
Minimal Effective Dose or Exposure	The minimal effective dose or exposure is not known. Lurbinectedin is a cytotoxic agent and dose selection in the dose escalation study was primarily determined based on safety evaluations.			
Maximal Tolerated Dose or Exposure	The maximum tolerated dose (MTD) was determined to be 4.0 mg/m ² in the dose escalation study A-001. Two patients experienced DLTs at 5.0 mg/m ² : Grade 4 AST increase and a combination of Grade 4 neutropenia, Grade 3 fatigue, and Grade 2 nausea, vomiting, and diarrhea.			
Dose Proportionality	Lurbinectedin exhibits dose proportional increase in exposure over the dose range of 0.02 to 6.9 mg/m ² . The 90% CI of the slope estimate of the power model includes unity.			
	Dose Range	PK Parameters	Slope Estimate (90%CI)	
	0.02 to 6.9 mg/m ²	C _{max}	1.09 (0.88; 1.29)	
		AUC _{inf}	0.995 (0.87; 1.13)	
Accumulation	There is no accumulation of lurbinectedin at the proposed Q3W dosing regimen.			
Variability	Based on NCA analysis of PK data obtained from 331 patients in Study B-005, the inter-individual variability in clearance is 61% and is 79% in V _{ss} .			
ABSORPTION				
Lurbinectedin is administered as an IV infusion over 60 minutes. T _{max} is achieved immediately after the end of infusion.				
DISTRIBUTION				
Volume of Distribution	Based on population PK, the estimated volume of distribution (V _d) of lurbinectedin is 504 L (62%).			
Plasma Protein Binding	in vitro, lurbinectedin is greater than 99% bound to plasma proteins in the concentration range of 50 to 500 ng/mL.			
Blood-to-Plasma ratio	The mean blood-to-plasma ratio is 0.7.			
ELIMINATION				
Mean Terminal Half-Life	Based on population PK analysis, the mean terminal half-life is 51 hours with an inter-individual variability of 50%.			
METABOLISM				
Primary Metabolic Pathways	Lurbinectedin is metabolized primarily by CYP3A4 to form five metabolites that are all active. M1, M2, M3, and M4 were quantified in plasma in the mass balance study while M5 was detected but not quantified. M1 and M4 were the major metabolites and represented 14% and 10% of the parent drug, respectively.			
	M1		M4	

	 <p>M1 (plasma, urine, feces)</p>	 <p>M4, PM030047 (plasma, urine, feces)</p>
Transporter Substrate	Lurbinectedin is a substrate of P-gp.	
EXCRETION		
Primary Excretion Pathway	Lurbinectedin is excreted in feces (89% of the dose), mainly as metabolites. The urinary excretion accounts for only 6% of the dose with 1% as unchanged compound.	
Interaction Liability (Drug as Perpetrator)		
Inhibition/Induction of Metabolism	The potential for lurbinectedin to inhibit CYP450 enzymes is low. The lowest estimated IC ₅₀ is 1.05 μM, which is orders of magnitude higher than the expected free lurbinectedin at the clinical C _{max} of 150 nM.	
Inhibition/Induction of Transporter	In vitro, lurbinectedin is an inhibitor of P-gp ([I] _{free} /IC ₅₀ =0.0004), OATP1B1, OATP1B3, and OCT1. An IC ₅₀ could not be calculated in the case of the latter 3 transporters with maximum inhibition reaching 37%, 26%, and 20%, respectively. Collectively, the potential for clinical drug-drug interaction is low.	

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes, the clinical pharmacology program provides supportive evidence of effectiveness. The primary evidence of effectiveness at the proposed 3.2 mg/m² Q3W dosage was obtained from study B005, an open-label, multi-center, single-arm, basket trial that included 105 SCLC. The primary efficacy endpoint ORR, defined as the percentage of patients with a confirmed response of CR or PR assessed by an Independent Review Committee, was 35% (95% CI: 26%; 45%). The median duration of response was 5.3 months (95% CI: 4.9; 6.4).

The Applicant conducted exposure-efficacy analyses based on data obtained from Study B005 for ORR and OS. There was a positive correlation between exposure to unbound lurbinectedin (AUC_u) and the probability of ORR (**Figure 8** Error! Reference source not found.), especially in the population with sensitive disease (i.e., CTFI < 90 days) compared patients with resistant

disease (i.e., CFTI > 90 days). The probability of ORR increases with increasing AUC_u; the probability of ORR reaches maximum at AUC_u greater than 1400 ng*h/mL.

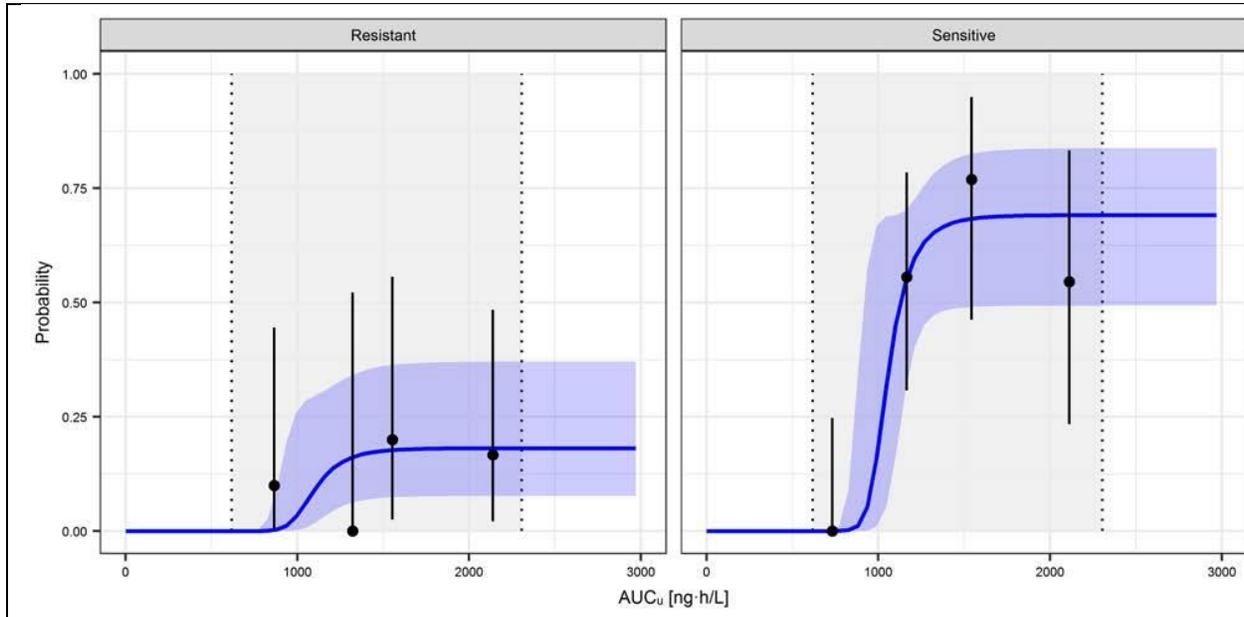


Figure 8: Relationship between ORR and AUC_u. Solid black dots represent the proportion of responders grouped by quartiles of AUC_u and plotted at the median AUC_u for each quartile, in resistant (left panel) and sensitive (right panel) patients. Bars represent the 95% confidence interval for the proportion of each quartile. Blue curve and shaded area represent predicted values and 95% confidence interval of model predicted ORR, respectively. The vertical point lines are the grey shaded area represent the 95% prediction interval of the observed AUC_u.

Source: Report CLPH-19003 submitted by the Applicant.

Increased lurbinectedin exposure is also associated with increased survival. Patients in the upper 3 exposure quartiles survived longer compared to patients in the lowest exposure quartile (**Figure 9**). The sensitive disease population had higher survival compared the resistant disease population.

The positive exposure-response (ER) relationships for ORR and OS suggest there is a potential that increasing lurbinectedin dose for SCLC patients with lower exposure (e.g., AUC_u (first cycle) lower than 1000 ng*h/L) might further improve the efficacy, especially for sensitive SCLC patients. However, the observed positive ER relationships for efficacy were based on the single dose level study with limited number of patients (n=92 for all SCLC and n=55 for sensitive SCLC). In addition, there might be unidentified confounding factors. Therefore, the causality relationship between lurbinectedin exposure and efficacy cannot be fully established. Given the promising efficacy results of lurbinectedin, the proposed 3.2 mg/m² Q3W is acceptable.

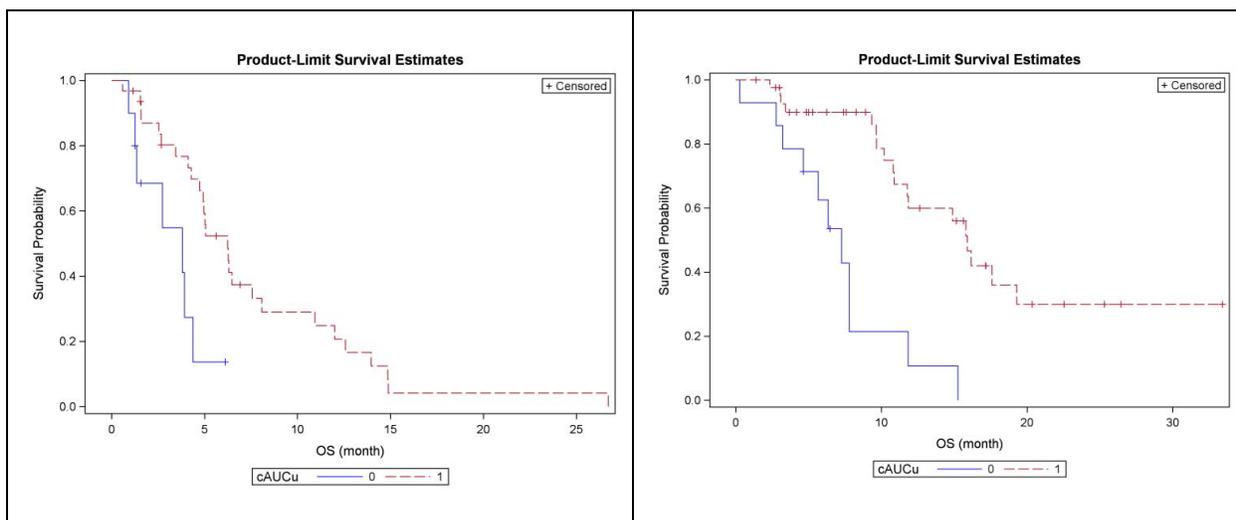


Figure 9: Kaplan-Meier OS plots vs. pooled categorized AUC of unbound lurbinectedin (cAUCu). Resistant patients (left panel) and sensitive patients (left panel) in the lowest quartiles of exposure (cAUCu = 0, blue lines) exhibit lower survival compared to patients in the upper 3 quartiles of exposure (cAUCu=1, red lines).

Source: Report CLP-19003 submitted by the Applicant.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen is appropriate for the general patient population for which the indication is being sought.

Dose Escalation and MTD Determination

The first-in-human Study A-001 investigated escalating doses of lurbinectedin in patients with advanced solid tumors. A total of 31 patients received lurbinectedin doses ranging from 0.02 to 5 mg/m² Q3W. Dose limiting toxicities were observed in 2 of 3 patients at the 5 mg/m² dose level. The dose limiting toxicities were Grade 4 transaminase (ALT and/or AST) increases and a combination of Grade 4 neutropenia, Grade 3 fatigue and Grade 2 nausea, vomiting and diarrhea despite primary antiemetic prophylaxis. As such, the MTD was declared as 4 mg/m². Of note, only 1 of 6 patients had a DLT of Grade 4 thrombocytopenia in the 4 mg/m² dose cohort. Subsequently, 9 additional patients were investigated at a 7 mg flat dose (equivalent to the 4 mg/m² dose, assuming a standard BSA of 1.8 m²).

Fixed Dose versus BSA-Based Dosing

Based on PK data from study A-001, the Applicant contended that there was no relationship between BSA and lurbinectedin clearance. The median total body clearance in the lowest BSA

(less than 1.5 m²) group was 20% higher than that in the higher BSA group. The 7 mg flat dose was selected as the recommended dose and was investigated in subsequent Phase 2 trials.

Emerging safety information from Phase 2 trials suggested that the Grade 3 or 4 thrombocytopenia and neutropenia was higher in patients with lower BSA; as a result, BSA based dose of 4 mg/m² was selected for subsequent investigation.

Using safety and PK data of 244 patients from five studies (A-001, A-005, B-001, B-002, and B-003; cutoff: January 15, 2016), the dose of 3.2 mg/m² Q3W showed lower incidence of Grade 4 neutropenia (11% vs. 14%) and lower incidence of Grade 4 thrombocytopenia (0.035% vs. 0.18%) compared to the 7.0 mg flat dose Q3W. Subsequently, the 3.2 mg/m² was selected for the pivotal Study B-005.

Exposure-Safety Analysis at the Proposed Dose

The probability of Grade 4 neutropenia or Grade 3+ thrombocytopenia increases with increasing free lurbinectedin exposure (AUC_u) (Figure 10). This relationship reached statistical significance.

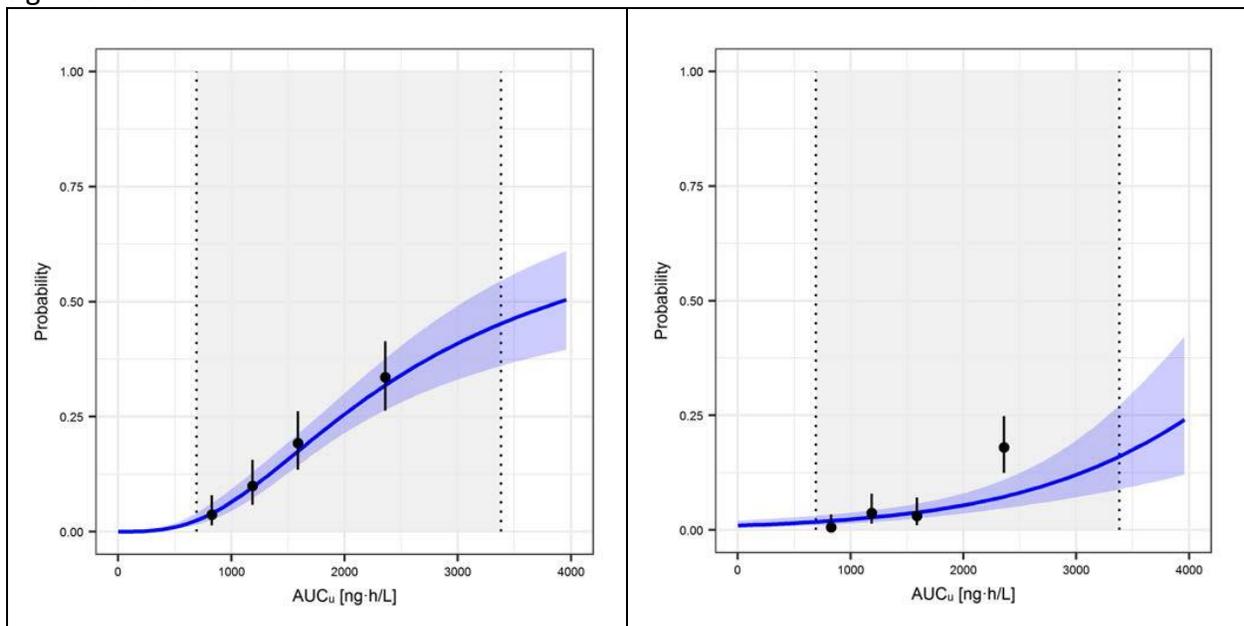


Figure 10: Relationship between AUC₀ and Grade 4 neutropenia (left panel) and Grade 3+ thrombocytopenia (right panel). Solid black dots represent the neutropenia G4 or thrombocytopenia Grade 3+ incidence by quartiles of AUC₀ and plotted at the median AUC₀ for each quartile. The bars represent the 95% confidence interval for the proportion of each quartile. Curve and blue shaded area represent predicted values and 95% confidence intervals of model-predicted risk of neutropenia G4 or thrombocytopenia Grade 3+, respectively. The vertical point lines and the grey shaded area represent the 95% prediction interval of the observed AUC₀.

Source: Report CLPH-19003 submitted by the Applicant.

Clinical Utility Index

Clinical Utility Index, defined as the difference between the probability of ORR and the probability of Grade 4 neutropenia, as function of lurbinectedin exposure provided further evidence to support the proposed dose of 3.2 mg/m². The probability of achieving ORR increases at AUC₀ greater than 1000 ng/mL and plateaus at AUC₀ greater than 1400 ng/mL whereas the probability of Grade 4 neutropenia increases gradually with increasing AUC₀; therefore, clinical benefit is maximized between the exposure levels of 1000 and 1700 ng/mL. The proposed 3.2 mg/m² results in a median exposure of 1400 ng/mL, which falls between the bounds of 1000 ng/mL and 1700 ng/mL (**Figure 11**).

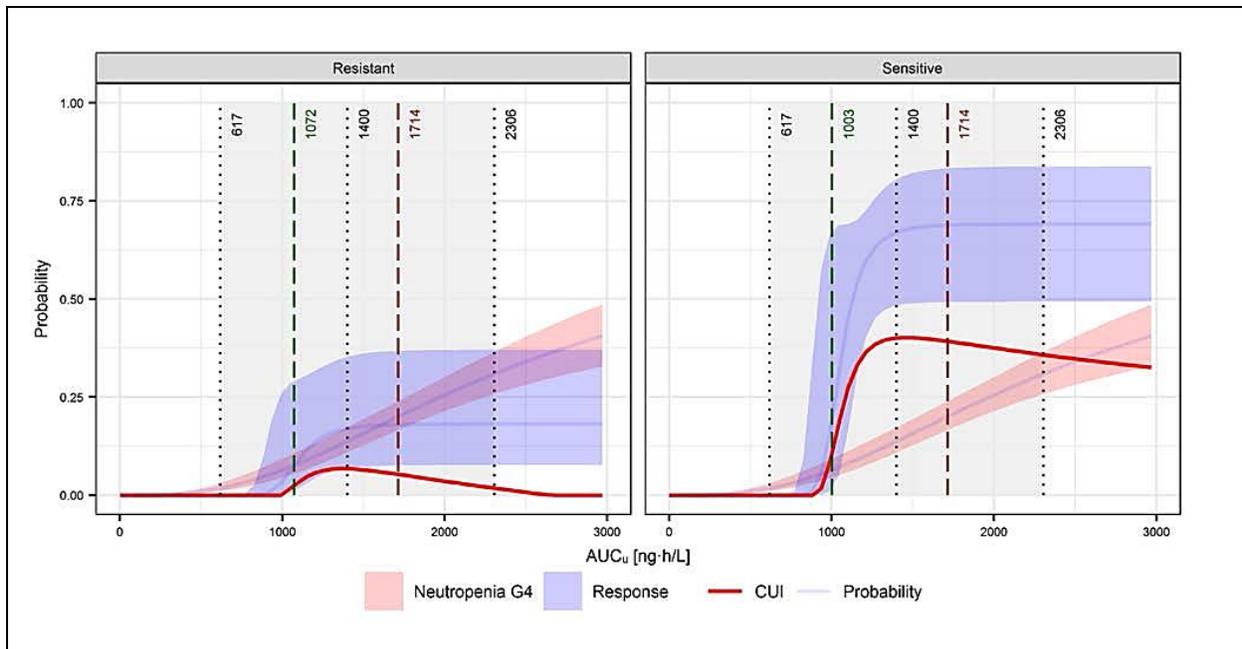


Figure 11: Clinical utility index with AUCu in patients with resistant (left panel) and sensitive (right panel) disease. Dashed green vertical line is the AUCu at topotecan ORR reported elsewhere for patients with resistant (7.45%) and sensitive (19.27%) disease. Dashed dark red vertical line is the AUCu at which the probability of Grade 4 neutropenia is 20%. The grey shaded area represent the 95% predication interval of the observed AUCu in SCLC patients. Black dotted vertical lines are percentile 5, 50, and 95 of AUCu.

Source: Report CLPH-19003 submitted by the Applicant.

The available safety data and integrated ER analyses demonstrated an acceptable balance of safety and efficacy at the proposed dosage of 3.2 mg/m² Q3W.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Based on population PK analyses, there were no differences in lurbinectedin PK based on age (18 to 85 years), body weight (39 to 154 kg), race, mild or moderate renal impairment, or mild hepatic impairment.

Hepatic Impairment

Based on population PK analysis, no dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin > 1 to 1.5 x ULN or AST > ULN). The results of the population PK analysis, including patients with normal hepatic function (n=625) and patients with mild hepatic function (n=125) at baseline, suggested that the status of mild hepatic impairment had no clinically meaningful effect (8% decrease in clearance) on lurbinectedin exposure; therefore, no dose adjustment is recommended for patients with mild hepatic impairment.

The effects of moderate (total bilirubin > 1.5 to 3 x ULN) and severe (total bilirubin > 3 x ULN) hepatic impairment on lurbinectedin exposure have not been studied and hepatic elimination is a major elimination pathway of lurbinectedin; therefore, a dedicated hepatic impairment study will be required as a PMR.

Renal Impairment

Results from the mass balance study A-005 demonstrated that the mean fraction of total radioactivity excreted in urine is 6%, with unchanged lurbinectedin representing 1% of total radioactivity. Population PK analysis included patients with normal renal function (CLcr > 89 mL/min, n=166), mild renal impairment (CLcr 60 – 89 mL/min, n=165), and moderate renal impairment (CLcr 30 – 59 mL/min, n=73). Compared to patients with normal renal function, patients with mild or moderate renal impairment had a decrease in median lurbinectedin clearance of 9% and 17%, respectively. Based on the results of the mass balance study and population PK analysis, no dose reduction is recommended for patients with varying degrees of renal impairment.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Lurbinectedin is administered intravenously. Lurbinectedin is metabolized by CYP3A4 in vitro; however, the effect of drug-drug interactions on lurbinectedin exposure has not been studied. The concomitant administration of drugs that inhibit CYP3A4 enzyme are expected to result in an increase of lurbinectedin exposure. The coadministration of lurbinectedin with strong or moderate CYP3A4 inhibitors should be avoided. If the concomitant administration with a moderate CYP3A4 inhibitor cannot be avoided, dose reductions should be considered based on adverse events, as clinically indicated.

The concomitant administration of drugs that induce CYP3A4 is expected to decrease lurbinectedin exposure and may result in loss of efficacy. The coadministration of lurbinectedin with strong or moderate CYP3A inducers should be avoided.

A safety analysis of patients receiving lurbinectedin at the proposed dosage regimen (3.2 mg/m² Q3W) and concomitant medications that are moderate or strong CYP3A4 inhibitors from Study B-005 and Study C-004 (ovarian cancer) was conducted. This analysis excluded patients who received unknown concomitant medications, unknown dose or timing of concomitant medication, or the timing of concomitant medication was more than approximately 5 half-lives after the administration of lurbinectedin. Three patients receiving concomitant medications that are strong CYP3A4 inhibitors and 39 patients receiving concomitant medications that are moderate CYP3A4 inhibitors met the dataset inclusion criteria.

Based on the safety analysis, patients who received concomitant medications that are known to be moderate inhibitors of CYP3A4 had similar safety profile to the overall patient population (**Table 6**). Since the effect of the concomitant administration of drugs that are known to be strong or moderate CYP3A4 inhibitors on lurbinectedin exposure has not been studied, coadministration of these inhibitors should be avoided. However, based on the clinical safety data, if the coadministration of moderate CYP3A4 inhibitors cannot be avoided, dose reductions based on adverse events should be considered.

Table 6: Safety analysis in the population receiving concomitant medications that are moderate CYP3A4 inhibitors compared to the overall population.

	Overall population (n=554)	Concomitant medication (moderate CYP3A4 inhibitors) (n=39)
Grade 3+ treatment related	63%	41%
Death*	3.6%	5%

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ZEPZELCA (Lurbinectedin)

Dose delays	47.3%	28%
Dose reductions	20.8%	13%
Dose discontinuations	9.2%	10%
Grade 3+ Neutropenia	41%	33%
Grade 3+ Thrombocytopenia	10%	23%

*Death in the overall population was due to progressive disease, while the two patients who died while receiving concomitant medications died due to AEs not related to the study drug.

Since the effects of concomitant CYP3A4 modulators on lurbinectedin exposure has not been studied, dosing recommendations cannot be made. A dedicated study to characterize the effect of itroconazole (a strong CYP3A4 inhibitor) on the PK of lurbinectedin is required as a PMR to inform a dose adjustment. Of note, lurbinectedin is also a substrate of P-gp. Itroconazole is a strong CYP3A4 inhibitor and an inhibitor of P-gp as well. The proposed drug interaction study will investigate the worst case scenario (i.e., the combined inhibition of CYP3A4 and P-gp).

Also, a dedicated study to assess the effect of concomitant administration of (b) (4) (a moderate CYP3A4 inducer) on the PK of lurbinectedin is required as a PMC. The purpose of this study is to inform a potential dose adjustment recommendation for the concomitant administration of moderate CYP3A4 inducers. A study with a strong inducer of CYP3A4 was not recommended given the likelihood of a substantial reduction in lurbinectedin exposure. The reduction in lurbinectedin exposure may result in compromised efficacy based on the observed exposure-response relationship, and a recommendation for dose increase may not be possible given the narrow safety margin of lurbinectedin.

X Salaheldin S. Hamed

Salaheldin S. Hamed, Ph.D. (DCP I)

Yangbing Li, Ph.D. (DPM)

Primary Reviewer

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Hong Zhao, Ph.D. (DCP II)

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Team Leader

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 7 lists all studies pertinent to the evaluation of the efficacy and safety of lurbinectedin as presented in this application. The primary evidence establishing the efficacy of lurbinectedin in patients with SCLC whose disease progressed on or after prior platinum-containing therapy is derived from PM1183-B-005-14 (Study B-005), a single-arm, multi-cohort, basket trial investigating lurbinectedin in patients with a variety of advanced solid tumors, including a cohort of patients with SCLC that progressed on or after first-line treatment.

The overall safety population consists of 554 patients, including 335 patients from Study B-005 and 219 patients with platinum-resistant ovarian cancer from PM1183-C-004-14 (CORAIL). All 554 patients received single-agent lurbinectedin at the dose of 3.2 mg/m² intravenously once every 21 days.

Table 7: Clinical Studies to Support Efficacy and Safety of Lurbinectedin

Trial Identity	Trial Design, Study Population	Regimen/schedule/route	Study Endpoints	Treatment Duration, Follow Up	No. of patients enrolled	No. of Centers and Countries
Studies to Support Efficacy and Safety						
PM1183-B-005-14 NCT no. 02454972	Multicenter, open-label, single-arm, multi-cohort trial in patients with 9 different advanced solid tumor types including patients with SCLC who progressed after first-line chemotherapy	Lurbinectedin 3.2 mg/m ² every 21 days by IV infusion	Primary: Investigator confirmed ORR Secondary: DOR, confirmed ORR/DOR by IRC, clinical benefit, PFS, PFS-4, PFS-6, OS-6, OS-12	Patients receive lurbinectedin until PD, unacceptable toxicity, treatment delay >3 weeks, requirement of >2 dose reductions, intercurrent illness precluding safe continuation of study, major protocol deviation affecting the risk:benefit ratio, investigator's decision, non-compliance with study requirements or patient refusal. Patients are followed for at least one year after the first lurbinectedin infusion. Patients with SCLC are followed until death.	Overall: N=335 SCLC cohort: N=110 enrolled N=105 treated	N=26 centers in 7 countries Great Britain: 1 Belgium: 1 France: 3 Italy: 2 Spain: 12 Switzerland: 2 USA: 5
Other Studies to Support Safety						
PM1183-C-004-14 NCT no. 02421588	Multicenter, open-label, randomized, controlled trial in patients with platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer	<u>Arm A:</u> Lurbinectedin 3.2 mg/m ² every 21 days by IV infusion <u>Arm B (Control):</u> Pegylated liposomal doxorubicin (PLD) 50 mg/m ² every 28 days by IV infusion OR Topotecan 1.5 mg/m ²	Primary: PFS by IRC Secondary: PFS by IA; OS; PFS-6, PFS-12 by IRC/IA; OS-12 and OS-24, best antitumor response by IRC/IA, DOR by IRC/IA, best response according to tumor marker evaluation	Patients receive lurbinectedin until PD, unacceptable toxicity, requirement of >2 dose reductions, intercurrent illness precluding safe continuation of study, major protocol deviation affecting the risk:benefit ratio, investigator's decision, non-compliance with study requirements or patient refusal.	Overall: N=442 Arm A: N=221 enrolled N=219 treated Arm B: N=221 enrolled N=213 treated	N=83 centers in 12 countries Austria Belgium Bulgaria Czech Republic France Great Britain Hungary Italy

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	who have received no more than 3 prior systemic chemotherapy regimens	daily on days 1-5 every 21 days by IV infusion		Patients are followed until PD, new antitumor therapy is started, death, or study termination.	PLD: N=127 enrolled N=126 treated Topotecan: N=94 enrolled N=87 treated	Romania Servia Spain USA
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7.2. Review Strategy

The FDA statistical and clinical review of this NDA consisted of one primary statistical reviewer of efficacy and one primary clinical reviewer for safety and efficacy.

The statistical and clinical review of efficacy focused on Study B-005, the trial used for the primary efficacy analysis to support the proposed indication and included the following:

- Review of current literature on SCLC and treatment of SCLC
- Review of Study B-005, including CSR, protocol, protocol amendments, SAP, and SAP amendments
- Review and assessment of Applicant analyses of lurbinectedin safety and efficacy in the CSR
- Review of datasets submitted as SAS transport files
- Review of patient narratives of serious adverse events, deaths and events of special interest
- Review of minutes of key meetings conducted during lurbinectedin development for SCLC
- Review and assessment of the Module 2 and Module 5 summaries, including the Summary of Clinical Efficacy, Summary of Clinical Safety, Integrated Summary of Efficacy, and Integrated Summary of Safety Requests of additional information from the Applicant and review of Applicant responses
- Requests for additional information from the Applicant and review of Applicant responses
- Formulation of the benefit-risk analysis and recommendations
- Review and evaluation of the proposed labeling

Summaries of data and statistical analysis by the clinical reviewer were performed using JMP 13.0 and JMP Clinical 7.1 (SAS Institute, Inc., Cary, NC). MedDRA Adverse Events Diagnostic 2.2 (MAED) (FDA, Silver Spring, MD) was also used to look for safety signals. Statistical analysis was conducted using SAS 9.4 (SAS Institute, Inc., CARY, NC.) by the statistical reviewer.

Data Sources

The electronic submission including protocols, SAPs, CSRs, SAS transport datasets in SDTM and ADaM format, and SAS codes for the NDA submission are located in the following network paths:

- Original submission: \\CDSESUB1\evsprod\NDA213702\0001
- 90-Day safety update: \\CDSESUB1\evsprod\NDA213702\0013

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study B-005

Trial Design

Study B-005 “A Multicenter Phase II Clinical Trial of Lurbinectedin (PM01183) in Selected Advanced Solid Tumors” is a open-label, exploratory study designed to assess lurbinectedin efficacy and safety administered as a single-agent at the dose of 3.2 mg/m² as a 1-hour intravenous infusion on Day 1 every 3 week in nine single-arm cohorts determined by tumor type. Cohorts include patients with pretreated advanced SCLC, head and neck (H&N) carcinoma, neuroendocrine tumors, biliary tract carcinoma, endometrial carcinoma, BRCA1/2-associated metastatic breast cancer, carcinoma of unknown primary site, germ cell tumors (GCTs), and Ewing’s family of tumors (EFTs).

Patients eligible for inclusion in the SCLC cohort of Study B-005 had a pathologically confirmed diagnosis of SCLC, Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2 and were treated with only one prior chemotherapy-containing line (other therapies such as immunotherapy could have been previously administered as a second line). Measurable disease by RECIST v.1.1, and documented progression were required before study entry. Patients with central nervous system (CNS) involvement were excluded.

Eligibility Criteria (Main criteria summarized)

Inclusion Criteria

1. Age ≥ 18 years.
2. Pathologically proven diagnosis of Small cell lung cancer (SCLC).
3. Have received one prior chemotherapy-containing line.
4. Measurable disease as defined by the RECIST v.1.1, and documented progression before study entry.
5. ECOG performance status (PS) ≤ 2
6. Adequate major organ function:
 - Hemoglobin ≥ 9 g/dl, prior red blood cell (RBC) transfusions are allowed if clinically indicated; ANC ≥ 2.0 x 10⁹/l; and platelet count ≥ 100 x 10⁹/l.
 - Alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤ 3.0 x upper limit of normal (ULN).
 - Total bilirubin ≤ 1.5 x ULN, or direct bilirubin ≤ ULN.
 - Albumin ≥ 3 g/dl.
 - Serum creatinine ≤ 1.5 x ULN.
 - Creatine phosphokinase (CPK) ≤ 2.5 x ULN.

Exclusion Criteria

1. Prior treatment with PM01183 or trabectedin.
2. Prior or concurrent malignant disease unless in complete remission for more than five years, except treated *in situ* carcinoma of the cervix, basal or squamous cell skin carcinoma, and *in situ* transitional cell bladder carcinoma.
3. Known central nervous system (CNS) involvement.
4. Relevant diseases or clinical situations which may increase the patient's risk:
 - History within the last year or presence of unstable angina, myocardial infarction, congestive heart failure, or clinically relevant valvular heart disease or symptomatic arrhythmia or any asymptomatic ventricular arrhythmia requiring ongoing treatment.
 - Grade ≥ 3 dyspnea or daily intermittent oxygen requirement within two weeks prior to the study treatment onset.
 - Active infection.
 - Unhealed wounds or presence of any external drainage.
 - Known chronic active hepatitis or cirrhosis.
 - Immunocompromised patients, including known infection by human immunodeficiency virus (HIV).
5. Pregnant or breastfeeding women.
6. Impending need for RT

Treatment Plan

Patients in the SCLC cohort received lurbinectedin at a dose of 3.2 mg/m² (capped at 6.4 mg) as a 60-minute intravenous infusion on day 1 of each 21-day treatment cycle until disease progression or unacceptable toxicity.

Patients were permitted to continue study treatment at a reduced dose if they presented with any of the following:

- Grade ≥ 3 treatment-related non-hematological toxicity.
- Grade 4 thrombocytopenia or grade 3 thrombocytopenia concomitantly with grade ≥ 3 bleeding.
- Grade 4 neutropenia, any grade febrile neutropenia or neutropenia associated with infection/sepsis.
- Frequent or prolonged (>1 week) dose delays due to treatment-related adverse events.

Up to two dose reductions (first reduction: 2.6 mg/m², second reduction: 2 mg/m²) were allowed per patient. Once the dose had been reduced for an individual patient, it was not re-escalated. Patients who experienced grade 3-4 hypersensitivity reactions were discontinued from study treatment.

On-Study Monitoring

Study assessments consisted of physical examination; laboratory studies; electrocardiogram (ECG); echocardiogram (ECHO)/MUGA scan; documentation of ECOG performance status (PS),

concomitant therapies and adverse events; and radiological tumor assessment, as outlined below:

- Physical examination, ECOG PS at screening and on day 1 of each cycle.
- Routine laboratory tests to assess complete blood count, serum chemistry, and liver function obtained at screening; on days 1, 8 and 15 of cycles 1 and 2; and on day 1 of each cycle thereafter.
- Coagulation panel at screening and on day 1 of each cycle beginning with cycle 2.
- ECG and ECHO or MUGA scan for left ventricular ejection fraction (LVEF) assessment at screening and repeated if clinically indicated.
- Concomitant therapies and adverse events are monitored throughout study treatment.
- Radiologic imaging (contrast-enhanced helical CT scan or MRI, as clinically indicated) every two cycles for the first 6 cycles, then every 3 cycles thereafter.

Study Endpoints

Primary Efficacy Endpoint:

- Confirmed overall response rate (ORR) as assessed by investigator (IA) per RECIST v1.1
Calculated as the number of patients who have had a confirmed complete response (CR) or partial response (PR) as overall best response, divided by the number of patients in the All Treated Patient population set.

Secondary Efficacy Endpoints:

- ORR by Independent Review Committee (IRC) per RECIST v1.1.
- Duration of Response (DOR) by IA and IRC-
Defined as the time between first documentation (not confirmation) of response date (PR or CR, whichever one is first reached) to the first date when progression, recurrence or death is documented.
- Progression-Free Survival (PFS) by IA and IRC-
Defined as the time from first infusion to PD, death (of any cause), or last tumor evaluation if alive with no progression.
- Overall Survival (OS)-
Defined as the time from first infusion to death, clinical cut-off if alive, or last contact if lost to follow-up.

Statistical Analysis Plan

The sponsor based their primary evaluation of efficacy on the comparison of ORR for lurbinectedin to a fixed historical control rate of 15%. The ORR was estimated using an exact binomial distribution and its 95% 2-sided exact confidence interval using the Clopper-Pearson method.

Reviewer Comment: Although the sponsor proposed a hypothesis test for evaluation of efficacy, the FDA is basing its efficacy evaluation on what it considers to be an adequate ORR magnitude with corresponding 95% confidence interval excluding clinically irrelevant response rates and a clinically meaningful duration of response. Additionally, while the statistical analysis plan included summary statistics of PFS and OS as secondary efficacy endpoints, FDA notes that single arm trials do not adequately characterize time-to-event endpoints, making these results uninterpretable without a comparator.

Sample Size Considerations

The sample size was updated in two protocol amendments. The first stage allowed for continuation of accrual to 25 evaluable patients if there was 1 response among the first 15 evaluable patients. The second stage allowed for continuation of accrual up to 100 evaluable patients if there were ≥ 2 confirmed responses in the first 25 evaluable patients.

With 100 patients there was 95% power to test the null hypothesis that 15% or less patients achieve a response ($p \leq 0.15$) versus the alternative hypothesis that 30% or more patients achieve a response ($p \geq 0.30$). If the number of patients who achieved a confirmed response was ≥ 23 , then this would allow the rejection of the null hypothesis.

Analysis Populations

All Included Patients, defined as all patients recorded in the database who have been included in the trial, regardless of whether they have received the study drug or not.

All Treated Patients, defined as all included patients who have received any partial or complete infusion of PM01183, will be used for the primary endpoint analysis of ORR and for the secondary endpoints of clinical benefit (ORR or stable disease ≥ 4 months), PFS (including PFS4/PFS6 months), and OS6/OS12 months.

All Responding Patients, defined as all evaluable patients who have had a confirmed CR or PR as overall best response according to RECIST v1.1, will be used for the secondary endpoint analysis of DoR.

Protocol Amendments

The original protocol (PM1183-B-005-14) was dated 07-October-2014. There have been 6

substantial amendments to this protocol. Primary reasons relevant to the SCLC cohort for each amendment are summarized below.

Protocol Amendment 01 (13-May-2015)

The primary reasons for this amendment were to:

- Update dosing based on new data available
- Clarified timing of AAGP assessments
- Modified timing of blood sample collection for pharmacogenetic analysis
- Clarified primary prophylactic antiemetics and their routes

Protocol Amendment 02 (04-February-2016)

The primary reasons for this amendment were to:

- The sample size of SCLC patients has been increased to 50 evaluable patients if the success boundary (≥ 2 confirmed responses) is reached in the first 25 evaluable patients
- Update Eligibility criteria to include use of magnetic resonance imaging for detecting brain metastases in SCLC
- Added information on statistical power using exact binomial distribution
- Mandates on timing of Pregnancy and albumen tests are amended
- a list of CYP1/CYP2/CYP3 inhibitors, inducers and substrates has been added

Protocol Amendment 03 (22-March-2016)

The primary reasons for this amendment were to:

- Correct typographic erratum from amendment #2 in the inclusion criterion

Protocol Amendment 04 (19-July-2016)

The primary reasons for this amendment were to:

- Extended PK sample collection windows
- Magnetic resonance imaging (MRI) has been included as an option for baseline radiological tumor assessment in SCLC patients
- The criteria for treatment continuation now include absence of active infection (including sepsis) and/or bleeding (any grade)
- Clarification of 'Day 0' and assessment windows

Protocol Amendment 05 (08-March-2017)

The primary reasons for this amendment were to:

- Allow up to 100 patients in the small cell lung cancer (SCLC) cohort of the study
- The statistical methods section has been amended to update the sequential test methodology and to provide further details on the control of type I and II error probability (alpha and beta), taking into account the two planned interim analysis performed at 15 and 25 patients per group for the expanded cohorts

- for all 100 patients in the SCLC cohort, anonymized copies of tumor assessments (CT-scan or magnetic resonance imaging, MRI) will be requested to the investigational sites for a possible independent review
- SCLC patients will be followed up until death to obtain survival results (in this cohort, the secondary endpoint will be overall survival instead of one-year overall survival)

Protocol Amendment 06 (18-July-2018)

The primary reasons for this amendment were to:

- IRC assessment of anti-tumor activity in the SCLC cohort added to secondary endpoints
- Total sample size updated to reflect expansion of cohorts
- Duration of recruitment period updated to address expanded cohorts
- After progression, SCLC patients will be followed-up every six months until death (a documented phone contact will be acceptable).
- Overall survival (OS) rate at 6 and 12 months will be determined in each cohort

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant submitted a statement indicating that all clinical studies contained in the application were conducted following Good Clinical Practice standards under the supervision of an institutional review board (IRB) or Independent Ethics Committee (IEC) in accordance with local legislation. All clinical trials were reported to be conducted in accordance with the Declaration of Helsinki and standard operating procedures that comply with the principles of ICH Good Clinical Practice.

Financial Disclosure

In accordance with 21 CFR 54.2(1)(b), the Applicant submitted Form FDA 3454 (Financial Interests and Arrangements of Clinical Investigators) certifying that study investigators had no financial conflicts of interest. The Applicant provided a list of Principal and Sub-investigators including 374 investigators for Study B-005, 118 for the QT sub-study, and 720 for CORAIL.

The Applicant submitted a Form FDA 3455 for one Principal Investigator (b) (6) who participated in Study B-005 and had disclosable equity (exceeding \$50,000 in current value) in the holding company of Pharma Mar at the time. The Applicant reports that an audit of (b) (6) clinical site was planned; however, as the site enrolled (b) (6) and the study was closed-out at the site in (b) (6) upon request of the investigator, the Applicant considered the likelihood of bias of clinical study results to be negligible and subsequently deemed the audit unnecessary.

Financial disclosure was not available for 3 investigators participating in Study B-005 and 1 investigator participating in CORAIL despite due diligence attempts made by Pharma Mar. The Applicant reports these investigators left the site without providing this information.

The financial disclosure information submitted for these clinical trials is summarized in Appendix, Section 19.3 of this document.

Reviewer Comment: Reviewer agrees that as the clinical investigator with disclosable equity had enrolled a single patient (1% of the total study enrollment) to a cohort other than SCLC, it is unlikely that any individual bias would have had an impact on the overall study results.

Data Quality and Integrity

Data appeared to be of sufficient quality. Checks performed between SDTM and ADaM data for relevant endpoints did not reveal any deficiencies.

Patient Disposition

The first patient was registered on the trial to this cohort on October 21, 2015 and the last patient registered October 15, 2018. Of the 159 patients screened for the trial 110 were registered and 105 received therapy. As of the January 15, 2019 database lock, treatment was discontinued by 90% (n=94) of patients, with 10% (n=11) patients still receiving therapy and 37% (n=39) still alive (Table 8). Eighty percent of discontinuations were due to progressive disease, 2% each for treatment related adverse events, patient refusal and death, and 4% by investigator decision. Of the 28 patients alive and off treatment, 25% (n=26) were still in follow-up for survival, 1% (n=1) was lost to follow-up and 1% (n=1) had withdrawn consent.

Table 8: Study B-005: Patient Disposition (January 15, 2019 cut-off)

Patient Disposition, n (%)	All SCLC N=105
Discontinued Treatment	94 (90%)
Progressive Disease	84 (80%)
Treatment Related Adverse Event	2 (2%)
Death	2 (2%)
Investigator's Decision	4 (4%)
Patient Refusal	2 (2%)
Ongoing at cut-off	11 (10%)
Total	105

Abbreviations: SCLC: small cell lung cancer;

Source: FDA Analysis of sponsor submitted data: ADSL

Protocol Violations/Deviations

At the time of the initial NDA submission, there were 49 major protocol deviations. The most commonly occurring major deviations were regarding assessments not being performed per protocol- at enrollment, or other timepoints, in 24 incidents. Nine deviations were due to eligibility including 3 patients with insufficient washout periods from previous therapy, 14 due to IP non-compliance and 2 for signing older versions of informed consent forms. No subject was excluded from analyses due to protocol deviations.

Table of Demographic Characteristics

Demographic information for all SCLC patients and by sensitive or resistant disease status as defined by chemotherapy-free interval (CTFI) is summarized in

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Table 9. Sensitive disease is defined as CTFI ≥ 90 days, and resistant disease as CTFI < 90 days. With a median CTFI of 106 days (range: 0-491), 43% of patients had resistant disease and 57% had sensitive disease at baseline.

Overall, patients were 60% male, had a median age of 60 years (range: 40-83), were 75% White, 1% Asian, 1% African American, 23% with race not reported due to local regulations, and 90% were from Europe. With a median age of 59 years (range: 44-79), 77% of sensitive patients were < 65 years old. The median age for resistant patients was 66 years (range: 40-83) and 49% were < 65 years old.

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Table 9: Demographic Characteristics of all SCLC Patients and by Sensitive or Resistant Disease

Characteristic, n (%)	All SCLC N=105	Sensitive CTFI≥90 N=60	Resistant CTFI<90 N=45
Sex			
Female	42 (40%)	25 (42%)	17 (38%)
Male	63 (60%)	35 (58%)	28 (62%)
Age (years)			
Median (min, max)	60 (40, 83)	59 (44, 79)	66 (40, 83)
<65	68 (65%)	46 (77%)	22 (49%)
≥65	37 (35%)	14 (23%)	23 (51%)
≥75	9 (9%)	5 (8%)	4 (9%)
Race			
White	79 (75%)	47 (78%)	32 (71%)
Asian	1 (1%)	1 (2%)	0 (0%)
Black or African American	1 (1%)	0 (0%)	1 (2%)
Other ¹	24 (23%)	12 (20%)	12 (27%)
Region			
Europe	94 (90%)	56 (93%)	38 (84%)
USA	11 (10%)	4 (7%)	7 (16%)

¹ Data on race and/or ethnicity were not collected in France and Belgium because of local regulations.

Abbreviations: SCLC: small cell lung cancer; CTFI: chemotherapy-free interval;

Source: FDA Analysis of sponsor submitted data: ADSL

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The majority of patients in the SCLC cohort had extensive-stage disease at initial diagnosis. At the time of study enrollment, 102 of the 105 patients had metastatic disease (either distant or locoregional metastasis). The remaining three patients had only one lesion restricted to lung at study entry (one of these patients had limited-stage disease at diagnosis, and the other two had lung and contralateral lymph node metastasis). Additionally, at study entry, 98 patients were classified as having extensive-stage SCLC.

Table 10 summarizes the key baseline characteristics of patients in Study B-005. Ninety-two percent of SCLC patients had ECOG performance status of 0-1, 92% were current/former smokers and 70% had extensive-stage disease at diagnosis. The majority of patients had BMI ≥ 25 (59%), creatinine clearance < 90 (52%), and albumin > 3.5 (84%). While only 9% of patients had paraneoplastic syndrome, 41% had liver metastases and 40% had bulky disease (

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Table 10).

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Table 10: Other Baseline Characteristics Study B-005

Characteristic, n (%)	All SCLC N=105	Sensitive CTFI ≥ 90 N=60	Resistant CTFI<90 N=45
ECOG performance status			
0	38 (36%)	27 (45%)	11 (24%)
1	59 (56%)	30 (50%)	29 (64%)
2	8 (8%)	3 (5%)	5 (11%)
Smoking Status			
Current/Former	97 (92%)	54 (90%)	43 (96%)
Never	8 (8%)	6 (10%)	2 (4%)
SCLC Stage at Diagnosis			
Extensive	73 (70%)	35 (58%)	38 (84%)
Limited	32 (30%)	25 (42%)	7 (16%)
BMI			
< 25	43 (41%)	22 (37%)	21 (47%)
≥ 25	62 (59%)	38 (63%)	24 (53%)
Creatinine Clearance			
< 90	55 (52%)	28 (47%)	27 (60%)
≥ 90	50 (48%)	32 (53%)	18 (40%)
Albumin			
≤ 3.5	17 (16%)	9 (15%)	8 (18%)
> 3.5	88 (84%)	51 (85%)	37 (82%)
Paraneoplastic Syndrome			
Yes	9 (9%)	5 (8%)	4 (9%)
Liver Metastases			
Yes	43 (41%)	19 (32%)	24 (53%)
Bulky Disease			
Yes	42 (40%)	18 (30%)	24 (53%)

Abbreviations: SCLC: small cell lung cancer; CTFI: chemotherapy-free interval; ECOG: Eastern Cooperative Oncology Group; BMI: Body Mass Index.

Source: FDA Analysis of sponsor submitted data: ADSL, ADMH (smoking, paraneoplastic syndrome)

Reviewer Comment: There were some numerical differences in baseline characteristics between the sensitive and resistant patients; 75% of resistant patients had ECOG of 1-2 compared to 55% of sensitive patients. Additionally, among resistant patients, 84% had extensive-stage at diagnosis compared to 58% of sensitive patients.

Therapy received prior to enrollment in Study B-005 is summarized in Table 11. Patients had received a median of 1 (range: 1-2) line of prior anti-cancer therapy; all patients had received prior platinum-based therapy and 8% had received prior immunotherapy. Two patients were listed as receiving prior surgery, one curative the other palliative. Prior radiotherapy was received by 72% of patients and 58% had prophylactic cranial irradiation (PCI). Fewer resistant patients were administered radiotherapy (42%) or PCI (31%) when compared to sensitive patients 95% and 78% respectively.

Table 11: Prior Therapy

Prior Therapy, n (%)	All SCLC N=105	Sensitive CTFI ≥ 90 N=60	Resistant CTFI<90 N=45
Prior Lines of Therapy median (range)	1 (1,2)	1 (1,2)	1 (1,2)
1 line	98 (93%)	57 (95%)	41 (91%)
2 lines	7 (7%)	3 (5%)	4 (9%)
Prior Radiotherapy	76 (72%)	57 (95%)	19 (42%)
Prophylactic Cranial Irradiation	61 (58%)	47 (78%)	14 (31%)
Prior Immunotherapy	8 (8%)	3 (5%)	5 (11%)

Abbreviations: SCLC: small cell lung cancer; CTFI: chemotherapy-free interval;

Source: FDA Analysis of sponsor submitted data: ADPR (prior radiotherapy), ADCAHIST (Prior Cranial Irradiation), ADCM (prior immunotherapy)

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

All study patients with SCLC received lurbinectedin with dose reductions and dose delays instituted as needed for toxicity (e.g., neutropenia). Patient disposition for this cohort is summarized in Table 8. There was no AE with the PT of overdose reported for these patients.

Protocol deviations relating to lurbinectedin administration are listed as follows:

- Five patients had at least one dose delayed due to investigator decision (four patients had a dose delay ≥2 weeks);
- Four patients should have had dose reduction for neutropenia but the dose was not modified accordingly;
- Four patients received lurbinectedin despite not satisfying retreatment criteria (ALT

- elevation [n=1]; neutropenia [n=2]; edema [n=1]);
- One patient had dose reduction due to a non-hematological toxicity (grade 2 neuropathy) that did not meet the minimum threshold according to protocol criteria (grade ≥ 3);
 - Two patients had a cycle delayed although blood counts were already recovered;
 - Five patients received a dose lower than appropriate for the patient based on BSA;
 - Two patients received a dose greater than appropriate for the patient based on BSA;
 - One patient received an infusion longer than 60 minutes, and one patient received an infusion for less than 60 minutes;
 - One patient received two cycles after disease progression.

Efficacy Results – Primary Endpoint

With 37 responders among 105 treated patients, the observed ORR by Investigator was 35% (95% CI: 26, 45). All responses were partial responses.

Table 12: ORR by IA in all SCLC Patients and by Sensitive or Resistant Disease

Investigator Assessed Response	All SCLC N=105	Sensitive CTFI ≥ 90 days N=60	Resistant CTFI <90 days N=45
Overall Response Rate	35%	45%	22%
(95%CI)	(26%, 45%)	(32%, 58%)	(11%, 37%)
Complete response, n (%)	0 (0%)	0 (0%)	0 (0%)
Partial response, n (%)	37 (35%)	27 (45%)	10 (22%)

Abbreviations: SCLC: small cell lung cancer; CTFI: chemotherapy-free interval;
Source: FDA Analysis of sponsor submitted data: ADBOR

Reviewer Comment: Although the number of responders is small and the trial was not designed to compare resistant and sensitive patients, FDA notes that the observed ORR by IA was 45% in sensitive patients and 22% in resistant patients.

Efficacy Results – Secondary and other relevant endpoints

ORR by IRC

The response rate as assessed by IRC was 30.5% (95% CI: 22, 40) and is summarized by sensitive and resistant disease status in Table 13. As with IA response, all were partial responses.

In considering how IRC differs from IA assessed response, the concordance rate was 78% with 29 common PR assessments. Three patients were assessed as partial response by IRC, but stable disease by IA. Eight patients were assessed as partial response by IA but 7 of those were assessed as stable disease and 1 as progressive disease by IRC.

Table 13: ORR by IRC in all SCLC Patients and by Sensitive or Resistant Disease

IRC Assessed Response	All SCLC N=105	Sensitive CTFI ≥90 days N=60	Resistant CTFI <90 days N=45
Overall Response Rate	30.5%	43%	13%
(95%CI)	(22%, 40%)	(31%, 57%)	(5%, 27%)
Complete response, n (%)	0 (0%)	0 (0%)	0 (0%)
Partial response, n (%)	32 (30%)	26 (43%)	6 (13%)

Abbreviations: IRC: independent review committee; SCLC: small cell lung cancer; CTFI: chemotherapy-free interval;
Source: FDA Analysis of sponsor submitted data: ADBOR

Reviewer Comment: Although the number of responders is small and the trial was not designed to compare resistant and sensitive patients, FDA notes that the observed ORR by IRC was 43% in sensitive and 13% in resistant patients.

Duration of Response

Median DoR was similar by IA and IRC assessment; 5.3 (95% CI: 4.1, 6.4) months by IA and 5.1 (95% CI: 4.9, 6.4) months by IRC (Table 14). The percentage of patients responding 6 months or longer was 35% by IA and 25% by IRC. For those with resistant disease the 10% had response lasting at least 6 months as assessed by IA compared to 0% by IRC.

Table 14: Duration of Response by IA and IRC

Duration of Response	All SCLC N=105	Sensitive CTFI ≥90 days N=60	Resistant CTFI <90 days N=45
Investigator Assessed Response			
Number of Responders	n=37	n=27	n=10
Median in months (95% CI)	5.3 (4.1, 6.4)	6.2 (3.5, 7.3)	4.7 (2.6, 5.6)
% with ≥6 months DoR	35%	44%	10%
IRC Assessed Response			
Number of Responders	n=32	n=26	n=6
Median in months (95% CI)	5.1 (4.9, 6.4)	5.3 (4.9, 7.0)	4.8 (2.4, 5.3)
% with ≥6 months DoR	25%	31%	0%

Abbreviations: IRC: independent review committee; SCLC: small cell lung cancer; CTFI: chemotherapy-free interval;
Source: FDA Analysis of sponsor submitted data: ADTTE

Progression-Free Survival

Median PFS was 3.52 months both by IRC and IA assessment, though with n=81 events there is 23% censoring per IRC compared to n=90 events and 14% censoring per IA.

Table 15: PFS by IRC and IA

	IRC N=105	IA N=105
Progression-free survival		
Events, n (%)	81 (77%)	90 (86%)
Censored, n (%)	24 (23%)	15 (14%)
Median time, months (95% CI)	3.52 (2.56 , 4.21)	3.52 (2.63 , 4.34)

Abbreviations: IRC: independent review committee; IA: investigator assessment;

Source: FDA Analysis of sponsor submitted data: ADBOR

Reviewer Comment: While PFS is listed as secondary endpoint for this trial, the Agency notes that time-to-event endpoints cannot be interpreted based on a single arm trial without a control.

Overall Survival

Median follow-up on Study B-005 was 17.1 (95% CI: 8.9, 22.5) months, providing a median overall survival estimate for all SCLC patients of 9.3 (95% CI: 6.3, 11.8) months. With n=66 death events, there was 37% censoring in this estimate.

Reviewer Comment: While OS is listed as secondary endpoint for this trial, the Agency notes that time-to-event endpoints cannot be interpreted based on a single-arm trial without a control.

Other Endpoints

The sponsor evaluated the following additional secondary endpoints:

- Clinical Benefit Rate: CR, PR or durable stable disease (lasting over 4 months)
- PFS4/PFS6: probability of being progression free at 4 and 6 months
- OS6/OS12: probability of being alive at 6 and 12 months

However, FDA did not conduct analyses based on these endpoints because they are considered exploratory, and as previously noted, time-to-event endpoints cannot be evaluated in single-arm trials.

Subpopulations

Efficacy in terms of ORR across different exploratory subgroups were similar when assessed by either IRC or IA (Table 16). Resistant patients' observed ORR per IRC 13% (95% CI: 5%, 27%) was numerically lower than observed ORR per IA 22% (95% CI: 11%, 37%). A similar result was noted for females: ORR per IRC was 24% (95% CI: 12%, 39%), and ORR per IA was 31% (95% CI: 18%, 47%).

Table 16: ORR among Exploratory Subgroups by IRC and IA Assessment

Category Value	IRC Assessed ORR				IA Assessed ORR			
	Response n	Total n	Overall Response Rate	95% CI	Response n	Total n	Overall Response Rate	95% CI
Sex								
Female	10	42	24%	(12%, 39%)	13	42	31%	(18%, 47%)
Male	22	63	35%	(23%, 48%)	24	63	38%	(26%, 51%)
Age Group								
<65	22	68	32%	(22%, 45%)	22	68	32%	(22%, 45%)
≥65	10	37	27%	(14%, 44%)	10	37	27%	(14%, 44%)
CTFI Category								
Resistant	6	45	13%	(5%, 27%)	10	45	22%	(11%, 37%)
Sensitive	26	60	43%	(31%, 57%)	27	60	45%	(32%, 58%)
SCLC Stage Diagnosis								
Extensive	15	73	21%	(12%, 32%)	19	73	26%	(16%, 38%)
Limited	17	32	53%	(35%, 71%)	18	32	56%	(38%, 74%)
Prior Treatment								
Immunotherapy	5	8	63%	(24%, 91%)	5	8	63%	(24%, 91%)

Abbreviations: IRC: independent review committee; IA: investigator assessment; ORR: overall response rate; SCLC: small cell lung cancer; CTFI: chemotherapy-free interval.

Source: FDA Analysis of sponsor submitted data: ADBOR

Reviewer Comment: Due to the nature of these exploratory subgroup analyses, such as the small sample size in the trial and small number of responding patients, subgroup results should be interpreted with caution. Of note, patients were enrolled into Study B-005 from October 2015 to October 2018, when standard therapy for extensive-stage SCLC, including metastatic disease, consisted of platinum-based chemotherapy. Accordingly, eligibility criteria for Study B-005 required patients to have received one prior platinum-containing regimen. Atezolizumab and durvalumab were approved in combination with platinum-based chemotherapy for first-line treatment in 2019 and 2020, respectively. As such, only 8 patients in the SCLC cohort received immunotherapy (atezolizumab or nivolumab) prior to enrolling in Study B-005, and of these, 5

patients demonstrated a partial response to lurbinectedin; however, conclusions cannot be drawn based on this small sample size. Therefore, based on the data submitted in this application, the efficacy of lurbinectedin in the second-line in patients who have previously been treated with immunotherapy and platinum-based chemotherapy is unknown at this time.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Not applicable.

Additional Analyses Conducted on the Individual Trial

Not applicable.

8.1.3 Integrated Review of Effectiveness

This application is supported by efficacy data derived from the SCLC cohort of a single clinical trial, Study B-005, as outlined above in section 8.1.2.

8.1.4 Integrated Assessment of Effectiveness

This application is supported by efficacy data derived from the SCLC cohort of a single clinical trial, Study B-005, as outlined above in section 8.1.2. In Study B-005, lurbinectedin administered in the second-line to patients with platinum-resistant and platinum-sensitive SCLC demonstrated an ORR and DOR that is clinically meaningful and were seen across subgroup of patients with SCLC who had “sensitive” or “resistant” disease. FDA considers response rate as an approval endpoint for SCLC because in the absence of therapy, tumors generally grow or remain stable rather than shrink.

8.2 Review of Safety

8.2.1 Safety Review Approach

The primary source of safety data in this NDA is the SCLC cohort of Study B-005, which consists of 105 patients with SCLC who progressed on or after prior platinum-based chemotherapy and subsequently received lurbinectedin. Furthermore, this safety data is also supported by patients with other advanced solid tumors who received lurbinectedin in Study B-005 (N=335) and in CORAIL (N=219), comprising an overall safety population of 554 patients.

The review of safety included analysis of the submitted study reports, datasets, line listings, case narratives, and CRFs from Study B-005 and CORAIL. Additionally, serious adverse events (SAEs) and adverse events of special interest (AESI) across the clinical development program, consisting of 19 clinical trials, were submitted. All AESIs across 19 clinical trials, and SAEs and death narratives for Study B-005 and CORAIL were reviewed. The 90-day safety analysis and datasets provided by the Applicant did not identify any new safety signals.

Key safety results from the SCLC safety population (N=105) were compared to the overall safety population (N=554). The review tools used included JMP, MAED and Excel programs.

8.2.2 Review of the Safety Database

Overall Exposure

Lurbinectedin exposure in the indication population and overall safety population is summarized in the following Table 17. The median duration of lurbinectedin exposure was 3.3 months (range: 7.7 days – 19.8 months) in the SCLC cohort and 3.1 months (range: 7.7 days – 37.9 months) in the overall safety population. Approximately 46% of patients with SCLC and 39% of patients in the overall safety population received at least 6 cycles of lurbinectedin, each cycle lasting 3 weeks. The median dose intensity and cumulative dose were similar across these study groups.

Table 17: Summary of Lurbinectedin Exposure

	SCLC Cohort N=105 (%)	Overall Safety Population N=554 (%)
Treatment duration (months), median (range)	3.3 (7.7 d – 19.8 m)	3.1 (7.7 d – 37.9 m)
Cycles administered per patient, median (range)	4 (1-24)	4 (1-52)
≥ 3 cycles	71 (67.6)	362 (65.3)
≥ 6 cycles	48 (45.7)	215 (38.8)
≥ 12 cycles	16 (15.2)	69 (12.5)
Dose intensity (mg/m ² /week), median (range)	1.0 (0.7-1.1)	1.0 (0.6-1.7)
Cumulative dose (mg/m ²), median (range)	12.8 (3.2-73.8)	12.6 (3.1-167.1)

Source: NDA 213702 - Summary of Clinical Safety, Table 2

Adequacy of the safety database:

The safety database submitted to support lurbinectedin for the treatment of patients with metastatic SCLC included 105 patients with SCLC who progressed after prior platinum-containing therapy and were treated with lurbinectedin at the proposed dosing of 3.2 mg/m² intravenously every 21 days. The overall safety population of 554 patients reflects patients with a variety of advanced solid tumors who were exposed to single-agent lurbinectedin at the recommended dosing regimen. This safety database is considered adequate for the review and characterization of adverse events and to provide guidance on toxicity management.

8.2.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The application contains all the agreed upon components of the electronic Common Technical Document. There were no significant issues with data integrity or submission quality.

Categorization of Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 16.1 was used for the

classification of AEs. The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 was used for AE reporting.

AEs were collected from the first dose of study drug up to 30 days after the last dose of study drug or until the start of a new antitumor therapy, whichever occurred first. For every AE, the investigator assessed severity and relationship to study treatment, categorizing the event as related (reasonable possibility that the investigational agent caused the AE), unrelated (there is no reasonable possibility that the investigational agent caused the AE and other causes are more probable) or unknown (only used in special situations when the investigator has insufficient information).

The Applicant considered the following to be AEs of special interest (AESI): infections occurring in the presence or absence of febrile neutropenia/neutropenic sepsis, injection site reactions and extravasations, musculoskeletal events in presence of creatinine phosphokinase (CPK) increase, and peripheral neuropathy.

Routine Clinical Tests

Routine clinical tests included complete blood count with differential, comprehensive metabolic panel, creatinine phosphokinase, and coagulation panel (PT/INR and PTT). In Study B-005, these assessments were obtained during the screening period; prior to lurbinectedin infusion on days 1, 8 and 15 of cycles 1 and 2; and on day 1 of each cycle thereafter. A complete physical examination including vital signs was performed on day 1 of each cycle. An electrocardiogram (ECG) and MUGA scan or echocardiogram (ECHO) for left ventricular ejection fraction (LVEF) assessment was obtained pre-treatment and repeated if clinically indicated.

8.2.4 Safety Results

An overview of treatment-emergent AEs reported in the safety population and efficacy population is shown in Table 18. In general, the incidence of AEs observed in the SCLC population is comparable to that in the overall safety population, which is composed of patients with a variety of advanced solid tumors. Drug discontinuation due to an adverse event occurred in 2% of the SCLC cohort, compared with 9% overall. Similar rates of dose reduction due to an adverse event were observed across patients with SCLC and the overall safety population.

Table 18: Overview of Adverse Events and Treatment Modifications

AE Category	SCLC Cohort N=105 (%)	Overall Safety Population N=554 (%)
Patients with ≥ 1 AE	103 (98)	545 (98)
Grade 3-5 AEs	62 (59)	353 (64)
Serious AE	36 (34)	226 (41)
Drug discontinuation due to an AE	2 (1.9)	49 (9)
Dose reduction due to an AE	26 (25)	117 (21)

Source: NDA 213702 - adae.xpt, adsl.xpt

Deaths

Summary

As of the data cut-off on September 13, 2019, a total of 412 deaths (74%) were reported among the 554 patients in the overall safety population. The Applicant's attribution of study deaths is summarized in Table 19. In the overall safety population, the majority (70%) of deaths were due to malignant disease. On-study deaths, defined as death due to any cause, including disease progression that occurred on or after the first dose of study drug and within 30 days of the last dose of study drug, were reported in 35 patients. Of the eight on-study deaths not due to disease progression, the Applicant attributed four deaths to an AE related to lurbinectedin (sepsis [n=2] and pneumonia [n=2]), all observed in patients with tumor types other than SCLC. Of the four remaining on-study deaths, the Applicant classified three deaths as the result of non-treatment related AEs (cardiorespiratory arrest, pneumonitis and septic shock) and one death due to other causes (cardiorespiratory arrest). In the overall safety population, the Applicant reported 14 deaths due to a cause of death listed as "other" or "unknown."

No treatment-related deaths were reported in the SCLC cohort. All on-study deaths in the SCLC cohort were due to underlying disease progression.

Table 19: Applicant Attribution of Study Participant Deaths

	SCLC Cohort N=105 (%)	Overall Safety Population N=554 (%)
All deaths	79 (75)	412 (74)
Disease progression	78 (74)	390 (70)
Adverse event	0	8 (1.4)
Other/unknown	1 (1.0)	14 (2.5)
Deaths within 30 days of last dose	4 (3.8)	35 (6.3)
Disease progression	4 (3.8)	27 (4.9)
Adverse event	0	7 (1.2)
Other	0	1 (0.2)

Source: NDA 213702 - Summary of Clinical Safety (Mod.5.3.5.3\ISS\Table 9.6.1)

Treatment-Emergent Deaths

FDA examined causes of death for patients receiving lurbinectedin in Study B-005 and CORAIL based on death narratives submitted by the Applicant. This reviewer's analysis of treatment-emergent patient deaths in the overall safety population is shown in Table 20. This reviewer attributes six of these eight deaths to lurbinectedin. In the SCLC cohort, this reviewer agreed with the Applicant's assessment that all four on-study deaths were due to disease progression.

Table 20: FDA Analysis of Deaths Within 30 Days of Study Drug

	SCLC Cohort N=105 (%)	Overall Safety Population N=554 (%)
On-study deaths	4 (3.8)	35 (6.3)
Disease progression	4 (3.8))	27 (4.9)
Treatment-related death	0	6 (1.1)
Sepsis	0	2 (0.04)
Septic shock	0	1 (0.02)
Pneumonia	0	2 (0.04)
Pneumonitis	0	1 (0.02)
Non-treatment-related death	0	2 (0.04)

Source: NDA 213702 - adsl.xpt, narratives of patient deaths, and Summary of Clinical Safety

Brief summaries of narratives for the eight patients from the overall safety population who died during the treatment-emergent period due to a cause other than malignant disease are presented below.

Patient (b) (6) (Study B-005) was a 66-year-old man with neuroendocrine tumor of sigmoid colon who died on study day 39 (17 days after receiving last dose of study treatment). He had widespread metastases to the thorax, liver, and abdominal lymph nodes. He previously received carboplatin, cisplatin, etoposide, gemcitabine, and topotecan. The patient developed grade 4 neutropenia and thrombocytopenia after receiving the second cycle of lurbinectedin. On study day 39, he was found to have chest CT findings consistent with pneumonia and died on the same day. The investigator reported pneumonia as the cause of death.

Reviewer Comment: The reviewer attributes this death to lurbinectedin due to pneumonia with myelosuppression.

Patient (b) (6) (Study B-005) was a 64-year-old woman with neuroendocrine tumor who died on study day 11 (10 days after receiving last dose of study treatment). She had metastases to the liver and multiple lymph nodes (mediastinal, abdominal, and pelvic). She previously received carboplatin, etoposide, gemcitabine, topotecan, cisplatin and holocranial radiation therapy. The patient was hospitalized on study day 7 for abdominal pain, renal insufficiency and pneumonia in the context of grade 4 neutropenia, grade 3 anemia and grade 4 thrombocytopenia. She was transfused, started on steroids and treated with antibiotics. She subsequently died and the investigator reported pneumonia as the cause of death.

Reviewer Comment: The reviewer attributes this death to lurbinectedin due to pneumonia with myelosuppression.

Patient (b) (6) (Study B-005) was a 46-year-old woman with endometrial cancer with peritoneal metastases who died on study day 36 (8 days after receiving last dose of study treatment). She previously underwent hysterectomy, bilateral pelvic lymphadenectomy, endometrial radiotherapy, vaginal dome radiotherapy and received carboplatin and paclitaxel. She was hospitalized on study day 36 for fever, esophagitis, abdominal pain and nausea/vomiting. Laboratory studies indicated grade 4 neutropenia, grade 3 anemia, hypokalemia and increased

creatinine. Imaging showed disease progression. Blood culture was positive for multiple pathogens including Klebsiella, E. coli, Strep viridans and other Strep. species. She received broad-spectrum antibiotics for sepsis; however, she died the same day. The investigator reported sepsis as the cause of death.

Reviewer Comment: The reviewer attributes this death to lurbinectedin due to sepsis with myelosuppression.

Patient (b) (6) (Study B-005) was a 59-year-old woman with endometrial cancer with bone and lymph node metastases who died on study day 24 (23 days after last dose of study treatment). She previously underwent hysterectomy, oophorectomy, lymphadenectomy, omentectomy, and received paraplatin and pegylated liposomal doxorubicin. The patient presented to the hospital on study day 7 with severe deterioration due to grade 4 symptomatic occlusive syndrome associated with suspected disease progression (no radiologic imaging performed). The patient was found to have myelosuppression including grade 2 neutropenia and was admitted for parenteral support, antibiotics, corticosteroids, and transfusion support. She developed grade 4 neutropenia during the admission which resolved by study day 13. She went into septic shock on study day 23 and died the following day. The investigator reported septic shock as the cause of death.

Reviewer Comment: The Applicant assessed this death as not related to study drug since neutropenia was resolved; however, the reviewer attributes this death to lurbinectedin due to septic shock in the context of resolving myelosuppression.

Patient (b) (6) (Study B-005) was a 50-year-old man with cholangiocarcinoma who died on study day 31 (6 days after receiving last dose of study treatment). He had widespread metastases including bone, lung, liver, rectum, and multiple lymph nodes. He previously received gemcitabine and oxaliplatin. Five days after receiving the second dose of lurbinectedin, the patient was hospitalized for dyspnea and respiratory distress with suspected pneumonia. Chest CT scan indicated multiple bilateral pulmonary parenchymal opacities and large right pleural effusion (culture was negative for bacterial infection). Investigators amended the diagnosis to pneumonitis. The patient received antibiotics, corticosteroids and supportive care. At the time of his death, the patient was found to have disease progression with new lesions in the lung and liver lymph nodes, as confirmed by imaging. The investigator reported pneumonitis as the cause of death.

Reviewer Comment: The reviewer acknowledges potential confounding etiologies for this patient's death; however, it cannot be ascertained that this patient's death was not at least possibly related to lurbinectedin due to pneumonitis.

Patient (b) (6) (CORAIL) was a 72-year-old woman with ovarian cancer who died on study day 38 (11 days after last dose of study treatment). She had widespread spread of disease including lymph node, peritoneal, pleural and soft tissue metastases. She previously underwent cytoreductive surgery, and received carboplatin, paclitaxel, doxorubicin and niraparib. While on study treatment, the patient had developed grade 3 intestinal subocclusion requiring nasogastric tube placement for management. She also experienced disorientation, fatigue, and

myelosuppression (grade 4 neutropenia, grade 2 anemia, grade 4 thrombocytopenia). On study day 38, while hospitalized for management of intestinal obstruction the patient clinically deteriorated. She died on the same day that her blood culture was found to be positive for E. coli and Pseudomonas. The investigator reported sepsis as the cause of death.

Reviewer Comment: The reviewer attributes this death to lurbinectedin due to sepsis in the context of myelosuppression.

Patient (b) (6) (CORAIL) was a 62-year-old woman with ovarian cancer with peritoneal and pleural metastases who died on study day 111 (20 days after last dose of study treatment). The patient had a medical history relevant for pulmonary fibrosis, pleuritis, right pleural effusion, and acute respiratory insufficiency. She previously underwent radical surgery (hysterectomy, bilateral oophorectomy, peritoneal and omental excision, recto-colectomy with terminal colostomy), and received carboplatin and paclitaxel. On study day 105 (14 days after cycle 5 dose), the patient was admitted for dyspnea, abdominal pain and abdominal distension. She was found to have an intestinal occlusion due to peritoneal carcinomatosis and a right pleural effusion, and underwent palliative ileostomy and right pleurostomy. Six days later she was reported to have a fatal cardiopulmonary arrest.

Reviewer Comment: The reviewer agrees with the Applicant's assessment that this death was not related to study drug.

Patient (b) (6) (CORAIL) was a 59-year-old woman with ovarian cancer with peritoneal metastases who died on study day 270 (12 days after last dose of study treatment). The patient had a medical history that included hypertension, chronic ischemic cardiopathy, and right bundle branch block. She previously underwent suboptimal cytoreductive surgery (hysterectomy, bilateral annexectomy, omentectomy) and received carboplatin and paclitaxel. On study day 270, she was hospitalized for dyspnea and hypoxia. She suffered from cardiorespiratory arrest and was intubated. She experienced a second cardiorespiratory arrest that was unresponsive to resuscitation. Laboratory studies confirmed myelosuppression; however, no indications of infection were reported.

Reviewer Comment: The reviewer agrees with the Applicant's assessment that this death was not related to study drug.

Non-treatment-emergent Deaths

FDA also examined causes of death for patients who received lurbinectedin in Study B-005 and CORAIL and died more than 30 days after the last dose of study drug. The Applicant's attribution of non-treatment-emergent patient deaths is shown in Table 21, and FDA's analysis is presented in Table 22.

Table 21: Applicant Attribution of Study Participant Deaths >30 Days After Study Drug

	SCLC Cohort N=105 (%)	Overall Safety Population N=554 (%)
Non-treatment-emergent deaths	75 (71)	377 (68)
Disease progression	74 (70)	363 (66)
Study drug related AE	0	1 (0.2)
“Other” with cause listed	0	7 (1.3)
“Other” with unknown cause or not reported	1 (1)	6 (1.0)

Source: NDA 213702 - Summary of Clinical Safety

One patient, a 73-year-old woman with platinum-resistant ovarian cancer participating in the CORAIL study, died from *Pneumocystis jirovecii* pneumonia 45 days after the last dose of study drug. The Applicant attributed this death to lurbinectedin due to associated myelosuppression, which included grade 4 lymphopenia. The FDA reviewer is in agreement with this assessment.

The Applicant reported seven non-treatment-emergent deaths in the overall safety population due to a known cause of death listed as “other.” These causes were as follows: pulmonary arterial hypertension, aplastic crisis, pneumonia/sepsis, cerebral ischemia, cardiac arrest, and cardiopulmonary arrest (n=2). The Applicant did not consider these seven deaths to be related to study treatment; however, upon examination of the case narratives, the FDA reviewer finds that one of these deaths may be attributable to lurbinectedin. This patient had ovarian cancer and died 89 days after last lurbinectedin dose due to pneumonia with resultant sepsis in the context of a recent diagnosis of grade 4 myelodysplastic syndrome. Myelosuppression is a commonly observed toxicity of lurbinectedin; therefore, the contribution of the study drug to this death cannot be ruled out.

Of the six non-treatment-emergent deaths in whom the cause of death was “unknown” or “not reported,” including one patient with SCLC, all had discontinued lurbinectedin due to progressive disease but had limited information available from the time of death (ranging from 114 to 365 days after last dose of study drug). One of these patients had received another antitumor agent (avelumab) after discontinuation of lurbinectedin.

Based on analysis of the submitted case narratives, the FDA reviewer assessment of deaths in lurbinectedin-treated patients is summarized in the table below.

Table 22: FDA Analysis of Deaths >30 Days after Study Drug

	SCLC Cohort N=105 (%)	Overall Safety Population N=554 (%)
Non-treatment-emergent deaths	75 (71)	377 (68)
Disease progression	74 (70)	363 (66)
Treatment-related death	0	2 (0.04)
Non-treatment-related death	0	5 (0.9)
Unknown (no narrative available)	1 (1)	6 (1.1)

Source: NDA 213702 - adsl.xpt and Summary of Clinical Safety

Serious Adverse Events

Treatment-emergent SAEs were reported in 34% of the SCLC cohort and 41% of the overall safety population. Table 23 summarizes the SAEs that occurred in 2% or more of patients with SCLC with corresponding rates in the overall safety population. The most common SAEs were pneumonia, myelosuppression related (neutropenia, febrile neutropenia, thrombocytopenia, anemia), dyspnea and respiratory tract infection. Pulmonary-related events such as pneumonia and dyspnea were more commonly observed among patients with SCLC. Gastrointestinal-related complaints (e.g., bowel obstruction, vomiting and abdominal pain) were more frequent in patients with other advanced solid tumors.

Table 23: Serious Adverse Events Reported in ≥2% Study Patients

	SCLC Cohort N=105 (%)	Overall Safety Population N=554 (%)
Any SAE (Grades 1-5)	36 (34)	226 (41)
Pneumonia ^a	7 (7)	13 (2.3)
Neutropenia ^b	6 (6)	28 (5)
Febrile neutropenia	5 (4.8)	34 (6)
Thrombocytopenia ^c	4 (3.8)	23 (4.2)
Anemia	4 (3.8)	18 (3.2)
Dyspnea	4 (3.8)	9 (1.6)
Respiratory tract infection ^d	4 (3.8)	6 (1.1)
General physical health deterioration	3 (2.9)	14 (2.5)
Abdominal pain	1 (1.0)	17 (3.1)
Vomiting	1 (1.0)	17 (3.1)
Nausea	1 (1.0)	11 (2.0)
Intestinal obstruction ^e	0	28 (5)

Source: NDA 213702 - adae.xpt, adsl.xpt

^a Includes pneumonia and lung infection.

^b Includes neutropenia and neutrophil count decreased.

^c Includes thrombocytopenia and platelet count decreased.

^d Includes respiratory tract infection, upper respiratory tract, infection, viral upper respiratory tract infection, and bronchitis.

^e Includes intestinal obstruction, small intestinal obstruction and large intestinal obstruction.

Discontinuations and Dosage Interruptions Due to Adverse Effects

In the overall safety population, 49 (9%) patients discontinued lurbinectedin due to an AE. AEs leading to discontinuation in at least 2 patients were general physical health deterioration (n=9), febrile neutropenia (n=4), anemia (n=2), thrombocytopenia (n=2), hypoalbuminemia (n=5), peripheral neuropathy (n=3), fatigue (n=2), ascites (n=2), and intestinal obstruction (n=2).

Discontinuation was less frequently observed in the SCLC cohort with 2 (1.9%) patients requiring withdrawal of lurbinectedin due to toxicity. The reasons for discontinuation in these patients were myelosuppression-related and peripheral neuropathy.

Two patients experienced dose interruption in the overall safety population due to infusion-related reaction and injection site reaction. Both patients had tumors other than SCLC.

A total of 117 (21%) patients in the overall safety population had at least one dose reduction, including 26 (25%) patients in the SCLC cohort. Neutropenia was the most common AE leading to dose reduction (8% overall and 16% in patients with SCLC), followed by febrile neutropenia and fatigue which occurred at similar rates (range: 2.5-4.5%) across all patients.

Dose delays occurred in 30.5% of patients in the SCLC cohort, and the median length of dose delay was 7 days. Myelosuppression was the leading cause of these dose delays.

Significant Adverse Events

The events of myelosuppression and hepatotoxicity are considered significant adverse events that have been included in the *Warnings and Precautions* section of the label.

Myelosuppression

Myelosuppression occurred at a substantial rate among patients treated with lurbinectedin (see Table 26). In the overall safety population, grade 3 or 4 neutropenia occurred in 41% of patients with a median time to onset of 15 days and a median duration of 7 days. Grade 3 or 4 thrombocytopenia occurred in 10% of patients, and grade 3 or 4 anemia occurred in 17% of patients. Rates of these adverse events were similar in the SCLC cohort.

Complications associated with bone marrow suppression including febrile neutropenia and sepsis occurred in 7% and 2% of all patients, respectively. All cases of sepsis occurred in patients with solid tumors other than SCLC, and 1% of these cases were fatal.

Given these findings, providers are advised to administer lurbinectedin only to patients with sufficient baseline neutrophil and platelet counts, and to monitor blood counts prior to each administration. Recommendations to withhold, reduce the dose, or permanently discontinue lurbinectedin based on severity of count suppression are described in the label. Further, the use of G-CSF is recommended for patients with severe neutropenia.

Hepatotoxicity

In the overall safety population, increased ALT was reported in 61% of patients and increased AST in 42%. Grade 3 elevations of ALT and AST were observed in 6% and 3% of patients, respectively, and grade 4 elevations of ALT and AST were observed in 0.4% and 0.5% of patients, respectively. The median time to onset of grade ≥ 3 transaminase elevation was 8 days (range: 3 to 49) with a median duration of 7 days. These findings were generally consistent in the SCLC cohort. Of note, grade 3 or higher bilirubin elevations were infrequent in the overall safety population, occurring at a rate of 2.4%. No patients met Hy's law criteria.

Although severe transaminase elevation was not a common occurrence, hepatotoxicity is listed in the *Warnings and Precautions* to inform providers of a potentially serious and clinically significant safety signal that may have implications for prescribing decisions and patient management. Accordingly, providers are advised to monitor liver function tests prior to initiating lurbinectedin and regularly throughout treatment, as listed in the label, with recommendations to withhold, reduce the dose or permanently discontinue based on severity.

Treatment Emergent Adverse Events and Adverse Reactions

The incidence of treatment-emergent AEs by MedDRA SOC, preferred term (including composite terms, where applicable), and by NCI CTCAE severity grading are presented in Tables 24 and 25. Nearly all patients experienced a TEAE. In general, AEs by SOC were observed at similar frequencies among the overall safety population and SCLC cohort with the exception of General disorders and administration site conditions; Metabolism and nutrition disorders; Respiratory, thoracic and mediastinal disorders; and Infections and infestations. Each of these SOC categories had at least a 10% difference in rate of incidence between the overall safety population and SCLC cohort with AEs more commonly observed among patients with SCLC.

Table 24: Adverse Events (All Grades) by SOC

MedDRA SOC	SCLC Cohort N=105 (%)	Overall Safety Population N=554 (%)
Patients with ≥ 1 AE	103 (98)	545 (98)
General disorders and administration site conditions	87 (83)	404 (73)
Gastrointestinal disorders	79 (75)	449 (81)
Metabolism and nutrition disorders	53 (50)	223 (40)
Respiratory, thoracic and mediastinal disorders	47 (45)	167 (30)
Blood and lymphatic system disorders	44 (42)	253 (46)
Musculoskeletal and connective tissue disorders	41 (39)	165 (30)
Infections and infestations	40 (38)	151 (27)
Nervous system disorders	33 (31)	155 (28)
Investigations	126 (23)	24 (23)
Skin and subcutaneous tissue disorders	83 (15)	18 (17)
Vascular disorders	14 (13)	83 (15)
Psychiatric disorders	13 (12)	88 (16)

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Cardiac disorders	8 (8)	33 (6)
Renal and urinary disorders	7 (7)	45 (8)
Eye disorders	4 (3.8)	13 (2.3)
Hepatobiliary disorders	2 (1.9)	18 (3.2)
Injury, poisoning and procedural complications	2 (1.9)	18 (3.2)
Reproductive system and breast disorders	1 (1)	23 (4.2)
Ear and labyrinth disorders	1 (1)	7 (1.3)
Neoplasms benign, malignant and unspecified	0	11 (2)
Congenital, familial and genetic disorders	0	1 (0.2)
Endocrine disorders	0	2 (0.4)
Immune system disorders	0	1 (0.2)
Product issues	0	1 (0.2)
Surgical and medical procedures	0	1 (0.2)

Source: NDA 213702 - adae.xpt, adsl.xpt and Summary of Clinical Safety (Table 5)

Table 25: Adverse Events Occurring in ≥ 5% of Study Patients

MedDRA Preferred Term	SCLC Cohort N=105 (%)		Overall Safety Population N=554 (%)	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Patients with ≥ 1 AE	103 (98)	60 (57)	545 (98)	334 (60)
Fatigue	81 (77)	13 (12)	350 (63)	56 (10)
Nausea	39 (37)	0	192 (35)	14 (2.5)
Musculoskeletal pain ^a	35 (33)	4 (3.8)	148 (27)	14 (2.5)
Decreased appetite	35 (33)	1 (1)	138 (25)	7 (1.3)
Constipation	33 (31)	0	178 (32)	4 (0.7)
Dyspnea	32 (30)	4 (3.8)	87 (16)	12 (2.2)
Vomiting	23 (22)	0	168 (30)	24 (4.3)
Cough ^b	21 (20)	0	59 (11)	1 (0.2)
Diarrhea	21 (20)	4 (3.8)	105 (19)	10 (1.8)
Respiratory tract infection ^c	19 (18)	5 (4.8)	36 (6)	7 (1.3)
Pyrexia	14 (13)	0	74 (13)	1 (0.2)
Abdominal pain ^d	13 (12)	1 (1)	147 (27)	19 (3.4)
Peripheral neuropathy ^e	12 (11)	4 (0.7)	51 (9)	4 (0.7)
Pneumonia ^f	11 (10)	7 (6.7)	23 (4.2)	10 (1.8)
Chest pain	11 (10)	0	23 (4.2)	0
Headache ^g	10 (10)	1 (1)	53 (10)	1 (0.2)
Stomatitis	9 (9)	0	50 (9)	3 (0.5)
Weight decreased	8 (8)	1 (1)	29 (5)	3 (0.5)
Edema ^h	5 (4.8)	0	62 (11)	3 (0.5)
Rash ⁱ	7 (7)	0	28 (5)	0
Dysphagia	6 (6)	1 (1)	9 (1.6)	2 (0.4)
Insomnia	5 (4.8)	0	48 (9)	0
Febrile neutropenia	5 (4.8)	5 (4.8)	37 (7)	37 (7)
Ascites	1 (1)	0	30 (5)	15 (2.7)

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Urinary tract infection ^j	1 (1)	0	30 (5)	8 (1.4)
Intestinal obstruction ^k	0	0	34 (6)	29 (5)

Source: NDA 213702 - *adae.xpt*, *adsl.xpt*, and *Summary of Clinical Safety*

^a Includes musculoskeletal pain, musculoskeletal discomfort, myalgia, arthralgia, arthritis, pain in extremity, musculoskeletal chest pain, non-cardiac chest pain, back pain, neck pain, and bone pain.

^b Includes cough, productive cough, and upper airway cough syndrome.

^c Includes respiratory tract infection, upper respiratory tract infection, viral upper respiratory tract infection, and bronchitis.

^d Includes abdominal pain, abdominal discomfort, gastrointestinal pain, abdominal pain upper, abdominal pain lower, epigastric discomfort and hepatic pain.

^e Includes neuropathy peripheral, neuralgia, paresthesia, peripheral motor neuropathy, peripheral sensory neuropathy, polyneuropathy, dysaesthesia, hypoesthesia, and hyperesthesia.

^f Includes pneumonia, lung infection, atypical pneumonia, *Pneumocystis jirovecii* pneumonia and pneumonia *Klebsiella*.

^g Includes headache, migraine and sinus headache.

^h Includes edema, edema peripheral, face edema, and peripheral swelling.

ⁱ Includes rash, dermatitis, dermatitis contact, dermatitis bullous, eczema, rash erythematous, rash maculopapular, rash papular and palmar-plantar erythrodysesthesia syndrome.

^j Includes urinary tract infection, urinary tract infection bacterial, cystitis, *Escherichia* urinary tract infection.

^k Includes intestinal obstruction, small intestinal obstruction and large intestinal obstruction.

Reviewer Comment: The most common AEs ($\geq 20\%$) observed in the SCLC cohort were fatigue (77%), nausea (37%), musculoskeletal pain (33%), decreased appetite (33%), constipation (31%), dyspnea (30%), cough (22%) and diarrhea (20%). Respiratory signs and symptoms (e.g., dyspnea and cough) and pulmonary infections (e.g., pneumonia) were reported at higher rates in the SCLC cohort, whereas gastrointestinal AEs, such as abdominal pain and intestinal obstruction, were infrequent in this cohort.

Laboratory Findings

Routine laboratory tests to assess complete blood count, serum chemistry (sodium, potassium, chloride, BUN, serum creatinine, glucose, magnesium, phosphorous, calcium), and liver function (ALT, AST, Alk phosphatase and bilirubin) were obtained at screening; on days 1, 8 and 15 of cycles 1 and 2; on day 1 of each cycle thereafter; and as clinically indicated.

Laboratory alterations from baseline throughout the study, graded per NCI CTCAE v4.0 are summarized in Tables 26, 27 and 28.

Hematologic Assessment

Hematologic changes from baseline in patients who received at least one dose of lurbinectedin are shown in the table below. Leukopenia and lymphopenia occurred most frequently in the SCLC cohort.

Table 26: Hematologic Lab Abnormalities Worsening from Baseline

Laboratory Abnormality	SCLC Cohort N=105 (%)			Overall Safety Population N=554 (%)		
	N*	All Grades	Grades 3-4	N*	All Grades	Grades 3-4
Decreased leukocytes	105	83 (79)	30 (29)	554	399 (72)	164 (30)
Decreased lymphocytes	105	83 (79)	45 (43)	554	392 (71)	180 (32)
Decreased hemoglobin	105	78 (74)	10 (9.5)	554	407 (73)	95 (17)
Decreased neutrophils	105	75 (71)	48 (46)	554	354 (64)	225 (41)
Decreased platelets	105	39 (37)	7 (6.7)	554	250 (45)	54 (9.7)

Source: NDA 213702 – adlb.xpt and Summary of Clinical Safety (Table 14 - Mod.5.3.5.3\ISS\Table 9.7.9)

*Denotes number of patients with at least one baseline and post-baseline measurement used as the denominator in percentage calculation.

Reviewer Comment: Myelosuppression occurred in the majority of patients and at generally similar rates and severity across safety populations.

Renal, Glucose and Electrolyte Assessment

Changes from baseline in basic metabolic panel are summarized in Table 27. Elevated creatinine and increased glucose levels were commonly observed across the overall safety population, including the SCLC cohort; however, grade 3-4 abnormalities occurred at a rate of <5%.

Table 27: Renal, Glucose and Electrolyte Lab Abnormalities Worsening from Baseline

Laboratory Abnormality	SCLC Cohort N=105 (%)			Overall Safety Population N=554 (%)		
	N*	All Grades	Grades 3-4	N*	All Grades	Grades 3-4
Increased creatinine	104	72 (69)	0	552	416 (75)	9 (1.8)
Increased glucose	104	54 (52)	5 (4.8)	550	263 (48)	25 (4.5)
Decreased sodium	104	32 (31)	7 (6.7)	552	201 (36)	57 (10)
Decreased magnesium	99	22 (22)	0	315	54 (17)	1 (0.3)
Increased potassium	104	17 (16)	0	552	83 (15)	6 (1)
Decreased potassium	104	18 (17)	1 (1)	552	117 (21)	22 (4)
Increased calcium	95	12 (13)	0	305	27 (8.9)	1 (0.3)
Decreased calcium	95	8 (8.4)	1 (1.1)	305	26 (8.5)	2 (0.7)
Increased sodium	104	4 (3.8)	0	552	26 (4.7)	0

Source: NDA 213702 – adlb.xpt and Summary of Clinical Safety (Table 16 - Mod.5.3.5.3\ISS\Table 9.7.12; and Table 18 - Mod.5.3.5.3\ISS\Table 9.7.15)

*Denotes number of patients with at least one baseline and post-baseline measurement used as the denominator in percentage calculation.

Reviewer Comment: The incidence and severity of electrolyte abnormalities were largely consistent across patients with various tumor types who received lurbinectedin.

Liver Function Assessment

Liver enzyme elevation and bilirubin changes from baseline are reported in Table 28. As noted previously, hepatotoxicity is listed as a *Warning and Precaution* in the label due to the notable incidence of ALT elevation (61% in the overall safety population and 66% in the SCLC cohort). AST elevation was less commonly observed with rates of 42% and 26%, respectively, in the selected safety populations.

Table 28: Liver Function Lab Abnormalities Worsening from Baseline

Laboratory Abnormality	SCLC Cohort N=105 (%)			Overall Safety Population N=554 (%)		
	N*	All Grades	Grades 3-4	N*	All Grades	Grades 3-4
Increased ALT	104	69 (66)	4 (3.8)	552	337 (61)	35 (6.3)
Increased AST	102	27 (26)	2 (2)	550	230 (42)	18 (3.3)
Decreased albumin	100	32 (32)	1 (1)	535	191 (36)	11 (2.1)
Increased alk. phos.	104	20 (19)	3 (2.9)	552	164 (30)	25 (4.5)
Increased bilirubin	104	10 (9.6)	0	552	62 (11)	13 (2.4)

Source: NDA 213702 – adlb.xpt and Summary of Clinical Safety (Table 16 - Mod.5.3.5.3\ISS\Table 9.7.12; and Table 18 - Mod.5.3.5.3\ISS\Table 9.7.15)

*Denotes number of patients with at least one baseline and post-baseline measurement used as the denominator in percentage calculation.

Reviewer's Comment: In comparison to increased transaminase levels, hyperbilirubinemia was an infrequent finding, and severe (grade 3 to 4) liver functional abnormalities were rare occurrences across the overall safety population, including patients with SCLC.

Vital Signs

Vital signs (temperature, heart rate, blood pressure and body weight) were assessed at screening and on day 1 of each treatment cycle prior to lurbinectedin infusion. No clinically meaningful changes from baseline were reported in the safety populations.

Electrocardiograms (ECGs)

Electrocardiograms were performed at baseline. Abnormalities in ECGs were reported as AEs. AEs with potential ECG abnormalities reported in the safety populations are shown in the table below.

Table 29: Cardiac Events with Potential for ECG Abnormality

MedDRA Preferred Term	SCLC Cohort N=105 (%)		Overall Safety Population N=554 (%)	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Tachycardia	4 (3.8)	0	10 (1.8)	0
Atrial fibrillation	1 (1)	0	5 (0.9)	1 (0.2)
Acute coronary syndrome	1 (1)	0	1 (0.2)	0

Angina pectoris	1 (1)	0	1 (0.2)	0
Sinus tachycardia	0	0	3 (0.5)	0
Palpitations	0	0	3 (0.5)	0
Myocardial infarction	0	0	1 (0.2)	1 (0.2)
Arrhythmia	0	0	1 (0.2)	0
Diastolic dysfunction	0	0	1 (0.2)	0
Tachyarrhythmia	0	0	1 (0.2)	0

Source: NDA 213702 - adae.xpt, adsl.xpt

QT

Treatment-emergent QTc prolongation was noted in one patient in the overall safety population. A 60-year-old man with head and neck carcinoma in Study B-005 developed grade ≥ 3 hypocalcemia, hypokalemia and hypophosphatemia after his first infusion of lurbinectedin. He was subsequently diagnosed with grade 4 QTc prolongation (584 ms), which was managed with intravenous electrolyte replacement. After improvement in duration of QTc interval, he resumed treatment with lurbinectedin. No treatment-emergent AEs related to QT interval were reported in the SCLC cohort.

A QT sub-study was conducted to assess the potential for QTc prolongation with lurbinectedin in 39 patients with advanced tumors participating in Study B-005. The full report for this QT study was provided in this application. The CDER Interdisciplinary Review Team for Cardiac Safety Studies team reviewed the submitted data and concluded that no large mean effect on the QTc was detected and a maximum increase in heart rate of 18.3 bpm was observed at 3-hr post end-of-infusion.

Immunogenicity

No immunogenicity study was included or required in this submission.

8.2.5 Analysis of Submission-Specific Safety Issues

8.2.5.1 Infections in Patients with SCLC

Myelosuppression was the most frequently observed adverse event across the overall safety population including the SCLC cohort. The most commonly occurring infections in patients with SCLC, in the absence or presence of neutropenia, were pneumonia and respiratory tract infections. Pneumonia was reported as a SAE in approximately 7% of patients (all grade 3-4) and respiratory tract infections occurred as a SAE at a rate of nearly 4% (all grade 3-4). Febrile neutropenia occurred as a SAE in 5% of patients with SCLC. Dose reduction was the most common action taken for patients diagnosed with an infection in the setting of neutropenia, and dose delays were typically instituted in the non-neutropenic setting. Treatment discontinuation was required in one patient for myelosuppression-related causes which included the adverse event of febrile neutropenia in the context of grade 3 pneumonia. There

were no cases of neutropenic sepsis or fatal outcomes due to infection reported in the SCLC cohort.

8.2.5.2 Select Adverse Events of Special Interest (AESI)

Across the clinical development program of lurbinectedin, there were five SAEs were considered to be adverse events of special interest. FDA reviewed narratives for these select cases. Of the five, a single SAE (myelodysplastic syndrome) occurred in a patient administered lurbinectedin at a dose of 3.2 mg/m² q3wk. This patient was a 77-year-old woman with ovarian cancer and metastases to lymph nodes and bones who was participating in CORAIL. She had a history of receiving two prior lines of chemotherapy including carboplatin, paclitaxel, bevacizumab, and pegylated liposomal doxorubicin. She received 33 cycles of lurbinectedin and discontinued study treatment due to disease progression. Approximately ten weeks later she was diagnosed with grade 4 myelodysplastic syndrome, and subsequently died of pneumonia. As noted in section 8.2.4, FDA attributed this patient's death to lurbinectedin.

The four remaining SAEs of special interest consisted of two instances of rhabdomyolysis, and one case each of ventricular arrhythmia and acute monocytic leukemia. However, these SAEs occurred in patients receiving alternative doses and regimens of lurbinectedin. There was no consistent pattern or safety signal detected from review of these AESI.

8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

No clinical outcome assessment or patient reported outcome data were submitted in this application.

8.2.7 Safety Analyses by Demographic Subgroups

Chemotherapy-free interval

An important factor to consider when evaluating treatment options in patients with SCLC who have relapsed or progressed after initial treatment is the chemotherapy-free interval (CTFI), which is the length of time from the completion of first-line platinum-based chemotherapy regimen to the time of relapse or disease progression. In SCLC, the likelihood of response in the second-line is highly dependent on the CTFI and distinguishes patients considered to have platinum-sensitive disease from those with platinum-resistant disease. Studies have shown that patients who relapse or progress within 90 days of platinum-based chemotherapy (resistant population) have a poor response rate (10% or less) to subsequent treatment, whereas patients who relapse or progress after 90 days (sensitive population) have a response rate of approximately 25%^{5,6}.

According to the definition aforementioned, approximately 43% of patients had platinum-resistant disease in the SCLC cohort of Study B-005 and the remaining 57% of patients had platinum-sensitive disease. Table 30 summarizes the key safety findings in these patient subsets.

Table 30: Overview of Adverse Events and Treatment Modifications in Patients with SCLC by Platinum Sensitivity

MedDRA Preferred Term	Platinum-Resistant Patients N=45 (%)		Platinum-Sensitive Patients N=60 (%)	
	All Grades	Grades 3-4	All Grades	Grades 3-4
N with any AE	44 (98)	27 (60)	59 (98)	33 (55)
SAE	21 (47)	18 (40)	15 (25)	15 (25)
Dose reduction due to AE	9 (20)	9 (20)	17 (28)	14 (23)
Dose delay due to AE	13 (29)	5 (11)	19 (32)	5 (8)
Discontinuation due to AE	0	0	2 (3.3)	1 (1.7)

Source: NDA 213702 - *adae.xpt*, *adsl.xpt*.

In general, regardless of chemosensitivity, patients with SCLC experienced similar rates of AEs and dose delay due to AE. The rate of dose reduction due to an AE was 20% in the platinum-resistant patients, and 28% in the platinum-sensitive patients. The incidence of SAEs was higher among patients with platinum-resistant disease, particularly with respect to myelosuppression-related events such as febrile neutropenia (occurring at a rate of 9% in the resistant population and 1.7% in the sensitive population). Study drug discontinuation occurred at a higher rate in platinum-sensitive patients but with no clear pattern identified and limited due to the small number of patients. Causes for discontinuation in this sub-group were myelosuppression and peripheral neuropathy.

As of the study cut-off, nearly 90% of patients with platinum-resistant disease had died, whereas 65% of patients with platinum-sensitive disease had died. Further, a greater proportion of patients died due to malignant disease in the resistant population than in the sensitive population, (87% vs. 65%, respectively). These statistics are in line with the premise that platinum-resistance portends a worse prognosis for patients with SCLC.

Reviewer Comment: Although generalizations regarding safety across these sub-groups cannot be adequately supported due to the limited number of patients in these cohorts, no obvious safety concerns were identified in these two subgroups.

Age

In the SCLC population, 65% of patients were younger than 65 years of age and the remaining 35% were 65 years of age or older. Rates of TEAEs (all grades) were generally similar across these age subsets; however, more severe (grade 3-4) AEs were more commonly reported in the older group (73% as opposed to 49% in the younger group). See Table 31 for further details on treatment-emergent AEs.

SAEs also occurred at higher rates in the older population (49% versus 26% in the younger population) with myelosuppression-related AEs being the most frequently observed (febrile neutropenia [11%], neutropenia [11%], thrombocytopenia [8%] and anemia [8%]). Dose delays

and dose reductions across age groups occurred at similar rates. Additionally, treatment discontinuation due to an AE occurred in one patient from each of these age groups, yielding a discontinuation rate of 1.4% in patients <65 years old and a rate of 2.7% in patients ≥65 years old.

Table 31: Adverse Events Occurring in ≥ 10% of Study Patients by Age

MedDRA Preferred Term	<65 Years of Age N=68 (%)		≥65 Years of Age N=37 (%)	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Patients with ≥ 1 AE	66 (97)	33 (49)	37 (100)	27 (73)
General disorders and administration site conditions	56 (82)	6 (9)	31 (84)	9 (24)
Fatigue	52 (76)	6 (9)	29 (78)	7 (19)
Chest pain	8 (12)	0	3 (8)	0
Pyrexia	7 (10)	0	7 (19)	0
Gastrointestinal disorders	47 (69)	4 (6)	32 (86)	3 (8)
Nausea	28 (41)	0	11 (30)	0
Constipation	22 (32)	0	11 (30)	0
Vomiting	15 (22)	0	8 (22)	0
Diarrhea	14 (21)	3 (4.4)	7 (19)	1 (2.7)
Abdominal pain ^a	8 (12)	0	5 (14)	1 (2.7)
Respiratory, thoracic and mediastinal disorders	30 (44)	5 (7)	17 (46)	4 (11)
Dyspnea	19 (28)	2 (2.9)	13 (35)	2 (5)
Cough ^b	12 (18)	0	9 (24)	0
Musculoskeletal and connective tissue disorders	30 (44)	4 (6)	11 (30)	1 (2.7)
Musculoskeletal pain ^c	27 (40)	4 (6)	8 (22)	0
Muscular weakness	0	0	4 (11)	1 (2.7)
Metabolism and nutrition disorders	28 (41)	0	25 (68)	8 (22)
Decreased appetite	18 (26)	0	17 (46)	1 (2.7)
Blood and lymphatic system disorders	26 (38)	18 (26)	18 (49)	15 (41)
Febrile neutropenia	1 (1.5)	1 (1.5)	4 (11)	4 (11)
Infections and infestations	25 (37)	8 (12)	15 (41)	5 (14)
Respiratory tract infection ^d	12 (18)	3 (4.4)	7 (19)	2 (5)
Pneumonia ^e	8 (12)	5 (7)	3 (8)	2 (5)
Nervous system disorders	20 (29)	4 (6)	13 (35)	2 (5)
Peripheral neuropathy ^f	11 (16)	1 (1.5)	1 (2.7)	0
Headache	5 (7)	1 (1.5)	5 (14)	0

^a Includes abdominal pain, abdominal discomfort, abdominal pain upper and hepatic pain.

^b Includes cough and productive cough.

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^c Includes musculoskeletal pain, myalgia, back pain, arthralgia, pain in extremity, musculoskeletal chest pain, neck pain, and bone pain.

^d Includes respiratory tract infection, upper respiratory tract infection, viral upper respiratory tract infection, and bronchitis.

^e Includes pneumonia and lung infection.

^f Includes neuropathy peripheral, neuralgia, paresthesia, peripheral sensory neuropathy, hypoesthesia, and hyperesthesia.

Gender

Of the 105 patients with SCLC in Study B-005, 40% were female and 60% were male. In general, rates of adverse events, including higher grade AEs and SAEs, as well as dose delays and treatment discontinuations were consistent among women and men. Dose reductions were more common among males (30% as opposed to 17% in females). No significant safety signal based on sex predisposition was detected.

8.2.8 Specific Safety Studies/Clinical Trials

Not applicable.

8.2.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant did not conduct carcinogenicity or tumor development studies based on the proposed patient population. These studies were not required by FDA.

Human Reproduction and Pregnancy

No reproduction or pregnancy studies with lurbinectedin were conducted or included in this application.

Pediatrics and Assessment of Effects on Growth

No pediatric study or assessment of lurbinectedin effect on growth was conducted or included in this application.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Lurbinectedin is administered intravenously. Based on the mode of administration and pharmacological properties, there are no concerns regarding the potential for abuse, withdrawal or rebound with lurbinectedin. No overdoses were reported with lurbinectedin in the SCLC safety population.

8.2.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Not applicable as lurbinectedin is not approved in any country.

Expectations on Safety in the Postmarket Setting

Although the safety of lurbinectedin appears to be adequately characterized in Study B-005 and CORAIL, FDA will monitor any post-marketing reports including safety reports that are submitted after accelerated approval. In general, FDA expects that the safety of lurbinectedin will be similar to that observed in the clinical trials reviewed in this application. Additional safety data will be obtained from the confirmatory trial that the Applicant is expected to conduct as per a post-marketing requirement.

8.2.11 Integrated Assessment of Safety

Safety data from patients with previously-treated SCLC and other advanced solid tumors who received lurbinectedin after disease progression have been presented in section 8.2.4. The safety profile of lurbinectedin is most notable for myelosuppression, fatigue, musculoskeletal pain, gastrointestinal AEs (nausea, vomiting, diarrhea) and respiratory AEs (dyspnea, cough).

Significant and serious adverse reactions such as myelosuppression and aminotransferase laboratory elevation are addressed in the *Warnings and Precautions* section of the label with recommendations to withhold, dose reduce or permanently discontinue as necessary depending on the severity of toxicity. Additionally, G-CSF prophylaxis is recommended for severe neutropenia.

In Study B-005, the following findings were specific to the SCLC cohort:

- There were no deaths on or within 30 days of study drug discontinuation that were attributable to lurbinectedin;
- Treatment-emergent SAEs were reported in 34% of patient. Pneumonia, dyspnea, upper respiratory tract infections, febrile neutropenia and myelosuppression were identified as the most commonly observed SAEs;
- Dose reductions occurred in 25% of patients with neutropenia (17%) representing the most common AE resulting dose reduction;
- Dose delays occurred in 31% of patients, most frequently due to myelosuppression;
- Drug discontinuation was infrequent (n=2).

The overall the safety profile of lurbinectedin is acceptable when assessed in the context of the treatment of a life-threatening disease, and in the context of current available therapies.

8.3 Statistical Issues

There are no major statistical issues related to the primary efficacy result of ORR. No inferential procedures were used to evaluate results from this single arm trial, efficacy evaluation was based on the magnitude of response rate and adequate duration of response. The IA assessed

ORR was 35% (95% CI: 26, 45) with a median duration of response of 5.3 (95% CI: 4.1, 6.1) months. The IRC assessed ORR was consistent at 30.5% (95% CI: 22, 40) with a median duration of response of 5.1 (95% CI: 4.9, 6.4) months. Efficacy was observed across exploratory subgroups including among both sensitive and resistant patients.

Additionally, although PFS and OS results were summarized, we noted that time-to-event endpoints are uninterpretable without a comparator arm.

8.4 Conclusions and Recommendations

Based on the evaluation of clinical data from Study B-005 and CORAIL, the review team recommends accelerated approval of lurbinectedin under the provisions 21 CFR 314.510 Subpart H for the treatment of adult patients with metastatic small cell lung cancer who have progressed after prior platinum-containing chemotherapy.

The basis of this recommendation is the favorable benefit:risk assessment for lurbinectedin in the second-line setting of metastatic SCLC, a serious condition and life-threatening condition. Data from Study B-005 demonstrated that lurbinectedin administered to previously-treated patients with SCLC resulted in an investigator-assessed ORR per RECIST v1.1 of 35% (95% CI: 26%, 45%), which was the primary endpoint, with a median duration of response of 5.3 months. Efficacy was observed in both the platinum-resistant and platinum-sensitive populations with ORR of 22% and 45%, respectively.

The most common adverse reactions in the SCLC population were myelosuppression, fatigue, elevated creatinine and liver enzymes, and musculoskeletal pain. The safety profile of lurbinectedin is acceptable given the life-threatening nature of metastatic SCLC.

In context of approved therapies for this patient population in the US, the favorable efficacy and safety findings reviewed in this application provide sufficient evidence to recommend lurbinectedin for accelerated approval.

Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s). The confirmatory trial (ATLANTIS) which the Applicant intends to use to verify and describe the clinical benefit of lurbinectedin in the treatment of patients with metastatic SCLC is currently ongoing. ATLANTIS is a randomized, controlled trial comparing the primary endpoint of OS in patients with SCLC who progressed after platinum-based chemotherapy and received either the study regimen of doxorubicin and lurbinectedin, or investigator's choice of chemotherapy (cyclophosphamide, doxorubicin and vincristine [CAV] or topotecan) as control.

X Flora Mulkey
Primary Statistical Reviewer

X Joyce Cheng
Statistical Team Leader

X Sonia Singh
Primary Clinical Reviewer

X Adnan Jaigirdar
Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The Division did not refer this NDA to an advisory committee because the application did not raise significant public health questions regarding the role of lurbinectedin for the proposed indication. The demonstrated benefit-risk profile for lurbinectedin is favorable in patients with metastatic SCLC who have progressed after first-line therapy.

10 Pediatrics

Pharma Mar was granted orphan-drug designation for lurbinectedin for the treatment of SCLC on August 1, 2018. Pursuant to section 505B(k)(1), applications for drugs or biological products for which orphan designation has been granted are exempt from the PREA, section 505B(a)(a)(A) requirement to conduct pediatric assessment.

11 Labeling Recommendations

11.2 Prescription Drug Labeling

The table below (Table 32) summarizes changes to the proposed prescribing information (PI) made by FDA. See the final approved PI for ZEPZELCA (Lurbinectedin) accompanying the approval letter for more information.

Table 32: Highlights of Significant Labeling Changes

Section	Proposed Labeling	Approved Labeling
Highlights		
Product Title	Dosage form missing. Route of administration listed as <div style="background-color: #cccccc; width: 100px; height: 1em; margin: 2px 0;">(b) (4)</div>	Dosage form and route of administration revised to: for injection, for intravenous use ; consistent with the FDA draft Guidance: <i>Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format</i>
Indication Heading		Established Pharmacologic Class of “alkylating drug” added to indication consistent with 21CFR 201.57(a)(6)
Full Prescribing Information		
INDICATIONS AND USAGE	<div style="background-color: #cccccc; width: 100%; height: 2em; margin-bottom: 2px;">(b) (4)</div>	<p>Revised to “treatment of adult patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy” to more accurately reflect the patients evaluated in key efficacy Study B-005.</p> <p>The appropriate age group (adult) was added to the indication as recommended in the FDA draft Guidance: <i>Indications and Usage Section of Labeling for Human Prescription Drug and Biological</i></p>

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		<i>Products — Content and Format.</i>
DOSAGE AND ADMINISTRATION, 2.2 <i>Dosage Modifications for Adverse Reactions</i>	Included a statement that (b) (4) in patients with (b) (4) prolonged (>2 weeks) dose delays.	Modified to state that a dose delay >2 weeks should result in drug discontinuation. Revised the presentation of the dose reduction table and revised the dosage modifications for adverse reactions text into a 3-column table. Dosage modification information concerning neutropenia and thrombocytopenia was revised: dosage modification information concerning hepatotoxicity was added.
DOSAGE AND ADMINISTRATION, 2.3 <i>Premedication</i>	(b) (4) antiemetic prophylaxis (corticosteroid and serotonin antagonist) prior to administration (b) (4)	Amended to advise prescribers to consider antiemetic prophylaxis prior to infusion as the emetogenic potential of lurbinectedin is unknown. Standard antiemetic prophylaxis was instituted early in the development of lurbinectedin based on a minimal number of patients with nausea and vomiting. (b) (4)
DOSAGE AND ADMINISTRATION, (b) (4)	(b) (4)	(b) (4)
CONTRAINDICATIONS	(b) (4)	Changed to state that there are no contraindications (b) (4) (consistent with 21CFR 201.57(c)(5)).
WARNINGS AND PRECAUTIONS 5.1 <i>Myelosuppression</i>	(b) (4)	The subsection title was revised to <i>Myelosuppression</i> . The description of neutropenia in the text was based only on the pooled dataset of patients with advanced solid tumors (b) (4)

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		(b) (4) The incidence of Grade 3 or 4 anemia in the pooled dataset of patients was added.
WARNINGS AND PRECAUTIONS (b) (4)		This subsection was removed as (b) (4)
WARNINGS AND PRECAUTIONS 5.2 Hepatotoxicity		The description of hepatotoxicity in the text was based only on the pooled dataset of patients with advanced solid tumors (b) (4) (b) (4)
WARNINGS AND PRECAUTIONS (b) (4) Embryo-Fetal Toxicity		Revised to reflect changes to subsections 8.1 and 8.3.
ADVERSE REACTIONS, 6.1 Clinical Trials Experience	Presented safety data in tables that highlight grade 3-4 adverse reactions in ≥10% of patients from the SCLC cohort (b) (4) Adverse reactions described in the tables were based on hematologic and non-hematologic adverse reactions.	Revised the description of the pooled safety database to reflect patients with SCLC and patients with advanced solid tumors. This section was amended to focus primarily on safety findings in the SCLC cohort of Study B-005. The adverse reactions tables were reorganized and revised to reflect common adverse reactions in ≥10% of patients with SCLC only (Table 3) and select laboratory abnormalities worsening from baseline in ≥20% of patients with SCLC (including corresponding rates of grade 3-4 reactions) (Table 4).

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		Included a list of serious adverse reactions.
DRUG INTERACTIONS, <i>7.1 Effect of Other Drugs on ZEPZELCA</i>	A section on drug interactions was not present in proposed labeling.	This section was added to provide specific practical instructions for preventing or managing clinically significant interactions and mechanism of the interaction. The effect of strong and moderate CYP3A inhibitors and inducers on lurbinectedin exposure and the clinical recommendations concerning these interactions was added.
USE IN SPECIFIC POPULATIONS, <i>(b) (4) Lactation</i>	Due to the potential for serious adverse reactions in breastfed children, advise women to (b) (4) 	Revised to specify that women should also not breastfeed for 2 weeks after the final dose. (b) (4)
USE IN SPECIFIC POPULATIONS, <i>8.3 Females and Males of Reproductive Potential</i>	Advise female patients of reproductive potential to use effective contraception during treatment and for (b) (4) months after use. Advise males with a female sexual partner of reproductive potential to use effective contraception during treatment and for (b) (4) months after use.	Revised to state that females of reproductive potential should use effective contraception for 6 months after use, and the specified male population should use effective contraception for 4 months after final dose.
USE IN SPECIFIC POPULATIONS, <i>8.5 Geriatric Use</i>	Provided the percentage of patients age (b) (4) 	Amended (b) (4) the SCLC cohort and included a description of the differences in safety between patients ≥ 65 years of age compared with patients < 65 years of age consistent with 21CFR 201.57(c)(9)(v)..
Use in Specific Populations, (b) (4)	(b) (4)	

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(b) (4)

DESCRIPTION	(b) (4)	<p>Modified to state ZEPZELCA is an alkylating drug (established pharmacologic class) consistent with 21CFR 201.57(c)(12).</p> <p>Added the dosage form and text concerning the calculated concentration based on the final volume.</p>
CLINICAL PHARMACOLOGY 12.1 <i>Mechanism of Action</i>		<p>Revised the text concerning the mechanism of action and included text concerning the inhibition of monocyte activity in vitro and reduced macrophage infiltration in implanted tumors in mice.</p>
CLINICAL PHARMACOLOGY, 12.2 <i>Pharmacodynamics</i>		<p>Added text stating that exposure-response relationships and the time course of pharmacodynamics response are unknown (consistent with 21CFR 201.57(c)(13)(i)(B)), and that increased neutropenia and thrombocytopenia were observed with increased lurbinectedin exposure.</p>
CLINICAL PHARMACOLOGY, 12.3 <i>Pharmacokinetics</i>		<p>Drug interaction information was revised and discussed in terms of in vitro studies and transporter system.</p>
NONCLINICAL TOXICOLOGY, 13.1 <i>Carcinogenesis, Mutagenesis, Impairment of Fertility</i>	<p>Stated that carcinogenicity testing has not been performed and that lurbinectedin is genotoxic to mammalian cells.</p>	<p>Added statements clarifying that fertility studies were not performed, and there were no findings in reproductive organs in general toxicology studies (noting that doses and exposures in these studies were lower than the human dose).</p>

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<p>CLINICAL STUDIES</p>	<p>Described the demographics of the SCLC cohort of Study B-005, including the proportion of patients who received prior radiotherapy and the number of lines of prior chemotherapy. Trial eligibility criteria and description of tumors assessments on study were not provided. Efficacy results according to investigator and IRC for the SCLC cohort presented in a table. (b) (4)</p>	<p>Included statements on the percentage of study patients with SCLC who also received prior immunotherapy (b) (4)</p> <p>Efficacy table revised to highlight ORR and DOR according to IA which was the primary endpoint of Study B-005. (b) (4)</p>
<p>PATIENT COUNSELING INFORMATION</p>		<p>Revised to be consistent with the recommendations in the FDA Guidance: <i>Patient Counseling Information Section of Labeling for Human Prescription Drug and Biological Products – Content and Format</i> (e.g., use of headings; focus on major risks of the drug and risks for which a patient may need to do something actionable). Also, revised based on revisions to the full prescribing information.</p>

Other Prescription Drug Labeling
 Not applicable.

12 Risk Evaluation and Mitigation Strategies (REMS)

No REMS is recommended for lurbinectedin.

13 Postmarketing Requirements and Commitment

The following Postmarketing Requirements and Commitments to verify the clinical benefit of lurbinectedin for the treatment of patients with metastatic SCLC and support conversion to regular approval were agreed upon by FDA and the Applicant.

Postmarketing Requirements (PMR)

PMR # 3831-1

Submit the final report and datasets for the overall survival and progression-free survival analysis as determined by an Independent Review Committee from a clinical trial to confirm the clinical benefit of lurbinectedin in small cell lung cancer that may inform product labeling. This could be from the Study titled, "Phase III Randomized Clinical Trial of Lurbinectedin (PM01183)/Doxorubicin Versus Cyclophosphamide, Doxorubicin and Vincristine (CAV) or Topotecan as Treatment in Patients With Small-Cell Lung Cancer (SCLC) Who Failed One Prior Platinum-containing Line (ATLANTIS)".

Schedule Milestones:

Trial Completion	02/2020
Final Report Submission	02/2021

Rationale: The proposed indication for lurbinectedin is treatment of adult patients with metastatic small cell lung cancer who have progressed on or after prior platinum-containing chemotherapy. Efficacy is based on data from a single, uncontrolled phase 2 study (PM1183-B-005-14), in which a cohort of 105 patients with SCLC, who had progressed following prior platinum-containing therapy, were treated with lurbinectedin as a single-agent. In this single cohort of SCLC patients treated with lurbinectedin, the applicant reported an investigator-assessed overall response rate (ORR) of 35.2% and median duration-of-response (DoR) of 5.3 months. Currently, overall response rate supported by duration-of-response from this single-arm trial is the basis for accelerated approval. The current available treatment (topotecan) was approved 20 years ago. Time-to-event endpoints such as overall survival (OS) and progression-free survival (PFS) cannot be adequately interpreted in single-arm clinical trials due to confounding effects of heterogeneity of the patient population. Long term efficacy outcomes including OS from a randomized controlled clinical trial are needed to confirm clinical benefit of lurbinectedin.

PMR # 3831-2

Submit the final report of a physiologically-based pharmacokinetic modeling with the results from the drug interaction trial with a strong CYP3A4 inhibitor, to assess the effect of concomitant administration of a moderate CYP3A inhibitor on

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lurbinectedin exposure, that will determine the magnitude of increase in the exposure of lurbinectedin and appropriate dosage recommendation for patients receiving concomitant medications that are moderate CYP3A inhibitors, that may inform labeling. Design and conduct the trial in accordance with the FDA Guidance for Industry titled; *“Clinical Drug Interaction Studies – Study Design, Data Analysis, and Clinical Implications.”*

Schedule Milestones:

Trial Completion	10/2024
Final Report Submission	10/2024

Rationale: Lurbinectedin is metabolized by CYP3A in vitro. The concomitant administration of drugs that are known to be moderate CYP3A inhibitors may increase lurbinectedin exposure, which may increase toxicity. This clinical trial is required to determine an appropriate dose adjustment recommendation for patients receiving concomitant medications that are known to be moderate CYP3A inhibitors.

PMR # 3831-3

Submit the analysis and datasets with the final report from a hepatic impairment clinical trial to evaluate the pharmacokinetics and safety of lurbinectedin in patients with mild, moderate, or severe hepatic impairment and determine the magnitude of increase exposure and appropriate dosage recommendations, that may inform product labeling. Design and conduct the trial in accordance with the FDA Guidance for Industry titled: *“Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.”*

Schedule Milestones:

Trial Completion	03/2025
Final Report Submission	09/2025

Rationale: Lurbinectedin is predominantly metabolized in the liver. Patients with hepatic impairment may have increased exposure of lurbinectedin, which may increase toxicity. This clinical trial is required to determine an appropriate starting dosage in patients with mild, moderate, or severe hepatic impairment.

PMR # 3831-4

Submit the final report and datasets from a clinical pharmacokinetic trial to assess the potential effects of Itraconazole on lurbinectedin in patients with advanced solid tumors and determine the magnitude of increase exposure and appropriate dosage recommendation of lurbinectedin when administered concomitantly with strong CYP3A inhibitors, that may inform product labeling. This trial should be

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designed and conducted in accordance with the FDA Guidance for Industry titled;
“Clinical Drug Interaction Studies – Study Design, Data Analysis, and Clinical Implications.”

Schedule Milestones:

Trial Completion	12/2023
Final Report Submission	06/2024

Rationale: Lurbinectedin is metabolized by CYP3A in vitro. The concomitant administration of drugs that are known to be moderate CYP3A inhibitors may increase lurbinectedin exposure, which may increase toxicity. This clinical trial is required to determine an appropriate dose adjustment recommendation for patients receiving concomitant medications that are known to be moderate CYP3A inhibitors.

Postmarketing Commitments (PMC)

PMC # 3831-5

Submit the final analysis of overall response rate and duration of response along with the datasets for the small cell lung cancer cohort enrolled in study PM1183-B-005-14 titled, *“Clinical Trial of Lurbinectedin in Selected Advanced Solid Tumors”* to provide additional long-term efficacy data that may inform product labeling.

Schedule Milestones:

Trial Completion	11/2020
Final Report Submission	05/2021

Rationale: Overall response rate in study PM1183-B-005-14 was not finalized at the time of the interim analysis. (b) (4)

(b) (4)
This PMC will provide updated ORR results from the study PM1183-B-005-14 based upon the protocol-specified timing for final analysis of ORR. (b) (4)

PMC # 3831-6

Submit the final report from a clinical trial to evaluate the effect of repeat doses of a moderate CYP3A inducer on the single dose pharmacokinetics of lurbinectedin and to determine the magnitude of decrease in lurbinectedin exposure, and appropriate dosage recommendation when lurbinectedin is coadministered with moderate CYP3A inducers, that may inform product labeling. Designed the trial in accordance with the FDA Guidance for Industry, titled *“Clinical Drug Interaction Studies – Study Design, Data Analysis, and Clinical Implication”*.

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Schedule Milestones:

Trial Completion	01/2024
Final Report Submission	07/2024

Rationale: Lurbinectedin is metabolized by CYP3A in vitro. The concomitant administration of drugs that are known to be moderate CYP3A inducers may decrease lurbinectedin exposure, which may compromise lurbinectedin efficacy. This clinical trial is required to determine an appropriate dosing recommendation for patients receiving concomitant medications that are moderate CYP3A inducers.

14 Division Director (DHOT)

X John Leighton

15 Division Director (OCP)

X Nam Atiqur Rahman

16 Division Director (OB) Comments

X Shenghui Tang

17 Division Director (Clinical) Comments

X Harpreet Singh

18 Office Director (or designated signatory authority) Comments

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X Marc Theoret

19 Appendices

19.2 References

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https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125514s059s064s076s083lbl.pdf

19.3 Financial Disclosure

See Section 8.1.2 Financial Disclosure for further details.

Covered Clinical Study (Name and/or Number): Study B-005 and CORAIL

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>1, 212</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u></p> <p>Significant payments of other sorts: <u>0</u></p> <p>Proprietary interest in the product tested held by investigator: <u>0</u></p> <p>Significant equity interest held by investigator in: <u>1</u></p> <p>Sponsor of covered study: <u>0</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>4</u>		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

19.4 Nonclinical Pharmacology/Toxicology

The Applicant did not conduct carcinogenicity or tumor development studies based on the proposed patient population. These studies were not required by FDA.

19.5 OCP Appendices (Technical documents supporting OCP recommendations)

19.5.1 Population PK analysis

The Applicant conducted a population PK analysis to characterize the PK of lurbinectedin, identify covariate factors that could affect lurbinectedin disposition and compare the individual exposure estimates for subsequent Exposure-Response (E-R) analysis. Data was collected in all patients enrolled across three phase I studies (PM1183-A-001-08, PM1183-A-002-10, PM1183-A-005-11), four phase II studies (PM1183-B-001-10, PM1183-B-002-11, PM1183-B-003-11, PM1183-B-005-14), and one Phase III study PM1183-C-004-14). The dataset included 9176 concentrations from 755 subjects. Samples collected before the first treatment (677), BLQ samples (568) and aberrant samples (35) were excluded from the analysis. The studies included in the population PK analysis and the dose level, number of subjects, PK sampling schedule are shown in Table 33.

Table 33: Overview of studies included in the population PK analysis.

Study	Dose level	Subjects treated	Subjects with PK data	Dosing days	PK sampling cycles	PK Sampling Schedule
PM1183-A-001-08	0.02 - 5.0 (mg/m ²)	31	31	1	1 & 2 ^a	Preinfusion, 5 min before EOI, and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 24, 48, 96 and 168 h after EOI.
PM1183-A-002-10	3.5 - 7.0 (mg FD)	24	23	1, 8	1 & 2	For C1D1 and C1D8: Preinfusion, 30 min before EOI, 5 min before EOI, and at 0.5, 1, 1.5, 2, 4, 7, 23, 47, 95 and 167 h after EOI. For C2D1: Preinfusion, 5 min before EOI, and at 0.25, 1, 2, 4, 7, 23, 71 and 167 h after EOI.
	1.0 - 3.0 (mg FD)	18	18	1, 2, 3	1	For C1D1: Preinfusion, 5 min before EOI, and at 0.5, 1, 2, 4, 7 and 23 h after EOI. For C1D3: Preinfusion, 5 min before EOI, and at 0.5, 1, 2, 4, 7, 23, 47, 95 and 168 h after EOI.
PM1183-A-005-11	3.0 - 5.0 (mg FD)	21	21	1, 8	1 & 3	Preinfusion, 5 min before EOI, and at 1.5, 2, 2.5, 3, 4, 5, 6, 7, 24, 72 and 168 h after EOI.
PM1183-B-001-10	7.0 (mg FD)	45	44	1	1 & 2	Preinfusion, 5 min before EOI, and at 0.25, 1, 2, 4, 7, 24, 72 and 168 h after EOI.
PM1183-B-002-11	7.0 (mg FD)	52	22	1	1 & 2	Preinfusion, 5 min before EOI, and at 0.25, 1, 2, 4, 7, 24, 72 and 168 h after EOI.
PM1183-B-003-11	7.0 (mg FD)	109	38	1	1 & 2	Preinfusion, 5 min before EOI, and at 0.25, 1, 2, 4, 7, 24, 72 and 168 h after EOI.
PM1183-B-004-13	7.0 (mg FD)	21	21	1	1 & 2	Preinfusion, 5 min before EOI, and at 0.25, 1, 2, 4, 7, 24, 72 and 168 h after EOI.
PM1183-B-005-14	3.2 (mg/m ²)	335	333	1	1 & 2	Preinfusion, 5 min before EOI, and at 0.25, 1, 3, 24 ^b , 72 ^b and 168 h after EOI.
PM1183-C-004-14	3.2 (mg/m ²)	219	204	1	1 & 2, 3 or 4	Preinfusion, 5 min before EOI, and at 1 and 168 h after EOI.

EOI, end of infusion; C, cycle; D, days; h, hours; min, minutes; PK, pharmacokinetic. ^aSubjects at RD were sampled on cycle 2. ^bOnly on cycle 1.

Source: CLPH-19-005, Page 45, Table 1.

Demographic data and laboratory values for subjects in each of the studies are shown in Table 34. The primary population of the subjects were white (76.0%). The median age of all subjects was 61 years old (range: 25-85), 32.3% were males and the median body weight and BSA were 70 kg (range: 39-154) and 1.76 m² (range: 1.29- 2.65), respectively. Medium value of albumin, AAG and total proteins were 4.0 (2.0 - 5.1) g/dL, 121 (39 - 421) mg/dL and 7.0 (4.1 - 9.0) g/dL, respectively. Hemoglobin, INR and CRP were 11.9 g/dL (range: 7.4 - 16.7), 1.0 mg/L (range: 0.8 - 3.5) and 11.1 mg/L (range: 0.2- 145.1), respectively. Median level of liver function tests AST, ALT, AP and total bilirubin were 0.6 x ULN (range: 0.2 - 4.9), 0.5 x ULN (range: 0.1 - 4.8), 0.8 x ULN (range: 0.2 - 14.2) and 0.4 x ULN (range: 0.0 - 1.9). Concomitant use of CYP3A inhibitors was found in 7.0% of subjects. In contrast, 98.3% of the subjects were treated concomitantly with CYP3A inducers. Neutrophils and platelets were 4.2 10⁹/L (range: 0.0 - 32.4) and 239 10⁹/L (range: 3 - 1247), respectively. LVEF, creatinine and CRCL were 64% (range: 43% - 92%), 0.8 mg/dL (range: 0.4 - 2.8) and 83 ml/min (range: 26 - 261), respectively. While, missing values have a high percentage for AAG (41.6%), CRP (79.9%), INR (28.1%) and CRCL (46.4%).

The majority of the 752 participants with available liver function test results were of normal liver function (625, 83.1%), 125 (16.6%) were of mild hepatic dysfunction, and 2 (0.3%) were of moderate hepatic impairment based on NCI-ODWG hepatic impairment classification. No severe hepatic impairment participant was enrolled in any study. 3 participants with missing value in AST were not assigned to any hepatic dysfunction groups. The majority of the 405 participants with available CRCL values, had normal (166; 41.0%) or mildly impaired (165; 40.7%) renal function, 73 (18.0%) had moderate renal impairment and only 1 (0.2%) had severe renal impairment. 350 participants with missing value in CRCL were not assigned to any renal dysfunction groups.

Table 34: Summary of continuous and categorical covariates.

Variable	PM1183-A-001-08	PM1183-A-002-10	PM1183-A-005-11	PM1183-B-001-10	PM1183-B-002-11
n	31	41	21	44	22
Age (y)	61 [21 - 77]	63 [20 - 80]	63 [39 - 75]	62 [42 - 83]	58 [35 - 77]
Height (cm)	167 [149 - 189]	171 [147 - 189]	167 [154 - 179]	168 [151 - 193]	163 [147 - 170]
Weight (Kg)	73 [51 - 136]	75 [45 - 133]	72 [50 - 141]	68 [39 - 114]	60 [45 - 105]
BSA (m ²)	1.83 [1.47 - 2.48]	1.86 [1.45 - 2.65]	1.80 [1.58 - 2.48]	1.75 [1.29 - 2.44]	1.62 [1.47 - 2.08]
LVEF (%)	62 [50 - 73]	58 [45 - 72]	68 [51 - 92]	64 [55 - 78]	68 [55 - 75]
Hemoglobin (g/dL)	12.8 [9.1 - 15.7]	9.2 [7.4 - 11.4]	12.0 [8.3 - 15.0]	12.1 [9.5 - 14.9]	12.2 [9.3 - 14.0]
AST (xULN)	0.6 [0.3 - 2.1]	0.6 [0.3 - 2.4]	0.6 [0.4 - 2.3]	0.7 [0.4 - 3.7]	0.5 [0.2 - 1.9]
ALT (xULN)	0.5 [0.1 - 1.2]	0.6 [0.2 - 2.9]	0.4 [0.3 - 1.5]	0.6 [0.2 - 2.8]	0.4 [0.2 - 2.2]
AP (xULN)	1.0 [0.5 - 2.3]	0.7 [0.4 - 1.8]	0.7 [0.4 - 3.9]	1.2 [0.4 - 3.8]	0.8 [0.4 - 2.9]
Bilirubin (xULN)	0.5 [0.2 - 1.0]	0.5 [0.2 - 1.1]	0.5 [0.2 - 1.2]	0.5 [0.2 - 1.7]	0.3 [0.1 - 0.9]
Albumin (g/dL)	4.0 [3.3 - 4.7]	3.4 [2.1 - 4.6]	3.8 [2.8 - 4.5]	3.9 [2.6 - 4.9]	3.8 [2.8 - 4.7]
AAG (mg/dL)	110 [72 - 219]	missing	missing	91 [44 - 206]	151 [106 - 371]
CRP (mg/L)	13.2 [0.2 - 113.9]	missing	25.0 [5.0 - 97.0]	7.6 [0.2 - 126.0]	11.5 [2.6 - 145.1]
INR	1.1 [0.9 - 3.2]	1.2 [1.0 - 1.6]	1.1 [1.0 - 2.5]	1.0 [0.9 - 1.4]	1.0 [0.8 - 1.2]
Creatinine (mg/dL)	0.9 [0.6 - 1.5]	0.8 [0.4 - 1.8]	1.0 [0.4 - 1.3]	0.7 [0.4 - 1.2]	0.7 [0.4 - 1.6]
CRCL (mL/min)	86 [52 - 168]	109 [48 - 200]	missing	missing	missing
Total proteins (g/dL)	7.6 [6.7 - 8.8]	6.2 [4.3 - 8.2]	6.8 [5.9 - 8.4]	6.9 [5.2 - 8.3]	7.1 [6.0 - 8.3]
Neutrophils (10 ⁹ /L)	5.0 [2.3 - 10.5]	0.2 [0.0 - 15.4]	4.2 [2.5 - 10.3]	4.1 [1.7 - 12.2]	4.0 [1.7 - 8.7]
Platelets (10 ⁹ /L)	276 [106 - 450]	23 [3 - 127]	241 [104 - 421]	248 [110 - 571]	261 [123 - 531]

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ZEPZELCA (Lurbinectedin)

Variable	PM1183-B-003-11	PM1183-B-004-13	PM1183-B-005-14	PM1183-C-004-14	Total	Missing covariates
n	38	21	333	204	755	-
Age (y)	52 [32 - 73]	65 [46 - 74]	60 [18 - 83]	63 [25 - 85]	61 [18 - 85]	0 (0.0)
Height (cm)	160 [147 - 172]	168 [152 - 190]	165 [141 - 193]	161 [147 - 177]	164 [141 - 193]	2 (0.3)
Weight (Kg)	70 [43 - 154]	74 [39 - 124]	71 [43 - 141]	66 [42 - 125]	70 [39 - 154]	0 (0.0)
BSA (m ²)	1.75 [1.36 - 2.41]	1.87 [1.36 - 2.25]	1.80 [1.34 - 2.61]	1.69 [1.34 - 2.40]	1.76 [1.29 - 2.65]	1 (0.1)
LVEF (%)	68 [55 - 86]	65 [54 - 77]	64 [43 - 82]	64 [50 - 80]	64 [43 - 92]	10 (1.3)
Hemoglobin (g/dL)	11.9 [9.0 - 14.9]	12.9 [10.0 - 16.7]	11.9 [8.8 - 16.5]	12.1 [9.0 - 15.1]	11.9 [7.4 - 16.7]	0 (0.0)
AST (xULN)	0.8 [0.5 - 4.8]	0.5 [0.2 - 1.0]	0.6 [0.2 - 4.9]	0.6 [0.2 - 2.5]	0.6 [0.2 - 4.9]	3 (0.4)
ALT (xULN)	0.5 [0.2 - 3.6]	0.4 [0.2 - 1.2]	0.5 [0.1 - 4.8]	0.4 [0.2 - 1.8]	0.5 [0.1 - 4.8]	0 (0.0)
AP (xULN)	0.8 [0.4 - 3.5]	0.7 [0.2 - 1.5]	0.8 [0.2 - 14.2]	0.7 [0.3 - 3.7]	0.8 [0.2 - 14.2]	2 (0.3)
Bilirubin (xULN)	0.4 [0.2 - 1.4]	0.4 [0.2 - 1.0]	0.4 [0.0 - 1.9]	0.3 [0.0 - 0.8]	0.4 [0.0 - 1.9]	0 (0.0)
Albumin (g/dL)	4.2 [3.6 - 4.7]	3.9 [3.2 - 5.0]	4.0 [2.6 - 5.1]	4.0 [2.0 - 4.9]	4.0 [2.0 - 5.1]	0 (0.0)
AAG (mg/dL)	104 [64 - 203]	141 [65 - 243]	122 [39 - 421]	missing	121 [39 - 421]	314 (41.6)
CRP (mg/L)	7.4 [0.5 - 37.1]	14.9 [0.5 - 77.3]	missing	missing	11.1 [0.2 - 145.1]	603 (79.9)
INR	1.0 [0.9 - 1.3]	1.0 [0.9 - 1.6]	1.0 [0.8 - 3.5]	missing	1.0 [0.8 - 3.5]	212 (28.1)
Creatinine (mg/dL)	0.6 [0.4 - 1.2]	0.9 [0.6 - 2.0]	0.8 [0.4 - 2.8]	0.8 [0.4 - 1.9]	0.8 [0.4 - 2.8]	0 (0.0)
CRCL (mL/min)	missing	missing	91 [26 - 261]	77 [33 - 195]	83 [26 - 261]	350 (46.4)
Total proteins (g/dL)	7.1 [5.2 - 8.5]	7.2 [6.3 - 9.0]	7.0 [4.1 - 8.8]	7.2 [4.5 - 8.5]	7.0 [4.1 - 9.0]	5 (0.7)
Neutrophils (10 ⁹ /L)	3.8 [1.7 - 7.8]	5.8 [2.5 - 19.4]	4.3 [1.4 - 32.4]	4.0 [1.6 - 12.1]	4.2 [0.0 - 32.4]	2 (0.3)
Platelets (10 ⁹ /L)	220 [122 - 610]	283 [161 - 556]	234 [102 - 894]	251 [101 - 1247]	239 [3 - 1247]	0 (0.0)

Summary of subject characteristics for continuous covariates at baseline, expressed as median and range in brackets. Missing covariates are expressed as number of subjects and percentage in parenthesis. AAG, alpha-1-acid glycoprotein; AP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BSA, body surface area; CRCL, creatinine clearance; CRP, C-reactive protein; LVEF, left ventricular ejection fraction; n, number of subjects; NA, not available.

Variable	Value	PM1183-A-001-08	PM1183-A-002-10	PM1183-A-005-11	PM1183-B-001-10	PM1183-B-002-11
Ascites	No	28 (90.3)	41 (100.0)	17 (81.0)	40 (90.9)	19 (86.4)
	Yes	3 (9.7)	0 (0.0)	4 (19.0)	4 (9.1)	3 (13.6)
CYP3A inducers	No	6 (19.4)	0 (0.0)	1 (4.8)	0 (0.0)	1 (4.5)
	Yes	22 (71.0)	41 (100.0)	20 (95.2)	44 (100.0)	21 (95.5)
	Missing	3 (9.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
CYP3A inhibitors	No	27 (87.1)	10 (24.4)	20 (95.2)	42 (95.5)	20 (90.9)
	Yes	1 (3.2)	31 (75.6)	1 (4.8)	2 (4.5)	2 (9.1)
	Missing	3 (9.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Liver metastasis	No	10 (32.3)	41 (100.0)	8 (38.1)	12 (27.3)	13 (59.1)
	Yes	21 (67.7)	0 (0.0)	13 (61.9)	32 (72.7)	9 (40.9)
Performance status	0	14 (45.2)	6 (14.6)	6 (28.6)	8 (18.2)	9 (40.9)
	1	17 (54.8)	23 (56.1)	15 (71.4)	36 (81.8)	12 (54.5)
	2	0 (0.0)	11 (26.8)	0 (0.0)	0 (0.0)	1 (4.5)
	Missing	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)
Race	White	27 (87.1)	0 (0.0)	18 (85.7)	41 (93.2)	16 (72.7)
	Black	3 (9.7)	0 (0.0)	1 (4.8)	1 (2.3)	0 (0.0)
	Asian	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Other/missing	0 (0.0)	41 (100.0)	2 (9.5)	2 (4.5)	6 (27.3)
Sex	Male	21 (67.7)	26 (63.4)	6 (28.6)	31 (70.5)	0 (0.0)
	Female	10 (32.3)	15 (36.6)	15 (71.4)	13 (29.5)	22 (100.0)

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Variable	Value	PM1183-B-003-11	PM1183-B-004-13	PM1183-B-005-14	PM1183-C-004-14	Total
Ascites	No	38 (100.0)	20 (95.2)	321 (96.4)	149 (73.0)	673 (89.1)
	Yes	0 (0.0)	1 (4.8)	12 (3.6)	55 (27.0)	82 (10.9)
CYP3A inducers	No	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)	10 (1.3)
	Yes	38 (100.0)	21 (100.0)	331 (99.4)	204 (100.0)	742 (98.3)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.4)
CYP3A inhibitors	No	38 (100.0)	20 (95.2)	326 (97.9)	196 (96.1)	699 (92.6)
	Yes	0 (0.0)	1 (4.8)	7 (2.1)	8 (3.9)	53 (7.0)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.4)
Liver metastasis	No	15 (39.5)	15 (71.4)	196 (58.9)	154 (75.5)	464 (61.5)
	Yes	23 (60.5)	6 (28.6)	137 (41.1)	50 (24.5)	291 (38.5)
Performance status	0	23 (60.5)	11 (52.4)	126 (37.8)	117 (57.4)	320 (42.4)
	1	15 (39.5)	10 (47.6)	187 (56.2)	80 (39.2)	395 (52.3)
	2	0 (0.0)	0 (0.0)	20 (6.0)	7 (3.4)	39 (5.2)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Race	White	35 (92.1)	21 (100.0)	240 (72.1)	176 (86.3)	574 (76.0)
	Black	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.8)
	Asian	0 (0.0)	0 (0.0)	6 (1.8)	2 (1.0)	9 (1.2)
	Other/missing	2 (5.3)	0 (0.0)	87 (26.1)	26 (12.7)	166 (22.0)
Sex	Male	0 (0.0)	16 (76.2)	144 (43.2)	0 (0.0)	244 (32.3)
	Female	38 (100.0)	5 (23.8)	189 (56.8)	204 (100.0)	511 (67.7)

Summary of subject characteristics for categorical covariates at baseline, expressed as number of subjects and percentage in parenthesis.

Source: CLPH-19-005, Page 48-51, Table 4-7.

The population PK analysis was conducted via nonlinear mixed-effects modeling with the NONMEM software, version 7.3.0 using the Stochastic Approximation Expectation Maximization (SAEM) and Monte Carlo Importance Sampling Expectation Maximization (IMP) estimation methods. Plasma concentration of lurbinectedin collected before the first dose were excluded from the PK analysis as well as post-dose observations that were below the limit of quantification (BLQ).

The plasma concentrations of lurbinectedin data were described by a three-compartment disposition model with first-order elimination. Log transformed concentration data was used for modeling in Applicant's analysis. Several covariates including albumin, AAG, CRP, BSA, concomitant CYP3A inhibitors, gender, performance status, ascites and C004 trial were tested for all the structural parameters with random effects based on linear and power functions. The final population PK parameters for lurbinectedin and bootstrap test result are presented in Table 35. The final PK model was parameterized in terms of total plasma elimination clearance (CL), apparent volumes of distribution of the central, shallow and deep peripheral compartment (V1, V2 and V3, respectively) and two intercompartmental distribution clearances (Q2 and Q3). Estimated fixed and random effect parameters were estimated with good precision (%RSE < 25.6%). The magnitude of the interindividual variability was moderate for CL/F (49.9%CV) and AAGC004 (54.2 %CV). Residual variability was moderate. The median of the bootstrap replicates were very similar to the population estimates, which were contained within the 95% CI obtained from the bootstrap analysis. 95% CIs did not contain any null value for any parameters.

Table 35: Parameter estimates and bootstrap results of final population PK model

Model description Model parameter	Final model	Non-parametric bootstrap (n=400)	
	Estimate (RSE%)	Median (RSE%)	CI95%
V1 (L)	12.8 (3.80)	12.4 (3.99)	11.3 - 13.4
CL (L/h)	10.6 (2.25)	10.5 (2.21)	9.95 - 10.9
V3 (L)	454 (2.26)	447 (3.16)	424 - 480
Q3 (L/h)	16.0 (2.05)	15.9 (2.36)	15.2 - 16.7
V2 (L)	37.5 (2.50)	37.0 (2.24)	35.5 - 38.7
Q2 (L/h)	31.8 (2.38)	31.7 (3.13)	29.9 - 33.9
RV (CV%)			
RV	31.7 (2.52)	30.9 (2.39)	29.4 - 32.5
IIV (CV%)			
V1	34.6 (13.2)	31.7 (31.2)	21.7 - 41.3
CL	49.9 (3.96)	50.0 (9.42)	45.7 - 54.4
V3	39.1 (5.33)	37.2 (31.2)	31.5 - 45.5
Q3	27.2 (6.54)	27.0 (19.1)	24.2 - 30.1
V2	33.4 (7.78)	30.7 (15.7)	25.6 - 35.0
RV	59.2 (3.42)	59.6 (15.7)	55.0 - 63.6
AAGC004	54.2 (13.6)	47.1 (27.7)	35.7 - 60.3
IIV correlation (%)			
Q3 – V3	77.0 (6.42)	75.7 (13.2)	77.5 - 72.4
Covariate parameters			
CLAAG	-0.627 (8.36)	-0.727 (10.3)	-0.858 - -0.568
CLALB	0.746 (19.6)	0.633 (28.2)	0.261 - 0.979
CLINH1	-0.408 (12.2)	-0.407 (14.6)	-0.517 - -0.275
Q3AAG	-0.578 (8.57)	-0.603 (8.18)	-0.697 - -0.504
Q3BSA	0.990 (14.2)	0.964 (15.3)	0.658 - 1.227
Q3SEXF	-0.195 (14.4)	-0.198 (16.3)	-0.254 - -0.130
V1AAG	-0.992 (9.78)	-1.032 (9.83)	-1.233 - -0.839
V2AAG	-0.653 (10.6)	-0.675 (9.99)	-0.803 - -0.541
V2BSA	0.423 (25.6)	0.390 (28.5)	0.188 - 0.630
V3AAG	-0.517 (11.8)	-0.600 (17.7)	-0.758 - -0.319
V3BSA	1.915 (8.70)	1.802 (10.1)	1.474 - 2.174
V3SEXF	-0.244 (13.1)	-0.245 (15.1)	-0.312 - -0.174
V1BSA	0.748 (21.3)	0.744 (23.1)	0.436 - 1.129
AAGC004	260 (7.53)	230 (9.42)	201 - 280

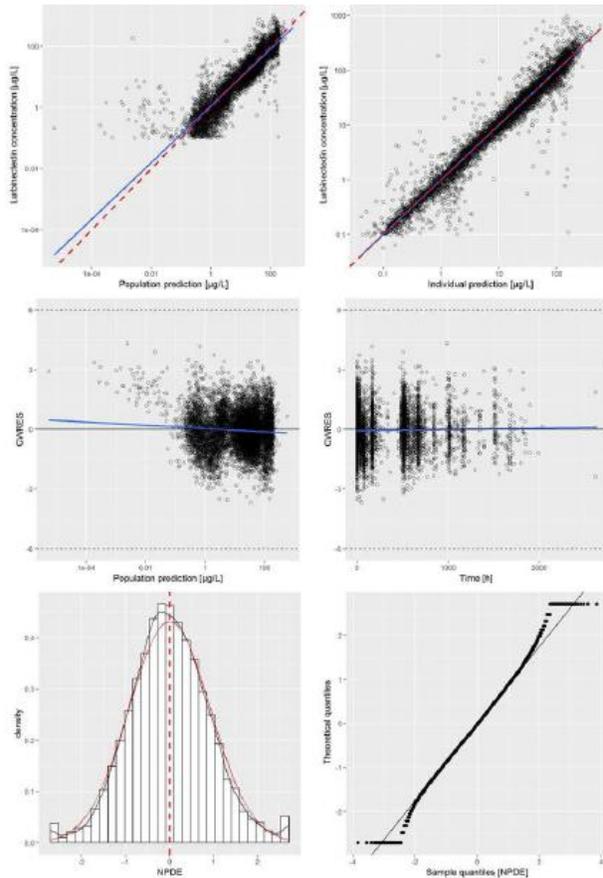
RSE, relative standard error; RV, residual variability; IIV, inter-individual variability; CI95%, confidence interval 95%; CL, clearance; Q2, intercompartmental clearance for shallow compartment; Q3, intercompartmental clearance for deep compartment; V1, apparent volume of distribution of central compartment; V2, apparent volume of distribution of shallow peripheral compartment; V3, apparent volume of distribution of deep peripheral compartment; AAG, alpha-1-acid glycoprotein; ALB, albumin; INH, CYP3A inhibitor; SEXF, gender; CLAAG, relationship between CL and AAG; CLALB, relationship between CL and albumin; CLINH, relationship between CL and CYP3A inhibitors; Q3AAG, relationship between Q3 and AAG; Q3BSA, relationship between Q3 and BSA; Q3SEXF, relationship between Q3 and gender; V1AAG, relationship between V1 and AAG; V1BSA, relationship between V1 and BSA; V2AAG, relationship between V2 and AAG; V2BSA, relationship between V2 and BSA; V3AAG, relationship between V3 and AAG; V3BSA, relationship between V3 and BSA; V3SEXF, relationship between V3 and gender; AAGC004, AAG in study C-004 CORAIL.

Source: CLPH-19-005, Page 53-54, Table 10.

The diagnostic plots for the final PK model are shown in **Error! Reference source not found.**
The VPC (visual predictive check) and pcVPC (Prediction-corrected visual predictive check) stratified by study on the final PK model are shown in **Error! Reference source not found.** and

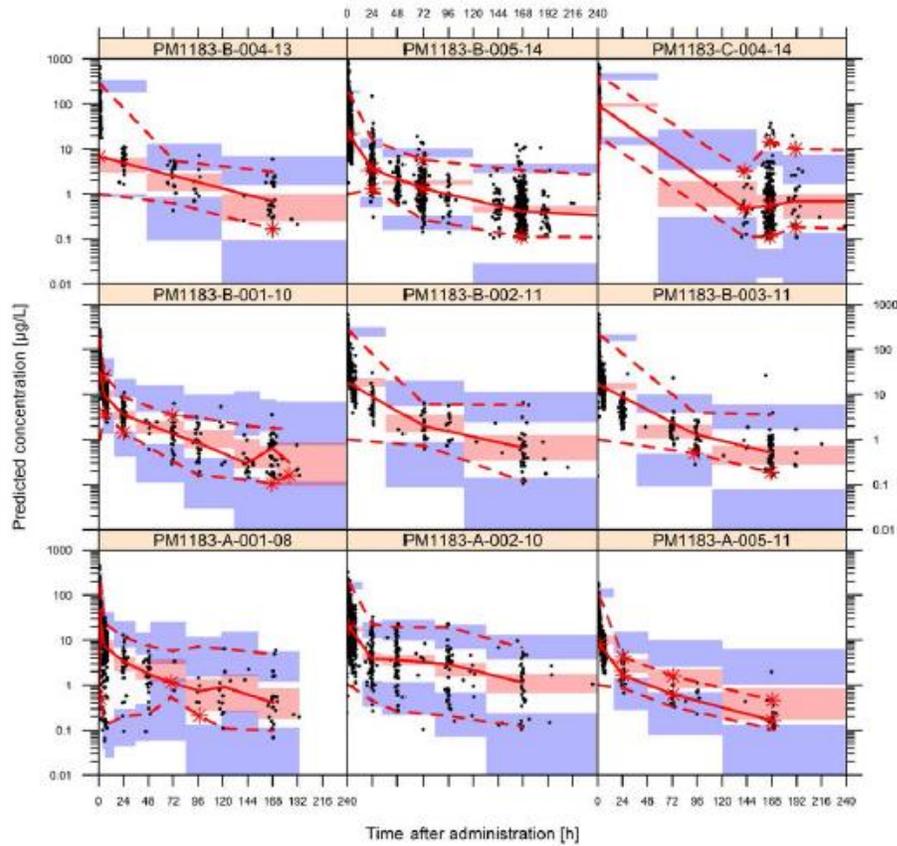
Error! Reference source not found.15. The model described the observed data well and the model predictions were generally within the 90% prediction intervals. No apparent bias was observed in the overall model fit for the data.

Figure 12: Diagnostic plots for the final population PK model



Source: CLPH-19-050, Page 163, Figure 32

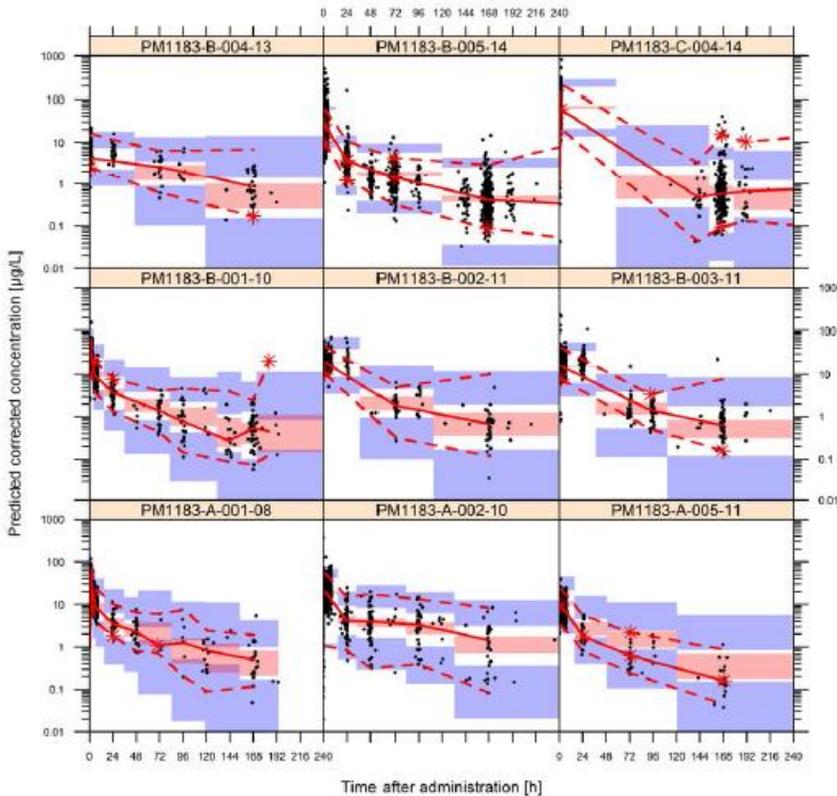
Figure 13: Visual predicted check for final population PK model



Slash and solid red lines correspond to the observed 5th, 50th and 95th percentiles. Red and blue shadow areas correspond to the CI 95% predicted by the final model. Dots are the observed concentrations.

Source: CLPH-19-050, Page 163, Figure 32.

Figure 14: Predicted corrected visual predicted check for final population PK model.

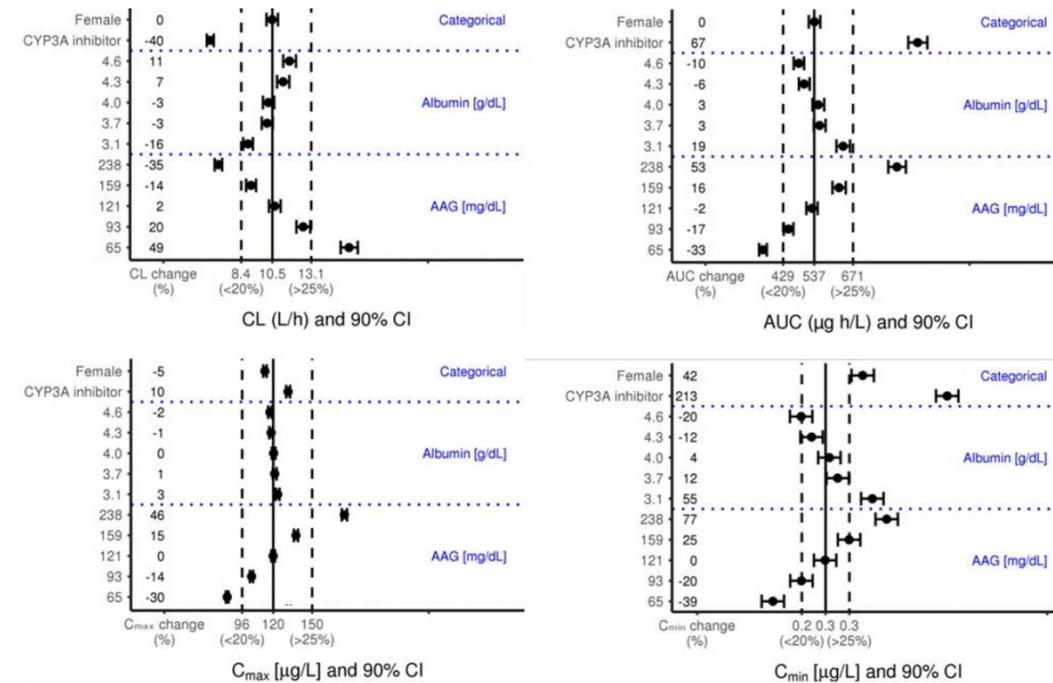


Slash and solid red lines correspond to the corrected observed 5th, 50th and 95th percentiles. Red and blue shadow areas correspond to the CI 95% predicted corrected by the final model. Dots are the corrected observed concentrations.

Source: CLPH-19-050, Page 164, Figure 33

Stochastic simulations were performed to evaluate the covariate effects for PK parameters. (Error! Reference source not found.16) The effects of covariates albumin and AAG on CL were higher than 20% at the extreme percentiles when compared to typical individual. The presence of CYP3A inhibitors showed a 40% reduction of CL. The effects of covariates on CL were inverse to those observed on AUC. At percentile 5 of albumin, AUC was 21% higher than the typical individual, and at percentile 95 if AAG, AUC was 46% higher. CYP3A inhibitors increased AUC by 67%. No significant change of AUC and CL were observed with the change of BSA at both BSA based dosing or FD dosing. (data not shown)

Figure 15: Forest Plot for CL, AUC, Cmax, Cmin.



Central vertical solid line: typical value; Vertical dashed lines: differences of 20% and 25% from typical value; Numbers at the left side: Percentage of change from typical value; Dots and error bars: percentage of change from typical value and 90% CI.

Source: CLPH-19-005, Page 166-169, Figure 35-41

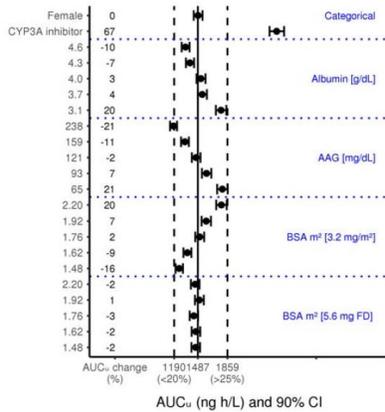
With the population PK model of lurbinectedin, the unbound AUC (AUC_u) was calculated from the *post hoc* prediction and *in vitro* protein binding data. The unbound fraction of lurbinectedin was mainly affected by AAG and albumin levels, which was calculated by the following equations:

$$AUC_u = \frac{AUC_{tot} * K_{d1} * K_{d2}}{L_1 * AAG * K_{d2} + L_2 * Albumin * K_{d1} + K_{d1} * K_{d2}}$$

where L_1 and L_2 are the scaling factors between lurbinectedin (MW 784.881) and AAG (MW 68000), and albumin (MW 42000). L_1 and L_2 were fixed to 0.01869 ($MW_{lurbinectedin}/MW_{AAG}$) and 0.01154 ($MW_{lurbinectedin}/MW_{Albumin}$), respectively assuming 1:1 molar binding ratio for both proteins. K_{d1} and K_{d2} are the equilibrium dissociation constants between lurbinectedin and AAG and albumin, respectively.

The effects of covariates albumin and AAG on AUC_u were not significantly different compared to typical individual for AUC_u . While presence of CYP3A inhibitors showed a 67% increase of AUC_u . (Figure 17)

Figure 16: Forest Plot for AUC₀.



Central vertical solid line: typical value; Vertical dashed lines: differences of 20% and 25% from typical value; Numbers at the left side: percentage of change from typical value; Dots and error bars: percentage of change from typical value and 90% CI.

Source: CLPH-19-005, Page 167, Figure 38.

Reviewer’s Comments:

The population PK model developed by the Applicant was verified by the reviewer. The model appears to be reasonable in general because there was a good agreement between observations and predictions.

Using the final population PK model, post hoc individual clearances (CL/F) were used to estimate the influence of renal impairment and hepatic impairment on PK. The results were similar as reviewer’s analysis and acceptable. (Table 36 and Table 37) There were no significant differences in apparent clearance of lurbinectedin in participants with mild or moderate renal impairment compared to participants with normal renal function and no significant differences in participants with mild hepatic impairment compared to participants with normal hepatic function.

Although the presence of CYP3A4 inhibitors was significant covariate for CL/F in the population PK model, evaluation of the influence of CYP3A4 inhibitors on PK with population PK result were not appropriate as there was not sufficient information (detailed dose given, the time of drug administration and the time of drug discontinuation during the treatment) recorded. The population PK dataset also showed that all 53 subjects who took CYP3A4 inhibitors also took CYP3A4 inducers during the study. Additionally, the analysis pooled all CYP3A4 inhibitors without making distinction between the various classes of inhibitors (i.e., weak, moderate, or strong inhibitors).

Table 36: Impact of mild, moderate and severe renal impairment on lurbinectedin apparent clearance.

Renal Function	Number of Participants	GMR (90% CI)
----------------	------------------------	--------------

Normal	166	Reference
Mild Impairment	165	0.89 (0.79, 0.99)
Moderate Impairment	73	0.77 (0.67, 0.88)
Severe Impairment	1	0.88

Source: Reviewer's analysis

Table 37: Impact of mild or moderate hepatic impairment on lurbinectedin apparent clearance.

Renal Function	Number of Participants	GMR (90% CI)
Normal	625	Reference
Mild Impairment	125	0.97 (0.88, 1.07)
Moderate Impairment	2	0.81

Source: Reviewer's analysis

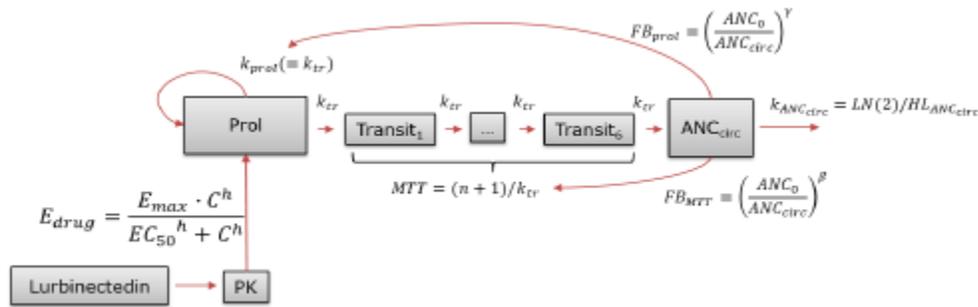
19.1.2 Population PD analysis

The Applicant conducted a population PKPD analysis to describe the time course of absolute neutrophil counts (ANC) and platelets (PLT) following the treatment of lurbinectedin. Data was collected in all patients with intravenous administration of lurbinectedin as a single-agent from two phase I studies (PM1183-A-001-08, PM1183-A-005-11) and three phase II studies (PM1183-B-001-10, PM1183-B-002-11, PM1183-B-003-11). The datasets included 3421 ANC observations, 3546 PLT observations from 244 subjects of which 156 were also sampled for lurbinectedin analysis with 2636 samples. Lurbinectedin concentration of pre-infusion samples (93), BLQ samples (72) and aberrant concentrations (7) were excluded from the analysis. One ANC sample was excluded as it presented extremely high value inconsistent with the profile and no PLT samples was excluded in the analysis.

The population PKPD analysis was conducted via nonlinear mixed-effects modeling with the NONMEM software, version 7.3.0 using the Stochastic Approximation Expectation Maximization (SAEM) and Monte Carlo Importance Sampling Expectation Maximization (IMP) estimation methods. Population PK parameters were fixed to the final parameters reported in CLPH-17-019, which is similar as the final population PK model described in section 19.4.1. The time course of ANC and plasma concentration of lurbinectedin were described by a multi-compartment transit model with eight compartments: one compartment represented the proliferative cells, such as stem cells and other progenitor cells; six transit compartments with maturing cells; and, one compartment of the circulating ANC cells. Two feedback loops incorporated into the models to describe the rebound of cells compared to the estimated baseline value of ANC and the reduction of mean transit time (MTT) when ANC decreased. The drug effect of lurbinectedin was assumed to reduce the proliferation rate or stimulation the

killing rate with E_{max} function. (Quartino A. L. et al Invest New Drugs (2012) 30:833–845) The model structure was shown in **Error! Reference source not found.8**. The Several covariates including CYP inducers, tumor type, BSA, ALB, AAG, CRP, gender, age and GCSF treatment for patients with G4 neutropenia were tested.

Figure 17: Presentation of the semi-mechanistic myelosuppression (ANC) model.



Source: CLPH-18-013, Page 22.

The final population PKPD parameters for the time course of ANC are presented in

Table 38. Model parameters, random effects and effects of covariates were estimated with good precision as RSE were <10%, <15%, and <30%, respectively. The final model included AAG and GCSF as significant covariates for the structural parameters MTT and AAG, SENS (ovarian and pancreatic tumors as sensitive) and GCSF for EC₅₀.

Table 38. Parameter estimates for ANC final population PKPD model

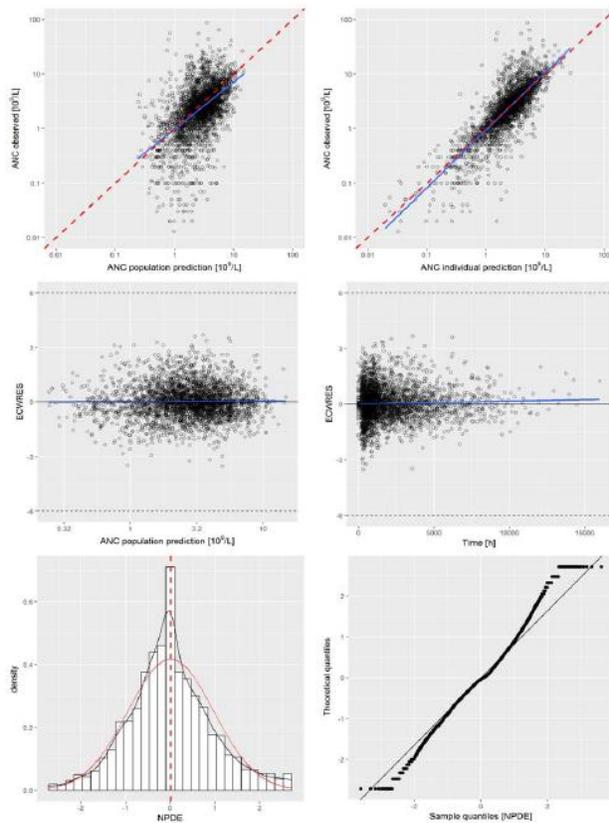
Model description	Final model	
run number	run18	
ofv	-1678	
cn	27.7	
Model parameter	Estimate (RSE%)	Shk (%)
Base ($10^9/L$)	-	
MTT (h)	140 (1.94)	
E_{max}	1.15 (9.82)	
EC ₅₀ ($\mu g/L$)	13.5 (15.2)	
β	0.243 (4.97)	
γ	0.379 (3.68)	
k_{e0} ($\times 10^{-2}$ 1/h)	1.99 (7.59)	
GCSFEC50	3.38 (3.72)	
GCSFMTT	-0.353 (0.695)	
RV (CV%)		
RV	51.8 (4.1)	9.19
ISV (CV%)		
η_{BASE}	-	-
η_{MTT}	16.6 (11)	35.1
$\eta_{E_{max}}$	-	-
$\eta_{EC_{50}}$	76.6 (10.1)	19.7
η_{RV}	59.1 (6.18)	11.2
Covariate parameters		
EC50AAG ($\times 10^{-3}$)	7.40 (27.7)	
MTTAAG ($\times 10^{-3}$)	-1.48 (22.6)	
EC50SENS	-0.377 (21.6)	

Source: CLPH-18-013, Page 51, Table 8.

The goodness of fit plots, VPC and pcVPC for the final model are shown in Error! Reference source not found. and

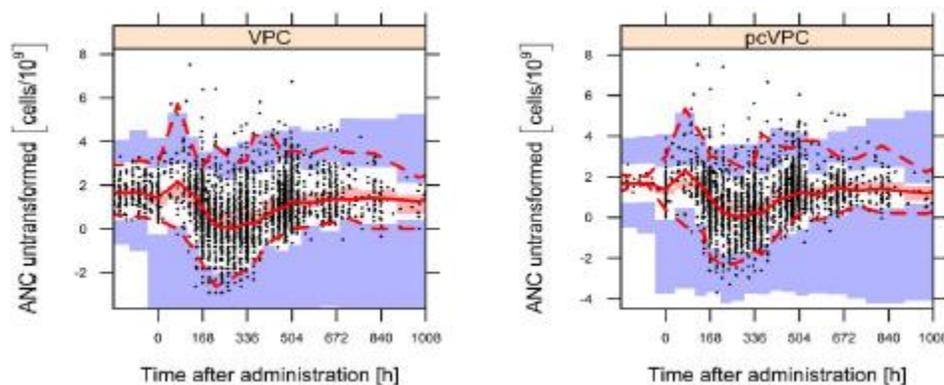
. No systematic bias was observed, and the model is adequate to describe the data. The results of VPC and pcVPC showed that the model was able to predict correctly the ANC observations and no time dependency in the time course of ANC is expected.

Figure 18: Goodness of fit plots of the final ANC model.



ECWRES, Monte Carlo calculated weighted residuals; NPDE, normalized prediction distribution error.
Source: CLPH-18-013, Page 102, Figure 10.

Figure 19: VPC (left) and pcVPC (right) pooled for final ANC model.



Source: CLPH-18-013, Page 121, Figure 22.

The time course of PLT and plasma concentration of lurbinectedin were described by a similar model as the ANC model. The administration of platelets bag was modeled as a dose of platelets in the circulating pool of platelets. The drug effect was modelled as a sigmoid E_{max}

function with Hill parameter. Covariates including LVMT, BSA, ALB, AAG, CRP, gender, age and GCSF treatment for patients with G4 neutropenia were tested and the final population PKPD parameters for the time course of PLT are presented in

Table 39. Model parameters, random effects and effects of covariates were estimated with good precision as RSE were <10%, <20%, and <40%, respectively. The shrinkage for MTT, EC50 and RV were lower than 40%. In the final model, SENS, BSA and AAG were identified as significant covariate for EC₅₀.

Table 39: Parameter estimates for PLT final population PKPD model

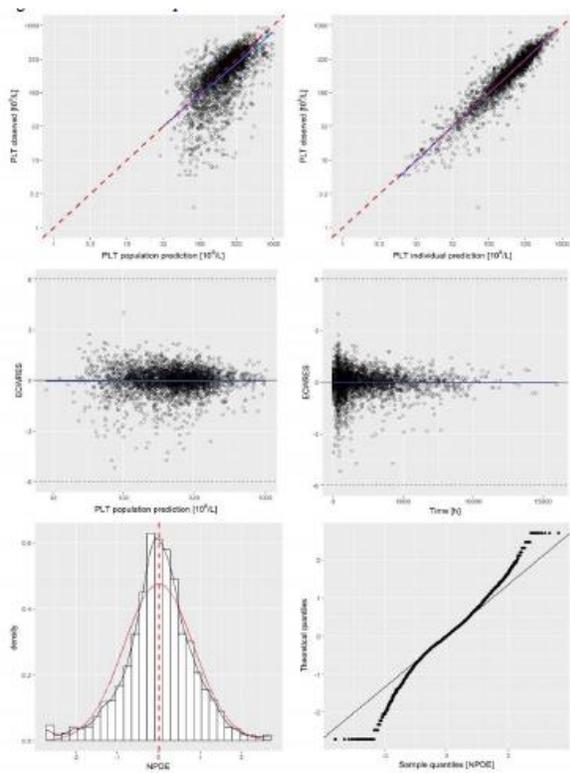
Model description	Final model	
run number	run18	
ofv	-7312.4	
cn	20.4	
Model parameter	Estimate (RSE%)	Shk (%)
MTT (h)	126 (0.84)	
E _{max}	-	
EC ₅₀ (µg/L)	4.93 (5.73)	
β	0.329 (3.93)	
γ	0.512 (2.93)	
Hill	5.71 (8.59)	
Pooled PLT (x 10 ⁹ /L)	87.2 (6.88)	
RV (CV%)		
RV	21.3 (1.87)	6.54
ISV (CV%)		
η MTT	8.93 (14.6)	31.8
η E _{max}	-	-
η EC ₅₀	47.3 (8.78)	25.6
Covariate parameters		
EC50AAG	0.907 (12.8)	
EC50BSA	0.481 (43.2)	
EC50SENS	-0.235 (25.5)	

Source: CLPH-18-014, Page 51, Table 8.

The goodness of fit plots, VPC and pcVPC for the final model are shown in Error! Reference source not found. **and**

. No systematic bias was observed, and the model is adequate to describe the data. The results of VPC and pcVPC showed that the model was able to predict correctly the PLT observations and no time dependency in the time course of PLT is expected.

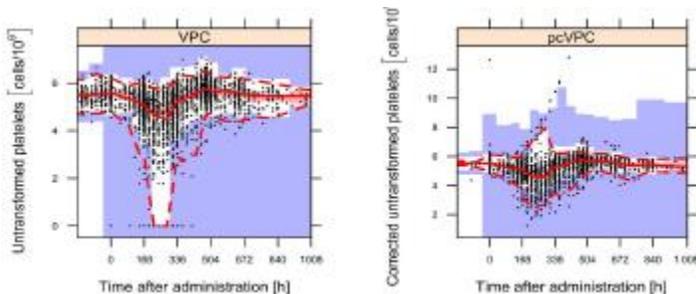
Figure 20: Goodness of fit plots of the final PLT model.



ECWRES, Monte Carlo calculated weighted residuals, NPDE, normalized prediction distribution error.

Source: CLPH-18-014, Page 100, Figure 9.

Figure 21: VPC (left) and pcVPC (right) pooled for final PLT model.



Source: CLPH-18-014, Page 119, Figure 21.

Reviewer's comments:

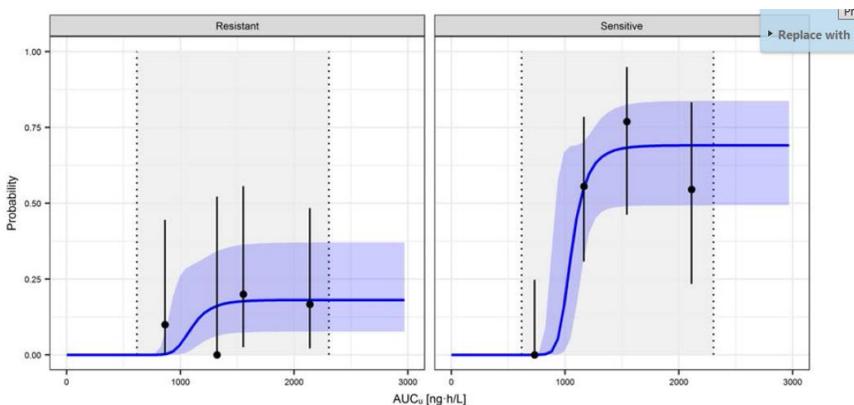
The population PKPD models developed by the Applicant were verified by the reviewer. In general, the models are reasonable because of the good agreement between observations and predictions. In the final ANC population PKPD model, GCSF is significant covariate for MTT, which is reasonable as GCSF is known to shorten the maturation time for ANC in the bone marrow. While the mechanism how GCSF affect the drug effect of lurbinectedin is unknown.

19.1.3 Exposure-Response (E-R) analysis

19.1.3.1 E-R analysis of efficacy of lurbinectedin

The E-R relationship of ORR and lurbinectedin exposure was evaluated with participants with small cell lung cancer (SCLC) in study PM1183-B-005-14. The participants were separated into resistant group (CTFI < 90 days) and sensitive group (CTFI ≥ 90 days). ORR assessed by IRC in the cohort of patients with SCLC (n=96) was 33.3% (95% CI: 24.0 - 43.7). ORR assessed in the sensitive (n=57) and resistant (n=39) patients was 45.6% (95% CI: 32.4 - 59.3) and 15.4% (95% CI: 5.9 - 30.5). The relationship between ORR and AUC_u was described by a sigmoid E_{max} model with a hill factor fixed to 10, where CTFI modified the E_{max} parameter. (**Error! Reference source not found.**) Statistically significant CTFI-dependent increase in ORR with high AUC_u values was found. In this sense, the maximum ORR for sensitive and resistant SCLC patients were 69.1% (95% CI: 49.3 - 83.8) and 18.1% (95% CI: 7.7 - 37.1), respectively. The 95% of the maximum ORR for sensitive and resistant patients was achieved for AUC_u higher 1337 and 1433 ng*h/L, respectively.

Figure 22: Relationship between ORR by IRC and AUC_u stratified by CTFI.



Solid black dots represent the proportion of responders grouped by quartiles of AUC_u and plotted at the median AUC_u for each quartile, in resistant (left panel) and sensitive (right panel) patients. Bars represent the 95% CI for the proportion of each quartile. Blue curve and shaded area represent predicted values and 95% CI of model-predicted ORR, respectively. The vertical point lines and the grey shaded area represent the 95% prediction interval of the observed AUC_u .

Source: CLPH-19-003, Page 72, Figure 2.

ORR simulations were performed for lurbinectedin administered at 3.2 mg/m² and at 5.6 mg FD in patients with resistant and sensitive disease and different BSA values. The result did not show significant differences in the two dosage groups. Relative to the equivalent lurbinectedin fixed dose, lurbinectedin BSA-based dosing showed a 12% reduction in the ORR between patients with BSA >1.95 m² and <1.65 m². (Table 40)

Table 40. Simulation of percentage of ORR at 3.2 mg/m² and 5.6 mg for resistant and sensitive patients with SCLC.

CTFI	ORR (CI 95%) at 3.2 mg/m ² (%)	ORR (CI 95%) at 5.6 mg (%)
Resistant	12.3 (10.6 - 14.2)	12.1 (10.5 - 13.9)
Sensitive	48.2 (43.8 - 52.8)	47.7 (43.0 - 51.8)

CTFI	BSA quartile	min - max BSA (m ²)	ORR (CI 95%) at 3.2 mg/m ² (%)	ORR (CI 95%) at 5.6 mg (%)
Resistant	1st	1.52 - 1.69	10.5 (5.0 - 14.8)	11.9 (6.6 - 15.5)
	2nd and 3th	1.70 - 1.90	12.3 (9.8 - 15.3)	12.0 (9.4 - 15.0)
	4th	1.97 - 2.24	14.0 (9.3 - 17.7)	12.6 (7.8 - 16.7)
Sensitive	1st	1.44 - 1.69	41.9 (29.4 - 56.2)	47.6 (36.3 - 60.8)
	2nd and 3th	1.70 - 1.97	48.7 (40.9 - 56.1)	47.4 (39.6 - 54.4)
	4th	1.98 - 2.61	53.2 (38.9 - 63.7)	48.2 (34.0 - 61.3)

Simulation of percentage of ORR at 3.2 mg/m² and 5.6 mg for resistant and sensitive SCLC and by BSA quartiles.

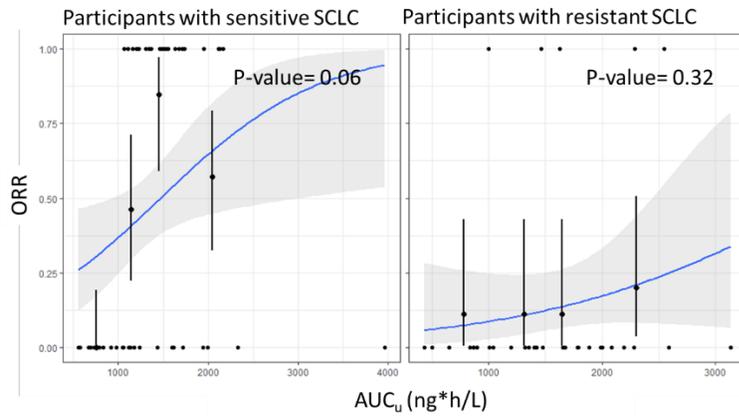
Source: CLPH-19-003, Page 48, Table 18-19.

Reviewer's comments:

The result of the sigmoid E_{max} model for ORR vs. lurbinectedin exposure was verified by the reviewer. The reviewer also conducted an independent E-R analysis for ORR and lurbinectedin exposures with logistic regression model for participants with resistant SCLC and sensitive SCLC. AUC_u was identified to be the best predictor for ORR in both groups and no other significant covariates were identified. The results were shown in **Error! Reference source not found.24**. A shallow and non-significant E-R relationship for participants with resistant SCLC was identified and there is no significant difference in ORR in different exposure groups. While participants with sensitive SCLC in lowest quartile of AUC_u had significant low ORR than other three quartiles. The level of AAG was slightly higher in the lowest quartile of lurbinectedin AUC_u comparing with other three quartiles. (**Error! Reference source not found.**) This is because that AAG could bind to lurbinectedin and affect the unbound concentration and AUC of lurbinectedin. The baseline tumor size was also slightly larger in the lowest quartile of lurbinectedin AUC_u . The positive exposure-response relationship for ORR suggests there is a potential that increasing lurbinectedin dose for SCLC patients with lower exposure (e.g., AUC_u (first cycle) lower than 1000 ng*h/L) might further improve the efficacy, especially for sensitive SCLC patients. But the relationship between drug exposure and efficacy has not been fully characterized due to the limit number of subjects ($n=92$ for all SCLC patients and $n=55$ for sensitive SCLC patients) and unidentified confounding factors. Given the promising efficacy results of lurbinectedin and orphan designation of ES-SCLC, the proposed 3.2 mg/m² Q3W appears to be acceptable.

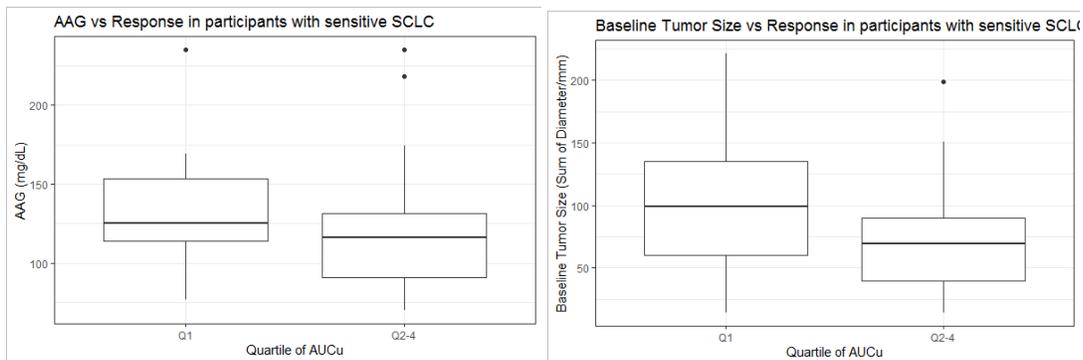
Although Applicant's simulation results of lurbinectedin BSA-based dosing in Table 40 showed a 12% reduction in the ORR between patients with BSA > 1.95 m² and <1.65 m², BSA was not identified as a significant predictor for ORR. A shallow, non-significant relationship between ORR and BSA was shown in **Error! Reference source not found.26** and there is no significant difference in ORR between different BSA quartiles for SCLC patients. And there is no significant difference between AUC_u of SCLC patients with BSA > 1.95 m² and <1.65 m² either.

Figure 23: Logistic regression analysis of ORR and AUCu in participants with resistant SCLC and sensitive SCLC from reviewer’s analysis.



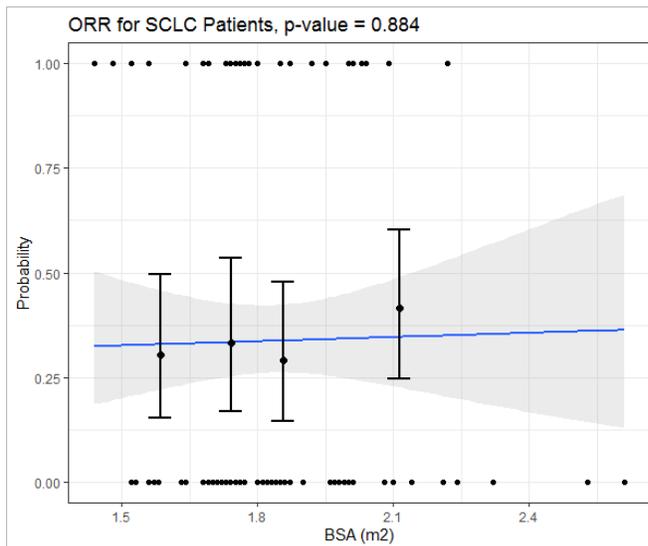
Source: Reviewer’s analysis

Figure 24: AAG (left) and baseline tumor size (right) for participants with lowest quartile of lurbinectedin AUCu- comparing with other quartiles from reviewer’s analysis.



Source: Reviewer’s analysis

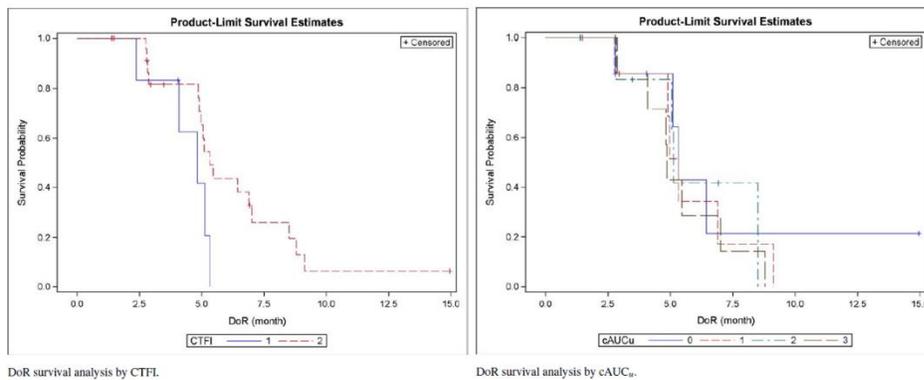
Figure 25: Relationship between ORR and BSA in SCLC patients.



Source: Reviewer's analysis.

The relationships of Duration of response (DoR) and CTFI or DoR and AUC_u of lurbinectedin were evaluated with participants with SCLC in study PM1183-B-005-14. Log-rank tests showed no significant differences in DoR in resistant vs sensitive patients or among the four quartiles of AUC_u. (**Error! Reference source not found.**)

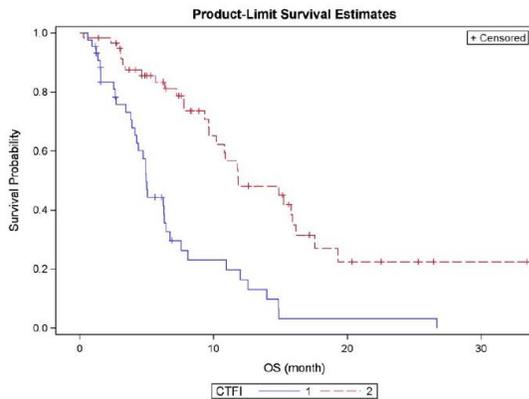
Figure 26: DoR survival analysis by CTFI and AUC_u



Source: CLPH-19-003, Page 73-74, Figure 3-4.

The relationships of overall survival (OS) and CTFI or OS and AUC_u of lurbinectedin were evaluated with participants with SCLC in study PM1183-B-005-14. Median OS in patients with sensitive disease (n=59) was 11.9 (95% CI: 9.7 - 16.2) months and was significantly longer than OS achieved in patients with resistant disease (n=44), 5.0 months (95% CI: 4.1 - 6.5). (**Error! Reference source not found.**)

Figure 27: OS survival analysis by CTFI

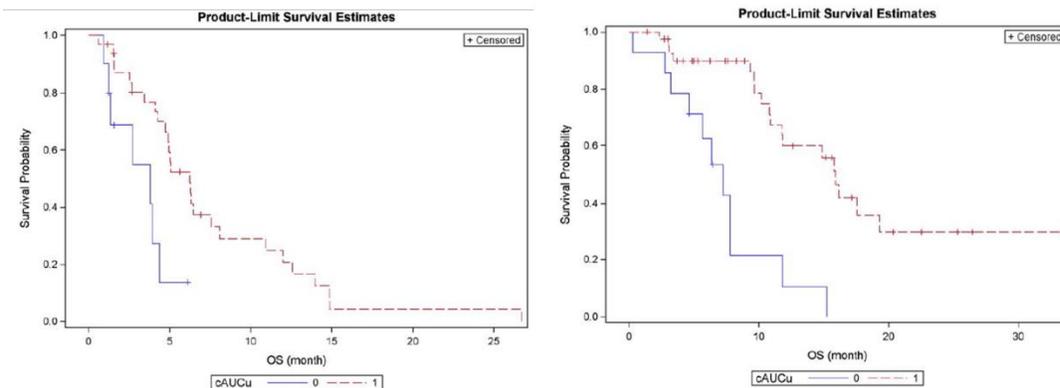


OS survival analysis by CTFI.

Source: CLPH-19-003, Page 75, Figure 5.

AUC_u was categorized into 4 groups according to quartiles (cAUC_u) to check for differences in OS. Median OS by cAUC_u showed differences the lowest cAUC_u group (0) presented the shortest OS (5.7 months) when compared to higher cAUC_u groups (1 to 3, OS about 11 months). Based on the differences in OS between CTFI groups, and between the lowest quartile (group 0) and the higher quartiles (groups 1, 2 and 3) of cAUC_u, the latter were pooled into a single group (1) and compared against the lowest quartile (group 0) and stratified by CTFI. Pooled cAUC_u (group 0 vs. 1 to 3) showed differences between groups in both resistant and sensitive patients. (**Error! Reference source not found.**) The results obtained in the OS analyses agreed with those observed in the ORR analyses, where a significant increase in the OS was observed in the higher quartiles of AUC_u when compared to the lowest quartile.

Figure 28: OS survival analysis by pooled cAUC_u in resistant and sensitive patients.



OS survival analysis by pooled cAUC_u in resistant patients.

OS survival analysis by pooled cAUC_u in sensitive patients.

Source: CLPH-19-003, Page 77-78, Figure 7-8.

Reviewer's comments:

The results of survival analysis for DoR and OS were verified by reviewer. No significant difference was identified in the two groups stratified by CTFI and four groups stratified by AUC_u for DoR. For OS, significant increase in the median survival time was observed in the higher quartiles of AUC_u when compared to the lowest quartile, especially for subjects with sensitive SCLC. The result suggests there is a potential that increasing lurbinectedin dose for SCLC patients with lower exposure (e.g., AUC_u (first cycle) lower than 1000 ng*h/L) might further improve the survival time, especially for sensitive SCLC patients. While due to the limit number of subjects in the study and potential unidentified confounding factors, the relationship between OS and AUC_u was not fully characterized.

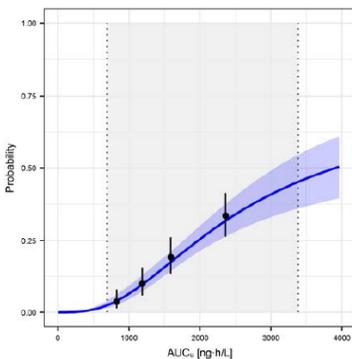
19.1.3.2 E-R analysis of safety of lurbinectedin

Neutropenia and thrombocytopenia were two main dose limiting toxicities associated to treatment with lurbinectedin. The relationships of these two AEs and lurbinectedin exposure at steady state were evaluated with participants across the studies (PM1183-B-001-08, PM1183-B-002-11 and PM1183-B-003-11, PM1183-B-005-14 and C-004 CORAIL).

The relationship of G4 Neutropenia and AUC_u of lurbinectedin was best described by a logistic Emax model. Covariates AAG, dose or BSA were not predictors for neutropenia. (

) Simulation of G4 neutropenia incidence for patients with different BSA at different doses (3.2 mg/m² and 5.6 mg FD) showed that both doses are associated with less than 20% incidence of G4 neutropenia. BSA based dosing had 18% less incidence of G4 neutropenia for subjects with BSA <1.65 m² and 22% more incidence of G4 neutropenia for subjects with BSA >1.96 m² comparing with the fixed dose. Simulation results also showed that dose reduction of lurbinectedin to 2.5 and 2.0 mg/m² could lower the incidence of G4 Neutropenia to approximately 11.3% and 7.5%, respectively, comparing with 16.5% at 3.2 mg/m².

Figure 29: Grade 4 Neutropenia incidence as a function of AUC_u .



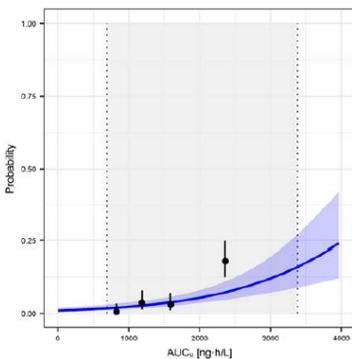
Solid black dots represent the G4 neutropenia incidence grouped by quartiles of AUC_u and plotted at the median AUC_u for each quartile. The bars represent the 95% confidence interval for the proportion of each quartile. Curve and blue shaded area represent predicted values and 95% confidence intervals of model-predicted risk of G4 neutropenia, respectively. The vertical point lines and the grey shaded area represent the 95% prediction interval of the observed AUC_u .

Source: CLPH-19-003, Page 78, Figure 9.

The relationship of $G \geq 3$ Thrombocytopenia and AUC_u of lurbinectedin was best described by linear logistic model, which included the covariates: platelets at baseline, BSA and albumin. (

) Simulation of $G \geq 3$ Thrombocytopenia incidence for patients with different BSA at different doses (3.2 mg/m^2 and 5.6 mg FD) showed that both doses are associated with less than 10% incidence of $G \geq 3$ Thrombocytopenia. BSA based dosing had 16% less incidence of $G \geq 3$ Thrombocytopenia for subjects with $BSA < 1.65 \text{ m}^2$ and 24% more incidence of $G4$ neutropenia for subjects with $BSA > 1.96 \text{ m}^2$ comparing with the fixed dose. Simulation results also showed that dose reduction of lurbinectedin to 2.5 and 2.0 mg/m^2 could lower the incidence of $G \geq 3$ thrombocytopenia to approximately 3.5% and 2.7%, respectively, comparing with 4.8% at 3.2 mg/m^2 .

Figure 30: $G \geq 3$ thrombocytopenia incidence as a function of AUC_u .



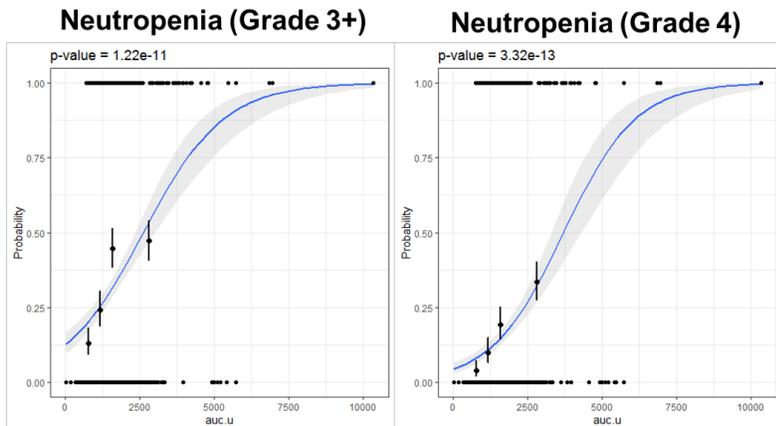
Solid black dots represent the $G \geq 3$ thrombocytopenia incidence grouped by quartiles of AUC_u and plotted at the median AUC_u for each quartile. The bars represent the 95% confidence interval for the proportion of each quartile. Curve and blue shaded area represent predicted values and 95% confidence intervals of model-predicted risk of $G \geq 3$ thrombocytopenia, respectively as function of AUC_u with platelets $243 \text{ } 10^9/\text{L}$, BSA 1.75 m^2 and albumin 4.0 g/dL . The vertical point lines and the grey shaded area represent the 95% prediction interval of the observed AUC_u .

Source: *The Applicant's population PK report (dmb-19-120-1), Page 117, Figure 26.*

Reviewer's comments:

*The E-R analysis models for $G4$ neutropenia and $G \geq 3$ thrombocytopenia with lurbinectedin exposures were verified by the reviewer. Positive relationship between the probability of $G4$ neutropenia and $G \geq 3$ thrombocytopenia with the unbound AUC of lurbinectedin was identified. An independent analysis of $G \geq 3$ & $G4$ neutropenia and lurbinectedin exposures with logistic regression model. (**Error! Reference source not found.**) AUC_u was also identified as significant predictors for the adverse events.*

Figure 31: Logistic regression analysis of Grade 3+ and Grade 4 Neutropenia with AUC_u.



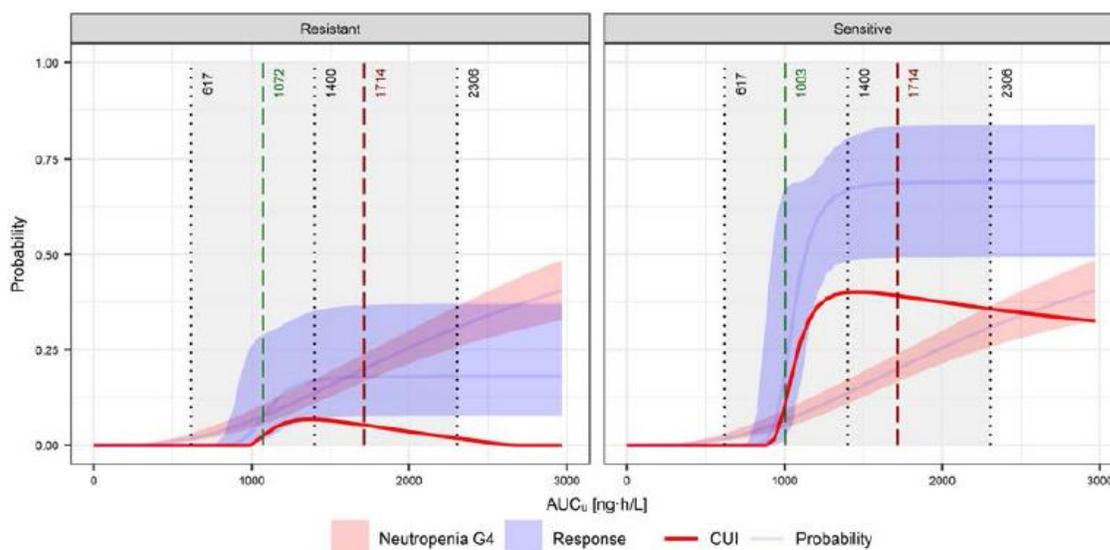
Source: Reviewer's analysis

19.1.3.3 Dose regimen justification based on the integrated exposure-response analysis

Clinical Utility Index (CUI) was estimated based on the probability of ORR and the probability of G4 neutropenia with 2:1 weighting scheme. The results showed that lurbinectedin unbound exposure (AUC_u) between 1072 (for resistant patients) or 1003 (for sensitive patients) and 1714 ng*h/L provided the best benefit/risk ratio for lurbinectedin. The results indicated that the current recommended dosing (3.2 mg/m² q3wk) with median AUC_u of 1400 ng*h/L could achieve the target exposure range. (

)

Figure 32: CUI with AUC_u in resistant (left panel) and sensitive (right panel) SCLC patients.



Dashed green vertical line is the lurbinectedin AUC_u providing an ORR of 7.5% (resistant) and 19.3% (sensitive), which are the ORR corresponding to topotecan. Dashed dark red vertical line is the AUC_u at which the probability of grade 4 neutropenia is 20%. The grey shaded area represent the 95% prediction interval of the observed AUC_u in SCLC patients. Black dotted vertical lines are percentile 5, 50 and 95 of AUC_u.

Source: CLPH-19-003, Page 81, Figure 14.

Reviewer's comments:

The CUI calculation result was checked by the reviewer. But the calculation of CUI was not defined in the analysis plan (CLPH-19-003, Page 83-111). The selection and weighing of attributes to CUI are critical and difficult to decide, which is not well discussed in the Applicant's report.

19.1.4 Summary of Bioanalytical Method Validation and Performance

The plasma and urine concentrations of lurbinectedin (PM01183) were determined using a validated UPLC-MS/MS developed at (b) (4) using deuterated lurbinectedin (PM01183-d₄) as the internal standard. Samples were analyzed by UPLC and triple quadrupole mass spectrometer. As summarized in **Table 41**, the method satisfied the criteria for method validation and application to routine analysis as outline in the *Guidance for Industry: Bioanalytical Method Validation*.

Table 41 : Lurbinectedin method validation summary

Parameter	Details
Method	LC/MS/MS

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213702
ZEPZELCA (Lurbinectedin)

Analyte	Lurbinectedin (PM11083)		
Internal Standard	PM11083-d ₄		
Inter-run accuracy & precision	QC	Accuracy	Precision
	0.1 ng/mL	5%	15.8%
	0.3 ng/mL	4%	10.7%
	3 ng/mL	-5%	6.2%
	40 ng/mL	6%	6.3%
	50 ng/mL	-1%	5.1%
Inter-run accuracy & precision	QC	Accuracy	Precision
	0.3 ng/mL	4%	6.6%
	3 ng/mL	2%	5.2%
	40 ng/mL	5%	3.1%
Dilution integrity	Dilution QC: 800 ng/mL (dilution factor: 20) <ul style="list-style-type: none"> • Accuracy: -5% • Precision: 3.6% 		
Selectivity	Acceptance criteria < 20% of the lower limit of quantification met when tested with doxorubicin, doxorubicinol, capecitabine, 5'-deoxyfluorouridine, 5-fluorouracil, α -fluoro- β -alanine, paclitaxel, cisplatin, gemcitabine, 2',2'-difluoro-2'-deoxyuridine, olaparib		
Recovery	66.4% to 86.6%		
Selectivity	No interfering peaks at the retention time of the standard or internal standard substances in chromatogram in plasma samples		
Linearity	Linearity within the calibration range with R ² > 0.999		
LLOQ	0.1 ng/mL		
Dilution Factor	Demonstrated for 50-fold		
Stability			
Freeze/Thaw Cycles	Demonstrated stability after 5 cycles at -80 °C		
Short term or bench-top temperature stability	Demonstrated for 16.5 hours at 25 °C and 8 hours at 37 °C		
Long Term Stability	Demonstrated stability up to 23, 245, and 853 days at -20 °C and -60 °C, and -80 °C		
Post-Operative Stability	Demonstrated stability up to 50 hours at 15 °C		
Standard Solution Stability	Demonstrated stability up to 2 months at -20 °C		

19.6 Additional Clinical Outcome Assessment Analyses

Not applicable.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	M. Anwar Goheer	OOD/DHOT	Sections: Section 5	Select one: <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
	Signature: Mohammad A. Goheer -S <small>Digitally signed by Mohammad A. Goheer -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300045035, cn=Mohammad A. Goheer -S Date: 2020.06.05 16:30:43 -04'00'</small>			
Nonclinical Supervisor	Whitney S. Helms	OOD/DHOT	Sections: Section 5	Select one: <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	Signature: Whitney S. Helms -S <small>Digitally signed by Whitney S. Helms -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000585776, cn=Whitney S. Helms -S Date: 2020.06.05 17:48:07 -04'00'</small>			
Nonclinical Team Division Director	John K. Leighton	OOD/DHOT	Sections: Section 5	Select one: <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	Signature: John K. Leighton -S <small>Digitally signed by John K. Leighton -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300085260, cn=John K. Leighton -S Date: 2020.06.08 09:05:44 -04'00'</small>			
Clinical Pharmacology Reviewer	Salaheldin Hamed	Office of Clinical Pharmacology/ Division of Clinical Pharmacology	Sections: 6 and 19.4	Select one: <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
	Signature: Salaheldin S. Hamed -S <small>Digitally signed by Salaheldin S. Hamed -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000952138, cn=Salaheldin S. Hamed -S Date: 2020.06.05 15:46:27 -04'00'</small>			
Clinical Pharmacology Team Leader	Hong Zhao	Office of Clinical Pharmacology/ Division of Clinical Pharmacology	Sections: 6 and 19.4	Select one: <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	Signature: Hong Zhao -S <small>Digitally signed by Hong Zhao -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Hong Zhao -S, 0.9.2342.19200300.100.1.1=1300136450 Date: 2020.06.08 07:26:13 -04'00'</small>			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED / APPROVED
Clinical Pharmacology Division Director	Nam Atiqur Rahman	Office of Clinical Pharmacology/ Division of Clinical Pharmacology	Sections: 6 and 19.4	Select one: <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	Signature: Nam A. Rahman -S Digitally signed by Nam A. Rahman -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Nam A. Rahman -S, 0.9.2342.19200300.100.1.1=1300072597 Date: 2020.06.08 08:08:52 -04'00'			
Pharmacometrics Reviewer	Yangbing Li	Office of Clinical Pharmacology/ Division of Clinical Pharmacology	Sections: 6, 19.4	Select one: <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
	Signature: Yangbing Li -S (Affiliate) Digitally signed by Yangbing Li -S (Affiliate) DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002587726, cn=Yangbing Li -S (Affiliate) Date: 2020.06.05 23:14:56 -04'00'			
Pharmacometrics Team Leader	Jiang Liu	Office of Clinical Pharmacology/ Division of Clinical Pharmacology	Sections: 6, 19.4	Select one: <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	Signature: Jiang Liu -S Digitally signed by Jiang Liu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jiang Liu -S, 0.9.2342.19200300.100.1.1=2000348510 Date: 2020.06.06 09:37:06 -04'00'			
Clinical Reviewer	Sonia Singh	Office of Oncologic Disease/Division of Oncology 2	Sections: 1.3, 1.4, 2, 3, 4, 8.1.3, 8.1.4, 8.2, 9, 10, 11, 12, 13, 19.2, 19.3, 19.6	Select one: <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
	Signature: Sonia Singh -S Digitally signed by Sonia Singh -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Sonia Singh -S, 0.9.2342.19200300.100.1.1=2002471660 Date: 2020.06.07 09:41:06 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Team Leader	Adnan Jaigirdar	Office of Oncologic Disease/Division of Oncology 2	Sections: All	Select one: <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	Signature: Adnan A. Jaigirdar -S Digitally signed by Adnan A. Jaigirdar -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000999266, cn=Adnan A. Jaigirdar -S Date: 2020.06.05 15:44:16 -04'00'			
Statistical Reviewer	Flora Mulkey	Office of Biostatistics/Division of Biometrics V	Sections: 7, 8.1 , 8.3	Select one: <input type="checkbox"/> Authored <input type="checkbox"/> Approved
	Signature: Flora M. Mulkey -S Digitally signed by Flora M. Mulkey -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001984421, cn=Flora M. Mulkey -S Date: 2020.06.05 17:43:26 -04'00'			
Statistical Team Leader	Joyce Cheng	Office of Biostatistics/Division of Biometrics V	Sections: 7, 8.1 , 8.3	Select one: <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	Signature: Joyce Cheng -S Digitally signed by Joyce Cheng -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Joyce Cheng -S, 0.9.2342.19200300.100.1.1=2001702039 Date: 2020.06.05 17:49:33 -04'00'			
Division Director (OB)	Shenghui Tang	Office of Biostatistics/Division of Biometrics V	Sections: 7, 8.1 , 8.3	Select one: <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	Signature: Shenghui Tang -S Digitally signed by Shenghui Tang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Shenghui Tang -S, 0.9.2342.19200300.100.1.1=1300224175 Date: 2020.06.09 07:57:34 -04'00'			
Associate Director of Labeling (acting)	Ann Marie Trentacosti	CDER/OND	Sections: 11	Select one: <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
	Signature: Ann M. Trentacosti -S Digitally signed by Ann M. Trentacosti -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300216343, cn=Ann M. Trentacosti -S Date: 2020.06.05 18:04:01 -04'00'			
Cross-Disciplinary Team Leader (CDTL)	Adnan Jaigirdar	Office of Oncologic Disease/Division of Oncology 2	Sections: All	Select one: <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	Signature: Adnan A. Jaigirdar -S Digitally signed by Adnan A. Jaigirdar -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000999266, cn=Adnan A. Jaigirdar -S Date: 2020.06.05 15:43:43 -04'00'			

Deputy Division Director (Clinical)	Harpreet Singh	Office of Oncologic Disease/Division of Oncology 2	Sections: All	Select one: <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	Signature:  Bonnie H. Moore -S <small>Digitally signed by Bonnie H. Moore -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001042285, cn=Bonnie H. Moore -S Date: 2020.06.09 14:27:55 -04'00'</small>			

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KWADWO KORSAH
06/12/2020 01:37:56 PM

MARC R THEORET
06/12/2020 02:15:00 PM

My signature indicates that I have considered the assessments and recommendations included in this Review in determining the regulatory action