CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213702Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 127944

MEETING MINUTES

Pharma Mar USA, Inc.
Attention: Sonia Vela
Project Leader
205 East 42nd Street
Suite 15003
New York, NY 10017

Dear Ms. Vela:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for lurbinectedin.

We also refer to the meeting between representatives of your firm and the FDA on August 7, 2019. The purpose of the meeting was to discuss the data intended to support the planned new drug application for lurbinectedin, for the proposed indication of the treatment of patients with small cell lung cancer (SCLC) (b) (4) , based on a disease-specific cohort of patients enrolled in Study PM1183-B-005-14. The planned NDA will be submitted under the accelerated approval regulations [21 CFR 314 Subpart H].

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-6630.

Sincerely,

{See appended electronic signature page}

Kwadwo Korsah, Pharm.D., M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Enclosure:

- Meeting Minutes
- PowerPoint Slides Presented at the Meeting

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	August 7, 2019; 12:00 PM – 1:00 PM, EST
Meeting Location:	White Oak Building 22, Conference Room: 1313 Silver Spring, Maryland 20903
Application Number:	IND 127944
Product Name:	Lurbinectedin
Indication:	Treatment of patients with small cell lung cancer (SCLC) (b) (4)
Sponsor/Applicant Name:	Pharma Mar USA, Inc.
Meeting Chair:	Erin Larkins
Meeting Recorder:	Kwadwo Korsah

FDA ATTENDEES

Patricia Keegan	Division Director, DOP2
Kwadwo Korsah	Regulatory Health Project Manager, DOP2
Erin Larkins	Clinical Team Leader, DOP2
Whitney Helms	Pharmacology/Toxicology Team Leader, DHOT
Pallavi Mishra-Kalyani	Statistical Team Leader, DBV
Somak Chatterjee	Statistical Reviewer, DBV
Hong Zhao	Clinical Pharmacology Team Leader, DCP5, OCP
Idara Udoh	Senior Regulatory Health Project Manager, DOP2
Koffi Amegadje	Pharmacy Student, DOP2
Mei-Yean Chen	Risk Management Analyst, DRISK/OSE
Youwei Bi	Pharmacometrics Reviewer, OCP

SPONSOR ATTENDEES

Ruth Curley	Regulatory Affairs Associate Director
Ali Zeaiter	Clinical R&D Director
Carmen Kahatt	Clinical Oncology Senior Manager
Cristian Fernández	Clinical Oncology Medical Specialist
Salvador Fudio	Clinical Pharmacology Senior Manager
Hervé Dhellot	Clinical Safety Manager, EEA QPPV
Javier Gómez	Biostatistics & Data Management Senior Manager
Antonio Nieto	Biostatistics Departmental Manager
Luis Mora	Managing Director

Attendees (via teleconference)

Ana Ruiz	Regulatory Affairs Associate Director
Carlos Fernández-Teruel	Clinical Pharmacology Technician
Rubin Lubomirov	Clinical Pharmacology Technician
Liliana Navarro	Clinical Safety Physician
Vicente Alfaro	Medical Writing Departmental Manager
José Antonio López-Vilariño	Clinical Oncology Medical Specialist
Pedro Berbil	Operations Director
Carmen Cuevas	Director
Pablo Avilés	NonClinical Senior Manager

External Experts

(b) (4)

BACKGROUND

Regulatory

On May 28, 2019, Pharma Mar submitted a request for a pre-NDA meeting to discuss the data intended to support the planned new drug application for lurbinectedin, for the proposed indication of the treatment of patients with small cell lung cancer (SCLC) (b) (4), based on a disease-specific cohort of patients enrolled in Study PM1183-B-005-14. The planned NDA will be submitted under accelerated approval regulations. On June 13, 2019, FDA granted the Type B meeting. The meeting package was received on July 5, 2019.

The regulatory history of this development program is summarized below.

- On December 15, 2008, an Investigational New Drug (IND) application, IND (b) (4), was submitted to the Division of Oncology Products 1 (DOP1) containing a new clinical protocol entitled "Phase 1, Multicenter, Open-label, Dose-escalating, Clinical and Pharmacokinetic Study of PM01183 in Patients with Advanced Solid Tumors," and became active January 16, 2009. This IND contains the development program for (b) (4).

- On December 17, 2014, a Type C Written Responses Only (WRO) meeting was held under IND (b) (4) to obtain advice on the clinical pharmacology development plan for lurbinectedin (PM01183).

- On October 9, 2015, Pharma Mar submitted IND 127944 to the Division of Oncology Products 2 (DOP2). This IND contained a new clinical protocol, Protocol PM1183-C-003-14, entitled "Phase 3 Randomized Clinical Trial of Lurbinectedin (PM01183) 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, this IND was placed on Full Clinical Hold because the study design was determined unable to meet its stated objectives. A Full Clinical Hold letter was issued on November 13, 2015 which provided information needed to resolve the deficiency, in addition to non-hold clinical and clinical pharmacology comments.

- On January 28, 2016, a Type A meeting was held to discuss Pharma Mar's proposal to address the clinical hold placed on IND 127944. To address the deficiency in the protocol design, FDA recommended an adaptive study design, with single-agent doxorubicin and single-agent lurbinectedin arms, with the opportunity to drop arms for futility at interim analysis, to allow isolation of the contribution of each drug to the regimen. The meeting minutes were issued on February 3, 2016.

- On February 12, 2016, Pharma Mar submitted a Response to the Full Clinical Hold letter that included a revised clinical protocol for the ATLANTIS study, with the revised title "Phase 3 Randomized Clinical Trial of Lurbinectedin (PM01183)/Doxorubicin (DOX) versus Cyclophosphamide (Cy), Doxorubicin (DOX) and Vincristine (VCR) (CAV) or Topotecan as Treatment in Patients with Small-Cell Lung Cancer (SCLC) Who Failed One Prior Platinum-Containing Line (ATLANTIS Trial)" and a revised statistical analysis plan (SAP). To potentially isolate the contribution of lurbinectedin to the combination, Pharma Mar added CAV as an option in the control arm and added choice of treatment (CAV or topotecan) as a stratification factor. Pharma Mar stated that the decision to treat with CAV or topotecan will be at the discretion of the investigator. A secondary endpoint was added comparing the lurbinectedin plus doxorubicin and 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 March 11, 2016, the clinical hold was removed.

- On August 1, 2018, lurbinectedin received orphan designation for the treatment of small cell lung cancer.

- On December 11, 2018, a Type B, End of Phase 2 meeting was held to discuss results from the SCLC cohort from Study PM1183-B-005-14, entitled "A Multicenter Phase 2 Clinical Trial of Lurbinectedin (PM01183) in Selected Advanced Solid Tumors." Pharma Mar stated their intent to use Study PM1183-B-005-14 to support accelerated approval of lurbinectedin for the treatment of patients with (b) (4) SCLC, (b) (4) and for the ongoing ATLANTIS study to serve as the confirmatory study to verify clinical benefit. With regard to the

preliminary results from Study PM1183-B005-14, FDA stated that the number of patients with platinum-resistant disease is small, the lower limit of the 95% confidence interval (CI) around the observed response rate is less than 12%, and the median duration of response is relatively short. Therefore, FDA is not certain that this effect is likely to predict clinical benefit, particularly considering the toxicity profile. FDA advised Pharma Mar to submit the top-line results based on independent review committee (IRC)-assessed response with a minimum of 6 months follow-up from the onset of response for all responders.

- On June 10, 2019, a Type C WRO meeting minutes were issued providing FDA's responses to questions posed on the data standardization strategy for non-clinical and clinical studies as well as integrated analyses to be included in the planned NDA submission. In their responses, FDA stated that "FDA does not agree with the proposal to include safety data from only Studies PM1183-B-005-14 and PM1183-C-004-14 in the Integrated Summary of Safety (ISS), since this does not capture all available safety data for lurbinectedin administered as a single agent. Pharma Mar states in the footnote to table 15.1.3 in the meeting package, 'Selection of studies to be pooled at the ISS to be discussed and agreed with the FDA during pre-NDA meeting.' Therefore, FDA cannot provide agreement at this time regarding Pharma Mar's proposed data standardization strategy for clinical studies supporting the evaluation of safety, since depending upon which studies will be pooled the use of different versions of MedDRA may be an issue." However, FDA confirmed that the proposed data standardization strategy appears acceptable for the nonclinical studies and the clinical pharmacology studies and analyses.

- On June 19, 2019, a pre-NDA CMC-only meeting was held to reach agreement on key issues relevant to the CMC parts of the NDA filing under accelerated approval provisions. During this meeting, FDA agreed that:
  - The planned facilities for commercial drug product (DP) and drug substance (DS) manufacture can be the same as the facilities used for clinical trials DP and DS;
  - The stability studies conducted 3 batches at long term storage stability testing at -20°C ± 5°C through 24 months and 3 batches at accelerated storage conditions defined as 5°C ± 3°C through 6 months, demonstrating no significant degradation may support a retest period of at least (b) (4) months. The data in the meeting package appears reasonable to support this. Pharma Mar should include this supporting data in the NDA or referenced DMF containing CMC information.
  - The proposed controls for (b) (4) are reasonable. Pharma Mar should include all data supporting the selection of these (b) (4) as starting materials (justified specification limits, demonstrated (b) (4) capability of API manufacturing process, representative batch analyses for lots used in clinical supply manufacture, and comparability data if the suppliers are new and have not been used for clinical supply material) in the NDA or referenced DMF containing CMC information.
  - The supplied data for lurbinectedin supports reproducible supply of material with adequate quality under the proposed control strategy. Pharma Mar should

include this supporting data in the NDA or referenced DMF containing CMC information.

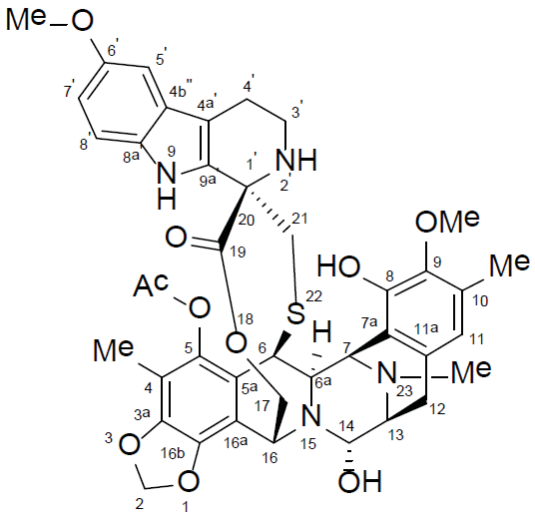
- The proposed control strategies for the DP manufacturing process are reasonable. Pharma Mar should include (b) (4)
- (b) (4)
- (b) (4)
- Proposed acceptance criteria also appear reasonable, however, proposed acceptance criteria for the degradation product impurity (b) (4) should be justified based on data in the NDA to support levels of this impurity closer to the high criteria limit. Final assessment of acceptance criteria will be determined on review of the NDA and supporting nonclinical studies. Proposed criteria (b) (4) should be justified based on the impact of the proposed levels in the drug product.
- At the time of the NDA submission, all drug product and drug substance commercial manufacturing sites are required to be ready for inspection by FDA authorized investigators. Approval of the NDA requires continuing compliance of the sites in meeting cGMP criteria, and pre-approval inspection/s may be required with a satisfactory outcome. To facilitate FDA's inspectional process, Pharma Mar should clearly identify *in a single location*, on the Form FDA 356h, all manufacturing facilities associated with the application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI (Facility Establishment Information) number, and specific manufacturing responsibilities for each facility. Pharma Mar should provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable).
- Inclusion of the (b) (4) facility as a drug product manufacturing site with 12 months of long term and 6 months of accelerated stability data for the

engineering batch (7K001), release data for the validation batch, and supported by the comparability protocol results in the original NDA.

- Pharma Mar will provide a risk assessment summarizing studies that show adventitious microbial contamination does not grow under the specified storage conditions (e.g., 24 hours at room temperature or 24 hours under refrigeration after reconstitution, and 24 hours at room temperature or 24 hours under refrigeration after further dilution with the specified diluents).
- **Late Minor Component:** Agreement on submission of a late minor CMC component, containing additional stability data, within 30 days after the initial NDA submission.

Chemistry Manufacturing and Controls (CMC)

Lurbinectedin is (b) (4) a single stereoisomer with the (1'R, 6R, 6aR, 7R, 13S, 14S, 16R) configuration.



$C_{41}H_{44}N_4O_{10}S$
MW = 784.87 g/mol

The lurbinectedin drug product is presented as a lyophilized powder for concentration for solution for infusion with a strength of 4 mg/vial. The drug product is reconstituted with water for injection (8 mL) to give a solution of 0.5 mg/mL lurbinectedin prior to use. For administration, the reconstituted solutions are diluted with glucose (5%) solution or sodium chloride (0.9%) solutions for infusion. The drug product is formulated with common excipients. A Type B Pre-NDA CMC-only meeting was held June 19, 2019 and meeting minutes issued June 20, 2019. This meeting established agreements regarding commercial manufacturing facilities, starting material controls, specifications, stability data, and controls for the drug product and drug substance.

Nonclinical

Lurbinectedin (PM01183) is an antineoplastic cytotoxic agent which induces double strand DNA breaks leading to a delay in cell cycle S phase, activation of DNA checkpoint damage repair systems, and/or cell death. In vitro, PM01183 demonstrated activity against a wide selection of tumor types. Pharma Mar states that they have completed nonclinical ADME, safety pharmacology, and toxicology studies in compliance with the ICH S9 Guidance. The complete listing of studies to be submitted in the planned NDA are listed in Table 27, beginning on page 47 of the meeting briefing package.

Clinical Pharmacology

Per Pharma Mar, clinical pharmacology program to support NDA includes multiple dose pharmacokinetics (from phase 2 and 3 studies), a mass-balance study, pharmacometric analyses (consisting of population-pharmacokinetics and integrated exposure-response analysis), and a QT study.

Clinical

Study PM1183-B-005-14
Study PM1183-B-005-14, entitled “A Multicenter Phase II Clinical Trial of Lurbinectedin (PM01183) in Selected Advanced Solid Tumors”, is an ongoing open-label, multicenter, activity-estimating basket trial to study the anti-tumor activity and safety of lurbinectedin in patients with various advanced solid tumors, including small cell lung cancer (SCLC). Patients are treated with lurbinectedin 3.2 mg/m^2 intravenously (IV) every 3 weeks (Q3W). Key eligibility criteria for the SCLC cohort are ECOG PS ≤ 2, pathologically proven SCLC, receipt of only one prior line of chemotherapy, and no evidence of CNS involvement (mandatory brain CT scan or MRI at baseline).

The primary endpoint is overall response rate (ORR) per RECIST 1.1 based on investigator assessment (IA). Secondary endpoints for the SCLC cohort include ORR and DOR based on RECIST 1.1 assessed by independent review committee (IRC), clinical benefit (response or stable disease lasting at least 4 months) assessed by IRC, progression free survival (PFS) assessed by IRC, and overall survival (OS). Assessment of antitumor activity by IRC was added as a secondary objective in the SCLC cohort via a protocol amendment on July 2018. As initially designed, the sample size was limited to 25 evaluable patients per cohort. The protocol was amended to increase the sample size for the SCLC cohort to 50 patients and later to 100 patients. According to Pharma Mar, the rationale for the increased sample size was to allow confirmation of the anti-tumor activity of lurbinectedin as a single agent in patients with SCLC.

Results
As of January 15, 2019, 110 patients were enrolled in the SCLC cohort, of whom 105 patients received lurbinectedin. The remaining 5 patients did not receive lurbinectedin. Of these 105 lurbinectedin-treated patients, 45 had sensitive disease (defined as chemotherapy-free interval [CTFI] ≥ 90 days) and 60 had resistant disease (CTFI < 90 days). Patient accrual for the SCLC cohort was conducted in Europe and USA.

Efficacy
The table below presents ORR per investigator and per IRC assessment for all 105 lurbinectedin-treated patients and in subgroups defined by CTFI.

Table 1: Summary of ORR in study PM1183-B-005-14 (based on Briefing Package Pre-NDA Meeting, Page 24, submitted July 5, 2019)

Response Evaluation	n	Investigator Assessment			Independent Review Committee		
		Response	%	95% CI	Response	%	95% CI
CTFI < 90	45	10	22.2	(11.2, 37.1)	6	13.3	(5.1, 26.8)
CTFI ≥ 90	60	27	45.0	(32.1, 58.4)	26	43.3	(30.6, 56.8)
Overall response	105	37	35.2	(26.2, 45.2)	32	30.5	(21.9, 40.2)

Based on IRC assessment, the median DOR was 5.1 months (median DOR for responding patients with CTFI <90 days was 4.8 months and median DOR for responding patients with CTFI ≥90 days 5.3 months). Median OS was 5 months in patients with CTFI < 90 and 11.9 months in patients with CTFI ≥ 90 days.

Safety
A total of 103 lurbinectedin-treated patients (98%) had at least one adverse event (AE). The most common AEs were fatigue (80%), nausea (37%), dyspnea (37%), constipation (32%), decreased appetite (36%), and cough (25%). The most common grade 3-4 AEs were fatigue (7%), febrile neutropenia (4.7%), and pneumonia (1%).

Pharma Mar states that, as of January 15, 2019, 1847 patients have been included in 19 clinical trials sponsored by Pharma Mar and three investigator-sponsored trials evaluating lurbinectedin in solid and hematologic tumors as a single-agent with different doses and schedules or in combination with other drugs. Twelve studies sponsored by Pharma Mar have administered lurbinectedin as a single agent in a total of 904 patients. Of these 904 treated patients, 568 received the proposed recommended dose of lurbinectedin administered as a single agent, 3.2 mg/m^2 every 3 week, in four studies [(b) (4), PM1183-B-004-13, PM1183-B-005-14 (Basket), and PM1183-C-004-14 (CORAIL)]. Pharma Mar proposes to use safety data from two (Studies PM1183-B-005-14 [Basket] and PM1183-C-004-14 [CORAIL, a randomized study in patients with platinum-resistant ovarian cancer) of the four studies for a total of 554 patients in the safety analysis for their proposed NDA. Pharma Mar proposes not to include data for the 14 patients treated in the two other studies. (b) (4)

and the final data from this study is not available. Study PM1183-B-004-13 is a study in 21 patients with NSCLC which includes three patients treated at the proposed recommended dose.

Proposed Study to Verify Clinical Benefit

ATLANTIS
Study PM1183-C-003-14 (ATLANTIS), entitled "Phase 3 Randomized Clinical Trial of Lurbinectedin (PM01183)/Doxorubicin (DOX) versus Cyclophosphamide (Cy), Doxorubicin (DOX) and Vincristine (VCR) (CAV) or Topotecan as Treatment in Patients with Small-Cell Lung Cancer (SCLC) Who Failed One Prior Platinum-Containing Line (ATLANTIS Trial)", is an ongoing, multicenter, open-label, randomized trial in 613 patients with SCLC previously treated with a platinum-containing regimen.

Randomization is stratified by CTFI after first line therapy (≥180 days vs. 90-179 days vs. <90 days), ECOG performance status (0 vs. 1-2), baseline CNS involvement (yes vs. no), prior immunotherapy against PD-1 or PD-L1 (yes vs. no) and investigator's preference of control arm treatment prior to randomization [topotecan vs. cyclophosphamide, doxorubicin, and vincristine (CAV)]. Enrollment in this study is complete. Eligible patients were randomly assigned in a 1:1 to two treatment arms:

- Experimental: doxorubicin 40 mg/m^2 IV on Day 1 followed by lurbinectedin 2 mg/m^2 IV on Day 1 Q3W for a maximum of 10 3-week cycles
- Control:
    - cyclophosphamide 1000 mg/m^2, doxorubicin 45 mg/m^2 and vincristine 2 mg flat dose IV on Day 1 Q3W.
    - topotecan 1.5 mg/m^2 IV daily on Days 1-5 Q3W.

Treatment will continue until disease progression, unacceptable treatment-related toxicity, or patient or investigator decision to discontinue.

At the data cut-off date of January 15, 2019, 592 of the 613 enrolled patients received study treatment, 302 in the experimental arm and 290 in the control arm. To evaluate the overall safety in both arms, an interim safety analysis was conducted for the first 150 patients enrolled. Efficacy endpoints were not analyzed in this interim analysis. The primary endpoint is OS. Pharma Mar expects the 508 events required for OS analysis to be observed by Q4 2019.

The design of the ATLANTIS study is based on data obtained in Study PM1183-C-003-10 which is a dose-finding study that evaluated the safety and activity of lurbinectedin administered with doxorubicin in patients with selected advanced solid tumors.

Proposed Content of the NDA

Chemistry, Manufacturing, and Controls
The information to be submitted in the planned NDA is described in the premeeting package for the July 9, 2019, CMC-Only meeting, with additional summarized in the final meeting minutes, issued June 20, 2019.

Nonclinical Pharmacology and Toxicology
Pharma Mar states that they have completed nonclinical ADME, safety pharmacology, and toxicology studies in compliance with the ICH S9 Guidance. The complete listing of studies to be submitted in the planned NDA are listed in Table 27, beginning on page 47 of the meeting briefing package.

Clinical Pharmacology
The completed clinical pharmacology studies and pharmacometric analyses based on pharmacokinetic data obtained in the following studies, abstracted from the ANNEX-2, Section 1.4 of the meeting briefing package.

Table 32 Clinical studies with lurbinectedin, sponsored by Pharma Mar, including pharmacokinetic assessments.

Clinical trial	Indication	Dose range	No. of patients	Dosing	Sampling days (no. of samples)	Integrated analyses
Phase 1. Single-agent studies						
PM1183-A-001-08	Solid tumors	0.02 – 5.0 mg/m²	33/31	1	C1D1[b] (14) & C2D1[c] (14)	Phase 1/2 PopPK & PKPD
PM1183-A-002-10	Hematological Tumors	3.5 – 7.0 mg FD	26/23	1 & 8	C1D1 (12), C1D8 (12) & C2D1 (9)	Phase 1/2 PopPK
		1.0 – 3.0 mg FD	19/18	1, 2, 3	C1D1 (7) & C1D3 (10)	
PM1183-A-005-11	Solid tumors	3.0 – 5.0 mg FD	21/21	1, 8	C1D1 (12) & C3D1 (12)	Phase 1/2 PopPK & PKPD
PM1183-A-013-15[a]	Solid tumors (Japanese	(b) (4)				
(b) (4)						
Phase 1. Combination studies						
PM1183-A-003-10	Solid tumors	3.0 – 5.0mg FD + DOX 50 mg/m²	74/73	1	(b) (4)	Phase 1/2 PopPK
		2.0 mg/m² + DOX 40 mg/m²	48/47	1		
PM1183-A-004-10	Solid tumors	2.5 – 3.5 mg FD + GEM 800 or 1000 mg/m²	47/45	1, 8		Phase 1/2 PopPK
PM1183-A-006-12	Solid tumors	2.0 – 5.0 mg FD + CAP 1650-2000 mg/m²/D	50/50	1, 8		Phase 1/2 PopPK
		2.2 – 2.8 mg/m² + CAP 1650	31/31	1		
PM1183-A-008-13	Solid tumors	0.5 – 1.7 mg/m² + CDDP 60 mg/m²	41/41	1		-

Clinical trial	Indication	Dose range	No. of patients	Dosing	Sampling days (no. of samples)	Integrated analyses
Phase 2 Studies						
PM1183-B-001-10	Pancreatic cancer	7.0 mg FD	45/44	1	C1D1 (9) & C2D1 (9)	Phase 1/2 PopPK & PKPD
PM1183-B-002-11	Ovarian cancer	7.0 mg FD	81/22[e]	1	C1D1 (9) & C2D1 (9)	Phase 1/2 PopPK & PKPD
PM1183-B-003-11	Breast cancer	7.0 mg FD	70/38	1	(b) (4)	Phase 1/2 PopPK & PKPD
(b) (4)						
PM1183-B-005-14[f]	Selected solid tumors & SCLC	3.2 mg/m²	305/303	1	C1D1 (8) & C2D1 (6)	Phase 2/3 PopPK & IERAES
PM1183-B-005-14-	Solid tumors	3.2 mg/m²	39/39	1	C1D1 (8) & C2D1 (6)	-
Phase 3 Studies						
PM1183-C-004-14 *"CORAIL"*	Ovarian cancer	3.2 mg/m²	432/210[e]	1	C1D1 (4) & C2-4 D1 (4)	Phase 2/3 PopPK & IERAES
PM1183-C-003-14 *"ATLANTIS"*[a]	SCLC	2.0 mg/m² + DOX 40 mg/m²	592/302[e]	1	(b) (4)	-

[a] Ongoing study; [b] At the RD, the urine samples during C1D1 were collected for PK analysis; [c] Patients at recommended dose; [d]
Urine and feces samples during C1D1 were collected for PK analysis; [e] Only patients in study arm with lurbinectedin; [f] Selected solid tumors, mostly SCLC, [g] QT study nested in PM1183-B-005-14 study.
ANC, absolute neutrophil count; BSA, body surface area; C, Cycle; CAP, capecitabine; CDDP, cisplatin; D, Day; DOX, doxorubicin; EOI, end of infusion; FD, flat dose; GEM, gemcitabine; h, hours; IERAES, Integrated Exposure Response Analysis of Efficacy and Safety; IRI, irinotecan; min, minutes; PAC, paclitaxel; Phase 1/2, phase 1 and phase 2 studies; Phase 2/3, phase 2 and phase 3 studies; PLT, platelets; w, with; wt, without.

Population PK analysis: Total plasma concentrations from 443 patients with solid and hematological malignancies treated in six phase 1 (PM1183-A-001-08, PM1183-A-002-10, PM1183-A-003-10, PM1183-A-004-10, PM1183-A-005-11 and PM1183-A-006-12) and three phase 2 trials (PM1183-B-001-10, PM1183-B-002-11 and PM1183-B-003-11) with lurbinectedin as single agent or combined with other agents, and using three different dosing schedules (Day 1, Day 1 and 8, and Days 1-3, q3wk), at doses ranging from 0.02 to 5.0 mg/m², included in the analysis.

The initial PopPK model was then updated using an independent dataset from late phase 2 and phase 3 trials with lurbinectedin at the recommended dose of 3.2 mg/m². This dataset included 537 patients; of whom 103 were patients within the intended indication for SCLC.

Integrated exposure-response analysis of efficacy and safety (IERAES): An IERAES was performed to justify the proposed treatment regimen of 3.2 mg/m2, using the Phase 2/3 dataset.

QT study: A QT evaluation study was performed in a subset of 12 sites in USA and Spain enrolling 39 patients in the phase 2 portion of PM1183-B-005-14 Basket trial. Based on Pharma Mar's conclusions that results of ΔQTcF and concentration-ΔQTc

modelling in this prospective study did not indicate clinically relevant QTc prolongation associated to treatment with lurbinectedin at 32 mg/m^2, no additional studies were conducted or planned.

DDI: The potential for drug interactions were assessed in in vitro studies with human liver microsomes, the popPK studies, and in phase 1 clinical studies assessing the effects of aprepitant, a moderate CYP3A4 inhibitor, on lurbinectedin. Based on the latter study, which showed a 33% reduction of lurbinectedin plasma clearance was observed in patients who received aprepitant. Further studies contraindicated the use of aprepitant with lurbinectedin and recommended that inhibitors and inducers of CYP3A4 should be carefully monitored or avoided, whenever possible.

Organ Impairment studies: No organ impairment studies have been conducted. A dedicated hepatic impairment study is planned but results will not be available prior to submission of the NDA.

Clinical

The clinical study reports and datasets for the studies listed in the table below (abstracted from ANNEX-2 of the meeting briefing package) will be provided in the planned NDA.

Table 28. Study reports to be included in the NDA filing.

Study code	Status	Design	Clinical Study Report
PM1183-A-001-08	Completed	First-in-human, single agent, phase 1 study	Final report
			(b) (4)
PM1183-B-005-14 (Basket)	Ongoing	Phase 2 basket study evaluating lurbinectedin 3.2 mg/m^2 q3wk in nine solid tumor types, including SCLC	Two interim reports: • Efficacy/safety data of the SCLC cohort • Pooled safety data from all nine cohorts
PM1183-B-005-14-QT[a]	Completed	QT study in a subset of patients of the Basket study	Final report plus an addendum with *post hoc* analyses
PM1183-C-004-14 (CORAIL)	Completed	Phase 3 study evaluating lurbinectedin 3.2 mg/m^2 q3wk vs. PLD/topotecan in platinum- resistant ovarian cancer patients	Final report

[a] Please, note that PM1183-B-005-14 QT was an independent study from Basket study.
Abbreviations: PLD, pegylated liposomal doxorubicin; q3wk, every three weeks; SCLC, small cell lung cancer.

The detailed analysis plan for the integrated summary of safety (ISS) is located in section 5.3.5.3 of the July 5, 2019, submission. Pharma Mar states that the following data will be included in the ISS.

Table 3.1: Summary of Total Number of Patients Treated with Lurbinectedin in Each Study

Study	Phase	Indication	N
PM1183-B-005-14	2	SCLC, head and neck carcinoma, neuroendocrine tumors, biliary tract carcinoma, endometrial carcinoma, BRCA 1/2-associated metastatic breast carcinoma, carcinoma of unknown primary site, germ cell tumors and Ewing's family of tumors	335
PM1183-C-004-14 Arm A	3	Ovarian	219

Pooled analyses will also be performed in the following subgroups

- **Group A:** All lurbinectedin-treated patients with SCLC in Study PM1183-B-005-14 (n=105).
- **Group B:** All lurbinectedin-treated patients in Study PM1183-B-005-14 across eight different indications in eight cohorts (all cohorts but SCLC cohort), head and neck carcinoma, neuroendocrine tumors, biliary tract carcinoma, endometrial carcinoma, BRCA 1/2-associated metastatic breast carcinoma, carcinoma of unknown primary site, germ cell tumors and Ewing's family of tumors (n=230_.
- **Group C:** All lurbinectedin-treated patients in Study PM1183-B-005-14 across nine disease-specific cohorts: SCLC, head and neck carcinoma, neuroendocrine tumors, biliary tract carcinoma, endometrial carcinoma, BRCA 1/2-associated metastatic breast carcinoma, carcinoma of unknown primary site, germ cell tumors and Ewing's family of tumors (n=355).
- **Group D:** All lurbinectedin-treated patients with ovarian cancer in Study PM1183-C-004-14 (CORAIL study, experimental arm) n=219
- **Group E:** All lurbinectedin-treated patients in Studies PM1183-B-005-14 and PM1183-C-004-14 CORAIL study (Group C plus Group D); n=554.

Pharma Mar describes plans for characterizing the demographics of the various pooled safety populations; plan for subgroup analyses; plan for submission of exposure data; analyses in specific populations; and assessment of adverse reactions, including serious adverse reactions and adverse events of special interest [sepsis/neutropenic septic/septic shock; myalgia; neuropathy peripheral; and extravasation to identified according to the SMQs on pages 124-138 of the ISS analysis plan]. Summary data will be provided for the proportion of patients receiving transfusions (red blood cell and platelets) and for the proportion of patients who received hematopoietic colony stimulating factors (CSF); CSF use will be further broken down by prophylactic and therapeutic use.

FDA sent Preliminary Comments to Pharma Mar on August 2, 2019.

DISCUSSION OF FDA RESPONSES TO SPONSOR QUESTIONS

Clinical

Pharma Mar's position on question #1 provided on page 20 of the briefing package.

1. Does the Agency agree that ORR and DoR obtained from a single phase 2 study data are sufficient to support NDA filing under accelerated approval regulations?

   FDA Response: ORR and DOR data obtained from a single multicenter activity-estimating study may be sufficient to support the filing of an NDA seeking approval under accelerated approval regulations if the results support an assessment that the drug provides a meaningful therapeutic benefit over existing treatments. The evaluation of the clinical significance of the ORR and the adequacy of the data to support accelerated approval would consider the magnitude and duration of the responses in a risk-benefit analysis during NDA review. For information regarding accelerated approval see the FDA Guidance for Industry entitled "*Expedited Programs for Serious Conditions – Drugs and Biologics*," found at http://www.fda.gov/downloads/Drugs/Guidances/UCM358301.pdf.

   Discussion During Meeting: No discussion occurred.

Pharma Mar's position on question #2 provided on page 22 of the briefing package.

2. Does the Agency agree that the ORR and DoR results obtained in the Basket study PM1183-B-005-14 are sufficient to support NDA filing under accelerated approval regulations?

   FDA Response: FDA agrees that the results would support filing of an NDA under the accelerated approval pathway for the treatment of patients with SCLC who have progressed after a prior platinum-containing combination regimen. The specific indication that would be supported by the proposed NDA will be determined during review of the NDA. (b) (4) [redacted].

   Pharma Mar's Response (provided via email on August 6, 2019): (b) (4) [redacted]

   - Comparative safety data (see Table 23, page 39 of the briefing document) show significantly lower rates for hematologic Grade 3-4 adverse events,

treatment related deaths and treatment related discontinuations for lurbinectedin relative to topotecan.

- Comparative efficacy data (see Table 22, page 42 of Annex 2 of the briefing document) shows similar clinical outcomes with somewhat higher point-estimates of overall response rate (investigator assessments for both drugs).
- Median duration of response to lurbinectedin in the resistant population (4.7 months, see Table 5, page 24 of briefing document) was longer than the reported median DoR to topotecan in the sensitive population (3.3 months, see Table 22, page 38 of the briefing document). The 4.7 month median DoR and the 10.9 month median survival in the responding chemo-resistant population represent a clinically meaningful benefit.

(b) (4)

Inclusion of this patient population in the indication for lurbinectedin would offer an approved therapy for this high unmet medical need.

Discussion During Meeting: FDA stated that this is a determination that will be made upon review of the NDA and encouraged Pharma Mar to present their argument (b) (4)

Pharma Mar's position on questions #3 and #4 provided on page 25 of the briefing package.

3. Does the Agency agree that to support NDA filing under accelerated approval regulations, the Summary of Clinical Safety will be based on integrated safety data from two studies at the proposed dose regimen supported by integrated exposure response analyses of safety based on data from relevant single-agent studies using different dose regimens?

FDA Response: FDA agrees that a Summary of Clinical Safety based on integrated safety data from 554 patients treated with single-agent lurbinectedin at the dose of 3.2 mg/m^2 Q3W, supported by integrated exposure response analyses of safety based on data from "relevant" single-agent studies using different dose regimens, would be acceptable. Provide justification for the relevance of the clinical trials selected for inclusion in the SCS and ISS rather than all Pharma Mar-sponsored trials of lurbinectedin.

Pharma Mar's Response (provided via email on August 6, 2019): Pharma Mar accepts the Agency's comments and provides the following clarifications: Reference is made to Table 1 for all single-agent studies regardless of dose regimen.

The exposure response analyses of safety were based on the Phase I and II single agent studies evaluating dose regimens different to that of the proposed dose regimen of 3.2 mg/m^2 as shown in Table 9, page 26 of the briefing package (main part). These analyses were performed before the proposed dose regimen was defined. These analyses included all single-agents studies that were completed by October 2016. The only studies that were excluded were those that were combination studies, leukemia, or ongoing studies at the time of analyses.

From Table 1 four studies were not included in the exposure-response analyses. These are:

- PM1183-A-013-15 – ongoing study in Japan, data not yet available
- (b) (4)
- PM1183-A-002-10 – leukemia study which is not appropriate for assessing hematological toxicity in patients with solid tumors.
- PM1183-B-004-13 – study completed after the October 2016 cut-off for the exposure-response analyses.

Does the Agency agree with this rationale?

Regarding the ISS, studies with the proposed dose regimen that will be available at the time of NDA are being included. Table 8, page 26 describes all studies with patients treated at the proposed dose regimen (four studies). In the ISS the only studies not included are:

- PM1183-A-013-15 – ongoing study in Japan, data not yet available at the time of the planned NDA submission, and
- PM1183-B-004-13 – most patients (18 of 21) were treated at a higher dose (7.0mg FD)

Does the Agency agree with this rationale?

Discussion During Meeting: Pharma Mar clarified that there are no randomized trials for which data would be excluded in the safety database. Therefore FDA agreed that clinical trials conducted in combination with other agents, leukemia or for which there are not yet reports for safety data do not need to be included in the ISS. FDA requested that serious adverse events across the database be included and Pharma Mar to provide SCIOM reports or narratives for SAEs regardless of attribution.

4. Integrated safety data from 554 patients treated with single-agent lurbinectedin at the dose of 3.2 mg/m^2 q3wk are sufficient to describe the safety profile at the proposed dose regimen?

FDA Response: FDA agrees that integrated safety data from 554 patients treated with single-agent lurbinectedin at the dose of 3.2 mg/m^2 Q3W should be sufficient to assess the safety profile of the proposed dosage regimen.

With regard to the adverse events of special interest, infectious events occurring in the absence of documented neutropenia should be described separately from adverse events of febrile neutropenia\neutropenic sepsis. Please propose a revised plan for analyses of these two events.

FDA strongly recommends that Pharma Mar submit a request for a WRO to obtain FDA feedback on the proposed approach to characterize the safety in the application. The submitted package should describe Pharma Mar's approach for aggregating preferred terms under composite terms for relevant AEs, such as a composite term for fatigue which would include fatigue and asthenia.

Pharma Mar's Response (provided via email on August 6, 2019): Pharma Mar accepts the Agency's comments and no further discussion is requested during the meeting.
Pharma Mar agrees to submit for FDA feedback the proposed approach to characterize the safety in the application by request for Written-Response-Only (WRO) as recommended.

Pharma Mar would like to agree a timeline for WRO, and proposed to submit a description of the proposed approach to characterize the safety by Monday August 19th. Can the FDA please respond by September 2nd?

Discussion During Meeting: FDA agreed that Pharm Mar can submit a WRO meeting request and FDA will attempt to provide a response by the end of September.

Pharma Mar's position on question #5 provided on page 33 of the briefing package.

5. Does the Agency agree that the efficacy and safety data for SCLC patients treated with lurbinectedin in the Basket study PM1183-B-005-14 provide a favorable clinical benefit [redacted] (b) (4)

FDA Response: Please see FDA response to Question 2.

Discussion During Meeting: No discussion occurred.

Pharma Mar's position on question #6 provided on page 40 of the briefing package.

6. Does the Agency agree that, based on the efficacy and safety data observed in the Basket PM1183-B-005-14 study, the benefit-risk in the second-line SCLC population treated with lurbinectedin is positive in the overall population as well as in the sensitive and resistant subpopulations?

   FDA Response: Please see FDA response to Question 2.

   Discussion During Meeting: No discussion occurred.

Clinical Pharmacology

Pharma Mar's position on question #7 provided on page 41 of the briefing package.

7. Does the Agency agree that the integrated exposure response analysis of efficacy and safety supports the proposed treatment regimen of 3.2 mg/m^2 q3wk?

   FDA Response: Pharma Mar's proposed integrated exposure response (E-R) analyses of safety and efficacy appear acceptable to support the proposed dosing regimen of 3.2 mg/m^2 of lurbinectedin Q3W as a single agent. A final determination regarding the adequacy of the integrated E-R analyses in support of the proposed dosing regimen of 3.2 mg/m^2 Q3W will be made during review of the NDA. FDA has the following recommendations on the analyses:

   a. Demonstrate the relationship between BSA and clearance and exposure in the PopPK report. Illustrate the difference in exposure achieved with the proposed regimen between patients with low BSA and patients with high BSA.

   b. Explore the relationship between efficacy (ORR, OS) and BSA in patients with SCLC in the phase 2 Basket study (PM1183-B-005-14).

   c. Explore the relationship between BSA and safety events (neutropenia and thrombocytopenia) in patients treated with 3.2 mg/m^2 Q3W. An exploratory analysis of data from 143 patients treated at 7.0 mg FD Q3W suggested that an increased occurrence of grade 3/4 thrombocytopenia was associated with lower BSA.

   Pharma Mar's Response (provided via email on August 6, 2019): Pharma Mar accepts the Agency's comments and no further discussion is requested during the meeting.

Pharma Mar's position on question #8 provided on page 43 of the briefing package.

8. Does the Agency agree that the completed QT clinical evaluation is sufficient to conclude that lurbinectedin has no clinically relevant effect on QT/QTc interval prolongation and proarrhythmic potential?

FDA Response: The final report and datasets from the QT Study PM1183-B-005-14-QT are currently under review by QT/IRT. FDA cannot draw any conclusions at this time. A final determination regarding the potential of lurbinectedin to prolong the QTc interval will be made upon completion of the review by QT/IRT.

Pharma Mar's Response (provided via email on August 6, 2019): Pharma Mar accepts the Agency's comments and no further discussion is requested during the meeting.

Pharma Mar's position on question #9 provided on page 43 of the briefing package.

9. Does the Agency agree that the *in vitro* studies with human transporters as summarized by the Applicant are sufficient to characterize the potential of lurbinectedin to act as substrate and/or inhibitor of relevant human transporters?

FDA Response: While the *in vitro* studies that Pharma Mar conducted to characterize the potential of lurbinectedin to act as a substrate and/or inhibitor of transporters appear sufficient to support filing the proposed NDA, FDA recommends Pharma Mar assess the *in vitro* potential of lurbinectedin to inhibit MATE2K.

In addition, the *in vitro* study results suggest that lurbinectedin is a P-gp substrate and is also an inhibitor of P-gp, OATAP1B1 and OATP1B3. FDA requests that Pharma Mar propose a plan to assess the *in vivo* drug-drug interactions between lurbinectedin and P-gp inhibitors and between lurbinectedin and P-gp and OATP1B1/3 substrates or provide adequate justification for not performing such *in vivo* studies.

Pharma Mar's Response (provided via email on August 6, 2019): (b) (4) [redacted]

Lurbinectedin as a P-gp substrate: As described in page 13 at the FDA Clinical Drug Interaction Studies Guidance (2017), a clinical DDI study with a P-gp substrate may be indicated when it must be transported into sequestered tissues

(e.g., tissues in the central nervous system) to exert a pharmacological effect, when it must be kept out of the sequestered tissues to avoid toxicity, or when intestinal absorption is likely to be a major cause of the variability in drug response.

In this sense, lurbinectedin is an antitumor agent given intravenously that exerts its pharmacological effect at the tumor site. Therefore, P-gp inhibition is not expected to impact its efficacy variability, or its access to the tumor site.

Moreover, as suggested in page 14 of the Guideline mentioned above, the planned dedicated DDI study with the strong CYP3A4 inhibitor itraconazole, also a P-gp inhibitor, will be able to assess the worst case scenario of CYP3A4 metabolism and P-gp efflux transport inhibition, in terms of variability in lurbinectedin exposure and safety outcomes.

Lurbinectedin as a P-gp, OATAP1B1 and OATP1B3 inhibitor: The *in vitro* inhibitory effect of lurbinectedin on P-gp and OATP1B1/3 was observed at concentrations more than 20-fold higher than lurbinectedin physiological concentrations (see Table 24, page 44 of the Briefing package (main part)). Therefore, the potential of lurbinectedin to produce a clinically relevant interaction with P-gp or OATP1B1, OATP1B3 and OCT1 substrates is negligible, so *in vivo* assessment of such potential is not deemed needed.

Does the Agency agree with Pharma Mar´s proposals?

Discussion During Meeting: Pharma Mar's proposals appears reasonable; however, the final determination of acceptance of these proposals will be made during the NDA review.

Pharma Mar's position on question #10 provided on page 44 of the briefing package.

10. Does the Agency agree with the Applicant's plan to complete the hepatic impairment study as a PMR?

FDA Response: Pharma Mar's proposal to complete a hepatic impairment trial as a Post-Marketing Requirement (PMR) is acceptable. However, FDA requests that a hepatic impairment trial with a full design rather than a reduced design be performed to allow for dosing recommendations for patients with varying degrees of hepatic function.

Pharma Mar's Response (provided via email on August 6, 2019): In cancer patients with severe hepatic dysfunction included in dedicated hepatic impairment studies, clinical benefit rate was <1%, while risk of death on study

was 25% (Juarez Stuart S *et al*. Invest New Drugs 2017; 35(3): 386-391 as provided).

Therefore, Pharma Mar proposes to [redacted] (b) (4) .

Does the Agency agree with Pharma Mar's proposal?

Discussion During Meeting: No. Pharma Mar's proposal is not acceptable. [redacted] (b) (4) . Pharma Mar proposed to do the study as a PMR and FDA requested the proposal be submitted for review and comment to the IND.

Pharma Mar's position on question #11 provided on page 45 of the briefing package.

11. Does the Agency agree with the Applicant's plan to complete the drug-drug interaction studies with strong inhibitors and inducers of CYP3A4 as a PMR?

FDA Response: FDA expects that the study reports for the dedicated drug-drug interaction studies with strong CYP3A4 inhibitors and inducers be included in the NDA submission to inform the product labeling on how to dose lurbinectedin with concomitant medications that are strong CYP3A inhibitors and inducers. Since these studies do not appear to have been conducted, Pharma Mar should include these DDI protocols in the IND submission for FDA review within 60 days of this meeting and initiate these studies as soon as possible after receipt of FDA's comments on these protocols. In the NDA, provide the post-marketing commitment to provide these data, including anticipated trial completion date and final study report submission date.

In addition, FDA requests that Pharma Mar confirm whether or not lurbinectedin has the potential to inhibit CYP3A4 and 2C9 *in vitro*.

Pharma Mar's Response (provided via email on August 6, 2019): Pharma Mar agrees to provide the study protocols of the dedicated drug-drug interaction studies with strong CYP3A4 inhibitors and inducers, within 60 days of this meeting and agrees to start the study as soon as possible after receiving FDA's comments.

Pharma Mar confirms that lurbinectedin at physiological concentrations does not have the potential to inhibit CYP3A4 and 2C9 *in vitro*. The results from these experiments will be provided in the NDA submission.

Discussion During Meeting: No discussion occurred.

Pharma Mar's position on question #12 provided on page 45 of the briefing package.

12. Does the Agency agree that the completed clinical pharmacology program is sufficient to support NDA filing under accelerated approval regulations?

FDA Response: No. In order support of filing of the proposed NDA, the clinical pharmacology package should also include the following information:

a. *In vitro* study reports for characterizing the potential of lurbinectedin to act as a substrate and/or an inhibitor of metabolic CYP enzymes and relevant human transporters

b. *In vivo* drug interaction study plans (see the responses to Questions 9 and 11.

c. Hepatic impairment study plan (see the responses to Questions 10).

d. Additionally, the clinical protocols for all studies contributing data to the population PK analyses should be submitted in Module 5 of the proposed NDA.

Pharma Mar's Response (provided via email on August 6, 2019): Pharma Mar accepts the Agency's comments and no further discussion is requested during the meeting on parts a and b. Parts c and d will be discussed under items 9 and 10.

Nonclinical

Pharma Mar's position on question #13 provided on page 47 of the briefing package.

13. Does the Agency agree that the completed nonclinical study program is sufficient to support NDA filing under accelerated approval regulations?

FDA Response: The nonclinical study program appears adequate to support an NDA filing; however, the acceptability of data from these studies will be determined during review of all data included in the NDA submission.

Pharma Mar's Response (provided via email on August 6, 2019): Pharma Mar accepts the Agency's comments and no further discussion is requested during the meeting.

Procedural

Pharma Mar's position on question #14 provided on page 52 of the briefing package.

14. Does the Agency agree with the planned clinical study reports to be included in the NDA filing?

FDA Response: FDA agrees that the clinical study reports for the studies identified in Table 28 in ANNEX-2 of the meeting briefing package for evaluation of safety and efficacy are adequate to support filing of the clinical section of the proposed NDA. Ensure that the content and format of the clinical study reports conform to the *Guideline for Industry: Structure and Content of Clinical Study Reports,* found at https://www.fda.gov/media/71271/download.

Pharma Mar's Response (provided via email on August 6, 2019): Pharma Mar accepts the Agency's comments and no further discussion is requested during the meeting.

Pharma Mar's position on question #15 provided on page 54 of the briefing package.

15. Does the Agency agree that, since the NDA consists of a single study to support efficacy, the Summary of Clinical Efficacy (Mod 2, Section 2.7.3) will satisfy the regulatory requirement for an Integrated Summary of Efficacy (ISE)?

FDA Response: FDA does not agree that the SCE will satisfy the regulatory requirement for an ISE. However, a standalone ISE will not be required if the clinical study report for Study PM1183-B-005-14 is inclusive of all data for the assessment of efficacy for the proposed indication and contains the information otherwise provided in the ISE, including appendices of tables and figures and appropriate datasets, as discussed in the *Integrated Summary of Effectiveness: Guidance for Industry,* found at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/integrated-summary-effectiveness.

FDA agrees with Pharma Mar's proposal to provide an SCE that will contain all the text information required in an ISE.

Pharma Mar's Response (provided via email on August 6, 2019): PharmaMar accepts the Agency's comments and no further discussion is requested during the meeting.

Pharma Mar agrees that at the time of NDA submission the clinical study report for Study PM1183-B-005-14 will include all data for the assessment of efficacy for the proposed indication and will contain the information otherwise provided in the ISE, including appendices of tables and figures and appropriate datasets.

Discussion During Meeting: FDA clarified that an ISE is required even when a single study provides the primary evidence of effectiveness. FDA stated that top level data describing results of anti-tumor activity in other cancers would suffice rather that full integrated analyses and data-sets. Additional information from ongoing studies in SCLC may also be included.

Pharma Mar's position on question #16 provided on page 54 of the briefing package.

16. Does the Agency agree with the planned Integrated Population PK and PKPD Study reports and associated datasets to be included in the NDA filing?

FDA Response: The proposal appears generally acceptable. Submit the analysis codes for the Population PK and PK/PD analyses along with datasets. For the Population PK analysis, include data from all lurbinectedin-treated patients with evaluable PK enrolled in the studies listed in Table 1 of the July 5, 2019 pre-NDA meeting package.

Pharma Mar's Response (provided via email on August 6, 2019): The Sponsor agrees to expand the Population PK analysis to the studies listed in Table 1 of the Pre-NDA meeting package. Study PM1183-A-013-15 is ongoing so data is not ready to be pooled yet, and study (b) (4) used a different bioanalytical method which is not cross validated with the reference one, so it is not deem appropriate to be pooled at the PopPK database.

Does the Agency agree with Pharma Mar's proposal?

Discussion During Meeting: Pharma Mar's proposal appears reasonable.

Pharma Mar's position on question #17 provided on page 55 of the briefing package.

17. Does the Agency agree with the electronic datasets and eCRFs to be included in the NDA submission?

FDA Response: FDA agrees that eCRFs should be submitted from the studies included in the ISS for patients who died within 30 days of receipt of the last dose of protocol-specified therapy or who discontinued adverse events regardless of relationship to the drug. However, FDA does not agree with the proposal for [redacted] (b) (4)

FDA expects that the NDA contain narrative summaries for all patients with serious adverse events regardless of relationship to the drug.

Pharma Mar's Response (provided via email on August 6, 2019): Pharma Mar accepts the Agency's comments on the eCRFs and narratives but respectfully requests a response to the other part of the question regarding the datasets we plan to submit in the NDA to support the clinical safety and efficacy review.

In the briefing package of August 5, Pharma Mar proposed to provide the following electronic datasets in the NDA submission:

- Clinical datasets for study PM1183-B-005-14 (Basket) (Investigator and IRC assessments) following CDISC standards (SDTM 1.4/SDTM IG 3.2/define.xml v2.0; and ADaM 2.1/ADaM IG 1.1/define.xml v2.0) with supporting documentation.
- Analysis datasets for the Integrated Summary of Safety (ISS) that includes data from studies PM1183-B-005-14 (Basket) and PM1183-C-004-14 (CORAIL), following CDISC standards (ADaM 2.1/ADaM IG 1.1/define.xml v2.0) with supporting documentation

Does the Agency agree with this proposal?

Discussion During Meeting: FDA agrees that the proposed approach is acceptable. FDA acknowledged that the data-sets for the FIH and mass balance studies will be provided in SAS Format.

ADDITIONAL FDA COMMENTS

18. Please confirm that the proposed NDA will contain a mock-up define file to show the variables which will be included in the derived datasets for the primary and key secondary efficacy analyses including, but not limited to, dates of IRC determined (as well as investigator assessed) progression. Please include in your submission

    a. SAS programs that produced all efficacy results

b. All raw as well as derived variables in .xpt format

c. SAS programs by which the derived variables were produced from the raw variables

d. Results of any interim analysis if ever performed.

Pharma Mar's Response (provided via email on August 6, 2019): Pharma Mar accepts the Agency's comments and no further discussion is requested during the meeting.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed, and the agreements reached are documented in these meeting minutes, the minutes for the June 19, 2019, CMC only meeting, and in FDA's Written Responses issued on June 10, 2019.

- Pharma Mar confirmed that the application will contain a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion was held on the need for a REMS, other risk management actions. FDA agreed that the application could be filed without a REMS. No Formal Communication Plan was proposed.

- We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application. **Late Minor Component:** Agreement on submission of a late minor CMC component, containing additional stability data, within 30 days after the initial NDA submission.

Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

NDA NUMBER: LATE COMPONENT - QUALITY

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration

are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Since lurbinectedin has orphan designation for the treatment of small cell lung cancer, you are exempt from these requirements provided the NDA is submitted prior to August 18, 2020. Please include a copy of the letter designating lurbinectedin as an orphan drug, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application.

Please be aware that Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See the link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting and no later than 210 days prior to submission of an NDA if that NDA will be submitted **after** August 18, 2020. The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of an initial Pediatric Study Plan (iPSP), including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/U CM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.ht m.

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided.

Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult FDA's Guidance on Formal Meetings Between the FDA and Sponsors or Applicants[2] to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

[2] See the guidance for industry *"Formal Meetings Between the FDA and Sponsors or Applicants."*
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

- Regulations and related guidance documents.

- A sample tool illustrating the format for Highlights and Contents, and

- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The

meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments,

and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[6]

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR[7]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- AssessmentAid[8]

ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

ACTION ITEMS

No action items.

ATTACHMENTS AND HANDOUTS

[6] https://www.fda.gov/media/85061/download
[7] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[8] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

Slide deck presented by Pharma Mar at the meeting.

2 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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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
08/14/2019 12:26:49 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 127944

MEETING MINUTES

Pharma Mar USA, Inc.
Attention: Sonia Vela Herrero
Project Leader
205 East 42nd Street, Suite 15003
New York, NY 10017

Dear Ms. Vela Herrero:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for lurbinectedin (PM01183).

We also refer to the meeting between representatives of your firm and the FDA held on December 11, 2018. The purpose of the meeting was to discuss whether the available clinical data from Study PM1183-B-005-14 may support a New Drug Application (NDA), to be submitted under the provisions of 21 CFR 314.500 (accelerated approval), should the data warrant, and to discuss the development of lurbinectedin (PM01183) (b) (4)

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4803.

Sincerely,

{See appended electronic signature page}

Stacie Woods, Pharm.D.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	End of Phase 2
Meeting Date and Time:	December 11, 2018
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room 1419, Silver Spring, Maryland 20903
Application Number:	127944
Product Name:	lurbinectedin (PM01183)
Indication:	Treatment of patients with (b) (4) SCLC, (b) (4)
Sponsor/Applicant Name:	Pharma Mar USA, Inc.
Meeting Chair:	Erin Larkins, M.D.
Meeting Recorder:	Mimi Biable, M.S.

FDA ATTENDEES
Patricia Keegan, M.D., Division Director, DOP2
Erin Larkins, M.D., Clinical Team Leader, DOP2
Luckson Mathieu, M.D., Clinical Reviewer, DOP2
Brenda Ye, M.D., Reviewer, DMIP
Alex Gorovets, M.D., Deputy Director, DMIP
Whitney Helms, Ph.D., Pharmacology/Toxicology Team Leader, DHOT
Pallavi Mishra-Kalyani, Ph.D., Statistical Team Leader, OTS
Amal Ayyoub, Ph.D., Clinical Pharmacology Reviewer, DCPV
Hong Zhao, Ph.D., Clinical Pharmacology Team Leader, DCPV
Mimi Biable, M.S., Lead Regulatory Health Project Manager, DOP2

SPONSOR ATTENDEES
Ana Irigaray, Regulatory Affairs Director
Ali Zeaiter, M.D., Clinical R&D Director
Carmen Kahatt, M.D., Clinical Oncology Senior Manager
Cristian Fernández, M.D., Clinical Oncology Medical Specialist
Javier Gómez, Biostatistics & Data Management Senior Manager
José Antonio López-Vilariño, M.D., Clinical Oncology Medical Specialist

Hervé Dhellot, M.D., Clinical Safety Senior Manager / EEA QPPV, via teleconference
Salvador Fudio, M.D., Clinical Pharmacology Senior Manager, via teleconference

BACKGROUND

Regulatory

Pharma Mar USA Inc. (PharmaMar) is conducting a multicenter, open-label, exploratory study, Study PM1183-B-005-14, entitled, "A Multicenter Phase 2 Clinical Trial of Lurbinectedin (PM01183) in Selected Advanced Solid Tumors," to evaluate the anti-tumor activity and safety of lurbinectedin in previously treated patients with advanced solid tumors including small cell lung cancer (SCLC).

On October 10, 2018, Pharm Mar submitted a request for a Type B, End of Phase 2 (EOP2) meeting to discuss the adequacy of the results from the SCLC cohort from Study PM1183-B-005-14 to support accelerated approval of lurbinectedin for the treatment of patients with (b) (4) SCLC, (b) (4), with the ongoing ATLANTIS study to serve as the confirmatory study to verify clinical benefit.

On October 19, 2018, FDA granted the Type B meeting. The meeting package was received on October 26, 2018.

The regulatory history of this development plan is summarized below.

- On December 15, 2008, an Investigational New Drug (IND) application, IND (b) (4), was submitted to the Division of Oncology Products 1 (DOP1) containing a new clinical protocol entitled "Phase 1, Multicenter, Open-label, Dose-escalating, Clinical and Pharmacokinetic Study of PM01183 in Patients with Advanced Solid Tumors," and became active January 16, 2009. The current indication under this IND is (b) (4).

- On December 17, 2014, a Type C Written Responses Only meeting was held under IND (b) (4) to obtain advice on the clinical pharmacology development plan for lurbinectedin (PM01183).

- On October 9, 2015, PharmaMar submitted IND 127944 to the Division of Oncology Products 2 (DOP2); this IND contained a new clinical protocol, Protocol PM1183-C-003-14 entitled, "Phase 3 Randomized Clinical Trial of Lurbinectedin (PM01183) 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, this IND was placed on Full Clinical Hold because the study design was determined by FDA to be unable to meet its stated objectives. A Full Clinical Hold letter was issued on November 13, 2015 which provided information needed to resolve the deficiency, in addition to non-hold clinical and clinical pharmacology comments.

- On January 28, 2016, a Type A meeting was held to discuss PharmaMar's proposal to address the clinical hold placed on IND 127944. To address the deficiency in the protocol design, FDA recommended an adaptive study design, with single-agent doxorubicin and single-agent lurbinectedin arms, with the opportunity to drop arms for futility at interim analysis, in order to allow isolation of the contribution of each drug to the regimen. The meeting minutes were issued on February 3, 2016.

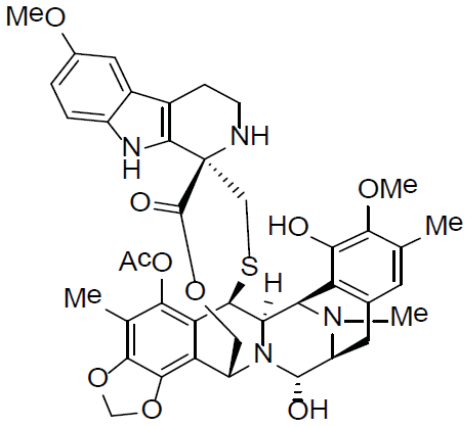
- On February 12, 2016, PharmaMar submitted a Response to the Full Clinical Hold letter that included a revised clinical protocol, Protocol PM1183-C-003-14, with the revised title "Phase 3 Randomized Clinical Trial of Lurbinectedin (PM01183)/Doxorubicin (DOX) versus Cyclophosphamide (Cy), Doxorubicin (DOX) and Vincristine (VCR) (CAV) or Topotecan as Treatment in Patients with Small-Cell Lung Cancer (SCLC) Who Failed One Prior Platinum-Containing Line (ATLANTIS Trial)" and a revised statistical analysis plan (SAP). To potentially isolate the contribution of lurbinectedin to the combination, PharmMar added CAV as an option in the control arm and added choice of treatment (CAV or topotecan) as a stratification factor. The decision to treat with CAV or topotecan will be at the discretion of the investigator. Inclusion as a secondary endpoint the analyses of efficacy for the lurbinectedin plus doxorubicin arm compared to the subgroup of patients treated with CAV were added as a secondary endpoint.

- On March 11, 2016, the clinical hold was removed.

- On August 1, 2018, lurbinectedin received orphan designation for the treatment of small cell lung cancer.

Chemistry, Manufacturing, and Controls (CMC)
Lurbinectedin is an alkaloid with the following chemical structure:

Figure 4. Molecular structure of lurbinectedin



Lurbinectedin drug product for injection is formulated as a lyophilized powder in one strength: 4 mg per vial. CMC information for lurbinectedin is provided by cross reference to PharmaMar's another IND (b) (4).

Clinical Pharmacology
Lurbinectedin is characterized by an apparent plasma clearance (CL/F) of 11.9 L/hour, and a terminal half-life of 44.3 hours. After an intravenous (IV) dose of 5 mg, approximately 95% of a [$_{14}$C]- lurbinectedin dose was recovered in feces and 5% in urine at 20 days after administration, mostly as metabolites. *In vitro* results indicate that CYP3A4 is the major CYP isoform involved in the metabolism of lurbinectedin (83%), followed by CYP2El (12%), CYP2D6 (3%), and CYP2C9 (1.4%) to a minor extent. The *in vitro* protein binding of lurbinectedin at plasma concentrations achieved following dosing at 3.2 mg/m^2 is ~99%.

The effect of CYP3A inhibitors on PM01183 PK was explored by means of a population pharmacokinetics (PopPK) analysis; PM01183 CL/F is reduced by approximately 30%. Pharma Mar states that physiologically-based pharmacokinetic (PBPK) models will be used to explore any potential effect of lurbinectedin as CYP3A4 inhibitor.

Per Pharma Mar, the upper bound of the 90% confidence interval (CI) of ΔQTcF at mean lurbinectedin C_{max} of 105 ng/mL is 5.1 msec at the 3.2 mg/m^2 Q3W regimen in 39 patients in study PM1183-B-005-14.

The recommended doses of lurbinectedin and doxorubicin administered IV on day 1 of each 21-day cycle (Q3W) was preliminarily based on the results of Study PM1183-A-003-10. Subsequently, a pooled analysis evaluating the toxicity of lurbinectedin and doxorubicin across multiple single arm studies identified the doses of lurbinectedin 2.0 mg/m^2 and doxorubicin 40 mg/m^2 IV Q3W as optimal based on a logistic regression analysis that suggested that patients with the lowest BSA had a greater risk of developing Grade 3/4 thrombocytopenia.

Clinical
PharmaMar stated that, as of October 1, 2018, 1807 patients were exposed to lurbinectedin as a single agent or in combination with other drugs across 21 clinical trials. Six of these clinical trials included patients with SCLC; these comprise four dose finding studies (two completed and two ongoing), one disease-specific cohort in an ongoing activity-estimating, multiple cohort study, and the ongoing randomized study (ATLANTIS).

<u>PM1183-A-003-10 (lurbinectedin plus doxorubicin)</u>
This dose-finding study evaluated the safety and activity of lurbinectedin administered with doxorubicin in patients with selected advanced solid tumors. This study has completed recruitment, with 122 patients enrolled and 120 treated, and the end of study has been reached. The initial dose level evaluated was lurbinectedin 3.0 mg intravenously (IV) and doxorubicin 50.0 mg/m^2 IV Day 1 of each 21-day cycle (Q3W). Following delivery of a cumulative doxorubicin dose of 450 mg/m^2, the recommended dose of lurbinectedin as a single agent was 7.0 mg [flat dose] or 4.0 mg/m^2 IV Q3W in patients without disease progression. The recommended doses were determined to be lurbinectedin 4.0 mg (flat dose) IV and doxorubicin 50.0 mg/m^2 IV Q3W without G-CSF prophylaxis.

Dose-limiting toxicities included grade 3-4 febrile neutropenia, grade 4 thrombocytopenia and grade 4 septic shock.

PM1183-A-007-13 (lurbinectedin and paclitaxel)
This completed dose finding study evaluated the safety and anti-tumor activity of lurbinectedin and paclitaxel with or without bevacizumab, in patients with advanced solid tumors. The study enrolled 55 patients who received lurbinectedin and paclitaxel (Cohort A) and 12 patients who received lurbinectedin, paclitaxel, and bevacizumab (Cohort B).

PM1183-A-008-13 (lurbinectedin and cisplatin)
This completed dose finding study evaluated the safety and activity of lurbinectedin and cisplatin in patients with selected advanced solid tumors. The recommended doses were determined to be cisplatin 60 mg/m^2 and lurbinectedin 1.1 mg/m^2 when aprepitant was given as part of the antiemetic regimen and cisplatin 60 mg/m^2 and lurbinectedin 1.4 mg/m^2 when aprepitant was not given as part of the antiemetic regimen.

PM1183-A-014-15 (lurbinectedin and irinotecan)
There are no results from this ongoing dose-finding study. The recommended phase 2 dose will be determined in patients receiving G- CSF prophylaxis.

Study PM1183-B-005-14
Study PM1183-B-005-14 is an ongoing study enrolling patients with various solid tumors, including SCLC, with disease progression after available therapy. Based on a pooled analysis of data from dose escalation and dose expansion studies, all patients received 3.2 mg/m^2 Q3W as there was a lower incidence of febrile neutropenia with this dose (as compared to 4.0 mg/m^2.Q3W). Key eligibility criteria for the SCLC cohort are ECOG PS $\leq$ 2, pathologically proven SCLC, and receipt of only one prior line of chemotherapy. Patients with CNS involvement are excluded (mandatory brain CT scan or MRI at baseline).

The primary efficacy endpoint is confirmed ORR per investigator assessment using Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1. Assessment of antitumor activity by an Independent Review Committee (IRC) was added as a secondary objective in the SCLC cohort via a protocol amendment on July 2018.

As initially designed, the sample size was limited to 25 evaluable patients per cohort. The protocol was amended to increase the sample size for the SCLC cohort to 50 patients and later to 100 patients. According to PharmaMar, the rationale for the increased sample size was to allow confirmation of the anti-tumor activity of lurbinectedin as a single agent in patients with SCLC and to support the ongoing ATLANTIS trial. In the current version of the analysis plan for the SCLC cohort, a sample size of 100 evaluable patients will be provide 90% power with a Type I error rate of 0.025 to test the null hypothesis of response rate of 15% versus an alternative hypothesis of 30%.

Initial Results for the SCLC cohort in Study PM1183-B-005-14
As of October 1, 2018, 325 patients received lurbinectedin on Study PM1183-B-005-14, including 97 patients with SCLC cohort. PharmaMar states that 88 patients are “evaluable for efficacy” and the remaining nine patients “had not enough data currently available in the database.” The 88 evaluable patients were enrolled at investigational centers in Spain (n=51),

France (n=16), the USA (n=9), Switzerland (n=5), Belgium (n=3), the United Kingdom (n=3) and Italy (n=1).

The ORR according to RECIST v1.1 as assessed by an independent review committee (IRC) in the "efficacy evaluable" population and in subgroups based on chemotherapy treatment free interval (CTFI) of less than 3 months or ≥ 3 months is shown the Table 1 below. The ORR in the "as treated" population (28 responses among 97 patients with SCLC) is 29% (95% CI: 20, 39).

Table 1: Efficacy in SCLC patients treated in the PM1183-B-005-14 study

Adapted from Sponsor's submission Meeting Package (page 32/62)

	Efficacy Evaluable (n=88)	**CTFI < 3 months (n=37)**	**CFTI ≥ 3 months (n=50)**
ORR per RECIST v1.1			
ORR, % (95%CI) confirmed response	31.8% (22.3 - 42.6%)	24.3% (11.8 – 41.2%)	38.0% (24.7 – 52.8%)
Kaplan-Meier estimated Duration of response (months), median (95% CI)	6.2 (5.1 – 7.3)	4.6 (2.6 – 5.6)	6.4 (5.5 – 8.8)

According to PharmaMar, the median number of cycles administered to the 88 evaluable SCLC patients was 4 (range 1-25 cycles). In this population, the most common adverse events (AEs) were fatigue (56% of patients), nausea (30%), decreased appetite (21%), vomiting (17%), diarrhea (14%), and constipation (11%). Febrile neutropenia was the only Grade 4 AE (3.4%). Grade 3 AEs were fatigue (3.4%) and pneumonia (3.4%), with diarrhea, febrile neutropenia, peripheral neuropathy and skin ulcer (1.1% each).

Study PM1183-C-003-14 (ATLANTIS)
ATLANTIS is an ongoing, multicenter, open-label, randomized, trial comparing the efficacy and safety of lurbinectedin, administered in combination with doxorubicin for 10 cycles, followed by lurbinectedin administered as a single agent with investigator's choice of chemotherapy [cyclophosphamide, doxorubicin, and vincristine (CAV) or topotecan] in patients with SCLC previously treated with one prior platinum-containing regimen. Patients who received more than one prior line of therapy and those with a chemotherapy-free interval (CTFI) of less than 30 days are ineligible.

Randomization is stratified by CTFI after first line therapy [≥180 days (very sensitive) *vs.* 90-179 days (sensitive) *vs.* <90 days (resistant); ECOG PS score; central nervous system involvement; prior immunotherapy against either PD-1/PD-L1; and Investigator's preference of treatment.

Patients are randomized 1:1 to receive:

- Arm A: Doxorubicin 40 mg/m2 and lurbinectedin 2.0 mg/m2 IV Q3W for 10 cycles, followed by single-agent lurbinectedin 3.2 mg/m2 IV Q3W
- Arm B
  - cyclophosphamide 1000 mg/m2, doxorubicin 45 mg/m2 and vincristine 2.0 mg IV Q3W (CAV)
  - topotecan (IV. daily on day1-day5 q3wk).

The primary endpoint is overall survival. A total of approximately 600 patients will be randomized. Assuming a median OS of 7.5 months in the control arm and a 25% reduction in the relative risk of death [hazard ratio (HR) =0.75] with the experimental arm, 508 events will provide at least 90% power at a one-sided 2.5% significance level, following exponential distributions and fulfilling the proportional hazard assumption. PharmaMar forecasts that an observed HR of approximately 0.84 will have enough power to reject the null hypothesis.

To evaluate the overall safety in both arms, an interim safety analysis is planned after the recruitment of 150 patients (i.e., approximately 75 patients in each arm). Recruitment will not be put on hold while the interim safety analysis is being performed. Efficacy parameters will not be formally analyzed in this interim analysis.

There is no intention to claim superiority before the necessary number of events for the OS analysis has been reached. However, if formal interim analyses are requested by the independent data monitoring committee (IDMC), Lan and DeMets error spending function that corresponds to the O'Brien-Fleming boundary will be used, calculated during the interim analyses to preserve an overall one-sided 0.005 false positive error rate; if early termination does not occur, the alpha level of the final analysis will be chosen to preserve an overall one-sided 0.025 false positive error rate.

Preliminary Results
As of August 2018, PharmaMar reported that 613 patients were enrolled; the trial is closed to accrual. As of the data cutoff date of October 1, 2018, 592 of thes 613 patients initiated protocol-specified therapy, with 302 patients receiving lurbinectedin plus doxorubicin and 290 receiving investigator's choice of chemotherapy.

PharmaMar predicts that 508 deaths will have occurred by Q4 2019.

FDA preliminary comments were sent to PharmaMar on December 6, 2018.

DISCUSSION OF FDA RESPONSES TO SPONSOR QUESTIONS

1. PharmaMar believes that treatment for relapsed SCLC remains a high unmet medical need. Does the Division agree?

   FDA's Response: Yes.

PharmaMar's Response received via email on December 10, 2018: No further discussion is needed.

Discussion During the 12/11/18 Meeting: There was no discussion.

2. Based on data from the SCLC cohort of the ongoing PM1183-B-005-14 study showing ORR=31.8% (95% CI, 22.3-42.6%) according to Investigators' assessment (confirmed responses by a second tumor assessment), median duration of response of 6.2 months (95% CI, 5.1-7.3 months), and the acceptable safety profile observed in SCLC which is consistent with that observed in around 500 patients treated with lurbinectedin 3.2 mg/m² q3wk in different indications, PharmaMar believes that the benefit/risk ratio of lurbinectedin in the studied population is positive and may support accelerated approval. Assuming that the ORR/duration of response results are verified by IRC review, does the Division agree that these results may support accelerated approval?

FDA Response: Based on the results reported for ORR and DoR, lurbinectedin has clinical activity in SCLC that has progressed following platinum-based chemotherapy. (b) (4) . There is insufficient information regarding the treatment effect in the subpopulation of patients with a chemotherapy free interval of less than 3 months. PharmaMar should complete the study as planned (accrual of 100 patients) and provide the updated ORR and DoR, as assessed by the IRC, when all responding patients have been followed for at least 6 months from the onset of response.

PharmaMar's Response received via email on December 10, 2018: PharmaMar seeks further clarification on the Agency´s statement" There is insufficient information regarding the treatment effect in the subpopulation of patients with a chemotherapy free interval of less than 3 months.

The sponsor acknowledges the limitations of cross trial comparison. The interim results from the SCLC cohort of the basket trial suggest that lurbinectedin provides a meaningful clinical advantage (b) (4) in terms of both efficacy and safety.

Data on the resistant population is provided in tables 4, 5, 13 and figures 7, 8, 9, and 10 of the Briefing Document, as well as in the Sponsor's presentation. Therefore, we respectfully request the Agency to clarify the type of information required to demonstrate the treatment effect for this subgroup.

With regards to the Agency´s comment:

¨*PharmaMar should complete the study as planned (accrual of 100 patients) and provide the updated ORR and DoR, as assessed by the IRC, when all responding patients have been followed for at least 6 months from the onset of response.*¨

The Sponsor understands that the Agency would be willing to accept an application under subpart H based on ORR and DoR by IRC from 105 patients followed for at least 6 months from the onset of the response, providing that the qualifying criteria for accelerated approval are fulfilled. Is the Sponsor's understanding correct?

The sponsor plans to request a pre-NDA meeting in 2Q2019 with the results of the primary analysis of the phase II study. The briefing package will contain data from a total of 105 treated patients, with at least two post-baseline tumor evaluations. At the time of the planned cut-off more than 85% of all responders are expected to have a progression or death event or will be alive with a follow-up longer than 6 months from the date of onset of their response. The sponsor´s commitment is to provide the agency with more mature data during the evaluation process, in case any responder patient has not reached at least 6 months follow-up at the time of the clinical cutoff for data submission.

Discussion During the 12/11/18 Meeting: FDA stated that the number of patients with platinum-resistant disease is small, the lower limit of the 95% confidence interval (CI) around the observed response rate is less than 12%, and the medium duration of response is relatively short. Therefore, FDA is not certain that this effect is likely to predict clinical benefit particularly considering the toxicity profile. FDA recommended accruing more patients with platinum-resistant disease.

PharmaMar stated that the accrual of the PM1183-B-005-14 study has been completed, with 105 patients enrolled and 104 patients treated with lurbinecdetin, and IRC assessment for tumor response is ongoing. FDA advised PharmaMar to request a teleconference when the topline results based on the IRC review is completed.

FDA requested that the topline summary results by IRC assessment should be submitted when a minimum of 6 months follow-up from onset of response in all responding patients is available unless the median duration of response is mature with shorter follow-up.

3. Assuming that data from the ongoing phase 2 study supports an accelerated approval under 21 CFR 314.500, Subpart H, PharmaMar proposes the ongoing phase 3 (ATLANTIS), open-label, randomized, clinical trial of lurbinectedin/doxorubicin versus CAV or topotecan in patients with SCLC who failed one prior platinum-containing line, as a confirmatory trial to support full approval. Does the Division agree?

FDA Response: FDA does not agree that the data from the SCLC cohort in Study PM1183-B-005-14 will support accelerated approval.

Regarding the ATLANTIS trial, FDA has continued concerns regarding its ability to support a marketing application for lurbinectedin, administered in combination with doxorubicin, because the trial is not adequate in design to isolate the individual contributions of lurbinectedin and of doxorubicin to the treatment effect observed with the combination.

As previously stated by FDA during the January 28, 2016 meeting with PharmaMar, there is a potential to isolate the contribution of lurbinectedin when administered with doxorubicin through a comparison of a stratified subgroup randomized to CAV or lurbinectedin plus doxorubicin, provided that the magnitude of the treatment effect for lurbinectedin plus doxorubicin compared with CAV is clinically meaningful. FDA stated that it is essential to demonstrate that the addition of lurbinectedin contributes to the combination of lurbinectedin plus doxorubicin in order to determine if there is substantial evidence of effectiveness for lurbinectedin. In their assessment for substantial evidence of effectiveness, FDA would look at the totality of the data, including information from Phase 2 studies and other clinical information, but FDA will not place great reliance on the nonclinical data.

Based on the results reported for ORR and DoR in the cohort of patients with SCLC treated in Study PM1183-B-005-14, lurbinectedin as a single agent has clinical activity in SCLC that has progressed following platinum-based chemotherapy. Therefore, PharmaMar will also need to characterize the contribution of doxorubicin to the treatment effect observed with the combination of lurbinectedin and doxorubicin. This assessment should be based primarily on clinical data, since FDA will place minimal reliance on the nonclinical data

PharmaMar's Response received via email on December 10, 2018: PharmaMar acknowledges the FDA concerns regarding the ATLANTIS trial, and understands that there is a potential to isolate the contribution of lurbinectedin when administered with doxorubicin through a comparison of a stratified subgroup randomized to CAV or lurbinectedin plus doxorubicin.

PharmaMar understands that ATLANTIS would be acceptable to support a marketing authorization provided that the magnitude of the treatment effect for lurbinectedin plus doxo compared with CAV is clinically meaningful. In this sense we would like to clarify that the ATLANTIS Protocol was amended and submitted to the Agency in May 2018. A new secondary objective was included in order to characterize the contribution of PM01183 to the PM01183/DOX combination in the stratum of patients with CAV as Investigator's choice:

Secondary Objective:

Difference in OS between PM01183/DOX and CAV, in patients with CAV as best Investigator's choice.

The analysis of the secondary endpoints will be performed using hierarchical methods and type I error correction for multiplicity (i.e. comparison with CAV and comparison in patients without baseline CNS).

In addition, a tertiary endpoint was included to assess the efficacy and safety profiles in the subgroups of the PM01183/DOX arm vs. CAV or topotecan.

Tertiary Objectives:

Subgroup analyses of the PM01183/DOX arm vs. CAV based on investigator's preference will be performed to isolate the contribution of PM01183 in the PM01183/DOX combination arm. Those for whom the investigator's preference was topotecan, it will be also analyzed independently.

Is the Sponsor's understanding regarding the Agency feedback on the ATLANTIS study correct?

Discussion During the 12/11/18 Meeting: PharmaMar stated that the ATLANTIS trial was revised in accordance with FDA's recommendations. FDA stated that, as revised, the trial has the potential to isolate the contribution of lurbinectedin to the combination arm (lurbinectedin and doxorubicin); however, it appears that assessment of the contribution of doxorubicin to the combination arm will be conducted as a cross-study comparison between Study PM1183-B-005-14 and the lurbinectedin-containing arm of ATLANTIS. FDA stated that whether the cross-study comparison would be adequate to isolate the contribution of doxorubicin to the combination arm will depend upon the similarities in the patient populations enrolled and the observed efficacy results between the two trials.

4. The safety profile observed for lurbinectedin 3.2 mg/m² q3wk in around 500 patients treated in the phase 2 basket trial (nine different indications) and the phase 3 CORAIL trial (ovarian cancer) is consistent. PharmaMar believes that these safety data are sufficient to define the safety profile of lurbinectedin for a reviewable application under accelerated approval. Does the Division agree?

FDA Response: See FDA's response to Question 3 regarding the inability of the results observed in the SCLC cohort from Study PM1183-B-005-14 to support accelerated approval.

Regarding the adequacy of the proposed safety data package, where the current safety experience includes data from at least 1807 patients exposed to lurbinectedin as a single agent or in combination with other drugs across 21 clinical trials, this experience is likely to be adequate to characterize the serious risks of lurbinectedin occurring at an incidence of 0.5%. However, FDA notes that there is limited description of the available safety data provided in the briefing package. A detailed description of available safety data for lurbinectedin as a single agent and in combination with doxorubicin should be provided in an amendment to the IND within 60 days of this meeting, so that FDA can provide comments on adequacy of the study to characterize safety signals. Please note that a future NDA would be expected to contain a safety data package that includes information on all patients exposed to lurbinectedin with adequate follow-up (at least one post-treatment safety assessment).

PharmaMar's Response received via email on December 10, 2018: The Sponsor seeks clarification regarding the Agency request to submit a detailed description of available safety data for lurbinectedin as a single agent and in combination with doxo in an

amendment to the IND within 60 days of the meeting.

Discussion During the 12/11/18 Meeting: FDA stated that additional information is needed regarding the difference between the 1807 patients exposed and the approximately 500 patients to be included in the safety database.

PharmaMar clarified that 544 patients received lurbinectedin as a single agent at the proposed recommended dose. FDA requested that PharmaMar also provide phase 1 safety data for lurbinectedin as a single agent obtained in Study PM1183-A-003-10. PharmaMar agreed to provide a summary of the proposed safety analysis populations in a meeting package for a future pre-NDA meeting.

5. Does the Division agree with the proposed IRC charter and statistical analysis plan?

FDA Response: FDA does not agree with the proposed analysis plan. The analysis population for the primary endpoint of ORR in Study PM1183-B-005-14 should include all patients who received one or more doses of lurbinectedin or doxorubicin. The charter is under review; comments on the charter will be sent under separate cover.

PharmaMar's Response received via email on December 10, 2018: The sponsor would like to clarify that the PM1183-B-005-14 concerns the evaluation of lurbinectedin as single agent and does not include any evaluation of doxorubicin.

The Sponsor understands that the SAP of the PM1183-B-005-14 should be amended to include in the analysis of the primary endpoint all patients who received one or more doses of lurbinectedin, currently a secondary analysis, and would appreciate to receive any other comment that the Agency might have on the proposed SAP.

Discussion During the 12/11/18 Meeting: FDA acknowledged that this study does not include doxorubicin and PharmaMar's proposal to modify the primary analysis population as requested by FDA is acceptable.

Regarding the charter for the IRC assessment, the charter is found to be largely acceptable. FDA requested that PharmaMar provide a response to the following requests for clarification in an amendment to the IND:

1) Per Section 7.2 Reviewer Blinding of the Imaging Charter, the independent radiologist readers will be given "site response assessments". It is unclear from the imaging charter what the site response assessments contain. If the site response assessments contain clinical information that could bias blinded image interpretation, we recommend the independent radiologists be blinded to site response assessments or have such clinical information removed from the site response assessments provided to the independent radiologists.

2) Confirm whether the blinded radiologists make lesion level measurements and also determine patient level response (Radiographic Time Point Response) for each time point.

3) Confirm whether the clinical information given to the adjudicator will be the same as given to the independent radiologist readers.

ADDITIONAL FDA COMMENTS

Clinical Pharmacology

6. In the Pre-NDA meeting package, justify the proposed dose selection of 3.2 mg/m^2 Q3W with integrated exposure-response analysis for efficacy and safety utilizing pharmacokinetic (PK) data from all relevant trials and across all treatment regimens tested.

PharmaMar's Response received via email on December 10, 2018: No further discussion is needed.

Discussion During the 12/11/18 Meeting: There was no discussion.

7. In the Pre-NDA meeting package, submit the QT prolongation analysis report and datasets to the FDA QT-IRT team for review of the adequacy of the assessment.

PharmaMar's Response received via email on December 10, 2018: No further discussion is needed.

Discussion During the 12/11/18 Meeting: There was no discussion.

8. In the Pre-NDA meeting package, specify the timeline for completion of studies assessing The *in vitro* potential of lurbinectedin to act as a substrate of P-gp, BCRP, and major hepatic transporters (e.g., OATP1B1/3), and as an inhibitor of OATP1B1, OATP1B3, OAT1, OAT3, OCT2, and MATE1/MATE2K transporters. For additional detail, refer to the following FDA Guidance for Industry, entitled, "Clinical Drug Interaction Studies – Study Design, Data Analysis, and Clinical Implications: available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf

PharmaMar's Response received via email on December 10, 2018: No further discussion is needed.

Discussion During the 12/11/18 Meeting: There was no discussion.

9. Please note that the current Agency's policy on use of PBPK analysis in evaluating a drug's tendency to act as a perpetrator of enzyme-based drug-drug interactions (DDIs) is limited to confirming the lack of such an interaction. Furthermore, when PBPK models

are used to predict the effects of lurbinectedin to inhibit and/or induce the metabolism, the models should describe each DDI mechanism separately (i.e., the model should not only consider the net DDI effects).

PharmaMar's Response received via email on December 10, 2018: No further discussion is needed.

Discussion During the 12/11/18 Meeting: There was no discussion.

10. Specify that the plasma concentrations of lurbinectedin major metabolite(s) will also be measured for assessing the effect of a strong CYP3A index inducer and inhibitor on lurbinectedin pharmacokinetics in lurbinectedin drug-drug interaction study(ies).

PharmaMar's Response received via email on December 10, 2018: No further discussion is needed.

Discussion During the 12/11/18 Meeting: There was no discussion.

11. Complete the planned hepatic impairment study, (b) (4) , and dedicated drug-drug interaction study(ies) with strong inhibitors and inducers of CYP3A4.

PharmaMar's Response received via email on December 10, 2018: No further discussion is needed.

Discussion During the 12/11/18 Meeting: There was no discussion.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Since lurbinectedin has an orphan drug designation for the treatment of small cell lung cancer, you are exempt from these requirements at this stage of development as the provisions of FDARA are not fully implemented **at this time**. If an NDA for lurbinectedin is submitted prior to August 20, 2020, please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your

application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

However, please be aware that Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See the link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) **within 60 days of an End of Phase 2 (EOP2) meeting and no later than 210 days prior to submission of an NDA if that NDA is submitted after August 18, 2020**. The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For the latest version of the molecular target list, please refer to https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm544641.htm

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

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

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

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the Guidance for Industry, Collection of Race and Ethnicity Data in Clinical Trials (available at: https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126396.pdf) and for more information.

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

OCE Real-Time Oncology Review and Assessment Aid

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR: https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm612927.htm. In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid: https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm612923.htm

ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

ACTION ITEMS

None

ATTACHMENTS AND HANDOUTS

PharmaMar presentation.

33 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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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/

STACIE A WOODS
12/12/2018