1 TITLE PAGE

Clinical Study Protocol

Clinical Study Protocol Number	VX15-984-001 EMD Serono Internal Study Number: MS201926-0001
Title	An Open-Label, Phase I, First in Human Study of the Safety, Tolerability, and Pharmacokinetic/Pharmacodynamic Profile of VX-984 in Combination With Chemotherapy in Subjects With Advanced Solid Tumors
Phase	I
IND Number	CCI
EudraCT Number	Not applicable
Coordinating Investigator	PPD Tel: PPD Fax: PPD
Sponsor	EMD Serono Research & Development Institute, Inc., Billerica, MA, USA Medical Responsible: PPD Merck KGaA, Global Clinical Development, Frankfurter Strasse 250, 64293 Darmstadt, Germany Tel: PPD Fax: PPD
Sponsor Legal Representative in the European Union	Merck KGaA Frankfurter Strasse 250 64293 Darmstadt, Germany
Clinical Study Protocol Version	21 August 2017 / Version 4.0 including Amendment 1 and 2
Replaces Version	21 April 2016 / Version 3.0

- [redacted] –

Summary of Changes to the Protocol

The previous version of this protocol (Version 3.0, 21 April 2016) was amended to create the current version (Version 4.0, 21 August 2017).

Protocol History

Version and Date of Protocol	Comments
Version 1.0, 11 August 2015	Original version
Version 2.0, 23 September 2015	• In response to regulatory feedback, the following changes were made: o Clarification was added to dose escalation guidelines o Eligibility criterion 2 was modified to clarify that subjects in Part B must have confirmed advanced primary endometrial cancer (locally advanced and incurable endometrial cancer) that has been treated with surgery and/or radiation or is ineligible for such treatment in order to participate in this study o Dose modification and delay criteria were clarified and revised to include guidelines for hand foot syndrome and stomatitis • Based on Investigator feedback, eligibility criteria were revised as follows: o Inclusion criterion 6a was changed from hemoglobin ≥ 8.0 g/dL to ≥ 9.0 g/dL for all subjects o Clarified that subjects receiving potassium, magnesium, or other supplementation for an otherwise controlled condition would be eligible for the study o Exclusion criterion 2 was updated to exclude subjects with uterine carcinosarcoma. • Based on Investigator feedback, added that repetition of screening assessments that do not meet eligibility criteria in subjects who receive red blood cell transfusions or fluid replacement therapy will not require authorization from the medical monitor. • The timing of urine β-hCG testing was clarified. • Footnote "n" of Table 3-3 was revised to clarify PK sample collection for subjects in Part A.
Version 3.0, 21 April 2016	• Due to sponsor decision, subjects with lymphomas will no longer be included in the study. • Safety clinical laboratory assessments were clarified as follows: o Coagulation parameter testing will be performed only at Screening o If blood urea nitrogen (BUN) cannot be collected, urea may be substituted. • Clarified that assessments to be performed at the "end of cycle" may be performed up to 5 days before Day 1 of the subsequent cycle. • Study drug dispensation and preparation instructions were revised to enable immediate dosing at study sites.

	• Minor updates were made to the definitions of analysis sets and planned analyses for clarity and consistency.
Version 4.0, 21 August 2017	Current version

The following changes were made in the current version:

Change and Rationale	**Affected Sections**
Due to the study being transitioned from Vertex Pharmaceuticals Incorporated, Sponsor name changed to: EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, Legal representative in the European countries: Merck KGaA, Frankfurter Strasse 250 64293 Darmstadt, Germany	Cover page
EMD Serono internal study number: MS201926-0001	Cover page
Coordinating Investigator has been identified as per Merck KGaA requirement: PPD Tel: PPD Fax: PPD	Cover Page
Medical Responsible has been identified as per Merck KGaA requirement: PPD Merck KGaA, Global Clinical Development, Frankfurter Strasse 250, 64293 Darmstadt, Germany Tel: PPD Fax: PPD	Cover page
Due to the changes in Sponsor, reference to “Vertex” changed to “the Sponsor”	Throughout protocol
Add EMD Serono compound code: M9831	Synopsis (Objectives, Investigational drug), Section 5
Due to the transition, Sponsor name changed from Vertex Pharmaceuticals Incorporated, Sponsor name changed to: EMD Serono Research & Development Institute	Section 9.5
The SAE reporting process was changed to comply with standard operating procedure	Section 13.1.2.3

Typographical and administrative changes were also made to improve the clarity of the document.

2 PROTOCOL SYNOPSIS

Title An Open-Label, Phase I, First-in-Human Study of the Safety, Tolerability, and Pharmacokinetic/Pharmacodynamic Profile of VX-984 in Combination With Chemotherapy in Subjects With Advanced Solid Tumors

Brief Title A Study to Evaluate Safety, Tolerability, and Pharmacokinetic/Pharmacodynamic Profile of VX-984 in Combination With Chemotherapy

Clinical Phase and Clinical Study Type Phase I, first-in-human (FIH)

Objectives

PART A

Primary

- To evaluate the safety and tolerability of VX-984 (EMD Serono internal compound code: M9831) administered alone and in combination with pegylated liposomal doxorubicin (PLD) in subjects with advanced solid tumors
- To determine the maximum tolerated dose (MTD) of VX-984 in combination with PLD in subjects with advanced solid tumors.

Secondary

- To evaluate the pharmacokinetics (PK) of VX-984 when administered alone and in combination with PLD in subjects with advanced solid tumors
- To evaluate the PK of PLD when administered in combination with VX-984 in subjects with advanced solid tumors
- To evaluate preliminary antitumor activity of VX-984 in combination with PLD in subjects with advanced solid tumors.

Exploratory

- CCI [redacted]
- To assess tumor response by tumor volume and tumor necrosis in subjects administered VX-984 in combination with PLD
- To assess correlations between prior treatment response and treatment outcome.

PART B

Primary

- To evaluate the safety and tolerability of VX-984 administered in combination with PLD in subjects with recurrent or metastatic endometrial cancer who have progressed on a prior platinum regimen
- To assess the overall response to VX-984 administered in combination with PLD in subjects with recurrent or metastatic endometrial cancer who have progressed on a prior platinum regimen.

Secondary

- To assess progression free survival (PFS) in subjects with recurrent or metastatic endometrial cancer who have progressed on a prior platinum regimen administered VX-984 in combination with PLD
- To assess response duration (RD) in subjects with recurrent or metastatic endometrial cancer who have progressed on a prior platinum regimen administered VX-984 in combination with PLD
- To assess overall survival (OS) in subjects with recurrent or metastatic endometrial cancer who have progressed on a prior platinum regimen administered VX-984 in combination with PLD
- To assess clinical benefit in subjects with recurrent or metastatic endometrial cancer who have progressed on a prior platinum regimen administered VX-984 in combination with PLD as measured by complete response (CR), partial response (PR), or stable disease (SD) of 4 months or greater
- To evaluate the PK of VX-984 when administered in combination with PLD in subjects with recurrent or metastatic endometrial cancer who have progressed on a prior platinum regimen.

Exploratory

- CCI [redacted]
- To assess tumor response by tumor volume and tumor necrosis in subjects with previously-treated endometrial cancer, administered VX-984 in combination with PLD
- To assess correlations between prior treatment response and treatment outcome
- CCI [redacted]

Endpoints

PART A

Primary

- Safety parameters, including adverse events (AEs), dose-limiting toxicities (DLTs), clinical laboratory values (serum chemistry and hematology), vital signs, echocardiogram, and electrocardiogram (ECG) assessments
- MTD of VX-984 in combination with PLD.

Secondary

- Plasma PK parameter estimates of VX-984, administered alone and in combination with PLD, derived from plasma concentration-time data
- Plasma PK parameter estimates of PLD administered in combination with VX-984, derived from plasma concentration-time data
- Preliminary evidence of anti-tumor activity, including tumor response as evaluated by Response Criteria Evaluation RECIST 1.1 and tumor markers.

Exploratory

- CCI [redacted]
- Tumor response as assessed by tumor volume and tumor necrosis using 3D computed tomography (CT) scans
- Tumor response as assessed by historical and on-treatment tumor growth dynamics
- CCI [redacted]

PART B

Primary

- Safety parameters, including AEs, clinical laboratory values (serum chemistry and hematology), vital signs, echocardiogram, and ECG assessments
- Objective response rate (ORR) as evaluated by CT scan per RECIST 1.1.

Secondary

- PFS
- RD as evaluated by CT scan and quantified by RECIST 1.1
- OS
- Clinical benefit (CR + PR + SD of at least 4 months)
- Plasma PK parameter estimates of VX-984 when administered in combination with PLD, derived from plasma concentration-time data.

Exploratory

- CCI [redacted]
- Tumor response as assessed by tumor volume and tumor necrosis using 3D CT scans
- Tumor response as assessed by historical and on-treatment tumor growth dynamics
- CCI [redacted]

Number of Subjects	Part A: approximately 50 subjects Part B: approximately 40 subjects
Study Population	At least 18 years of age, with tumors measurable by RECIST 1.1 Part A: male and female subjects with advanced solid tumors who have progressed through standard therapeutic options and for whom no standard therapy is available or PLD may be considered standard of care Part B: female subjects with recurrent or metastatic endometrial cancer who have progressed on a prior platinum regimen
Investigational Drug	Active substance: VX-984 (EMD Serono internal compound code: M9831) Activity: DNA-dependent protein kinase (DNA-PK) inhibitor Strength and Route of Administration: VX-984 suspension (in 0.5% methyl cellulose) for oral administration Dose: up to 3000 mg
Study Duration	Screening: All subjects will have a Screening Visit within 14 days before the first dose of study drug. Treatment Periods**:** Part A: Subjects in Part A will receive VX-984 as a single agent on Days -14 to -12 in a 14-day lead-in followed by VX-984 in combination with PLD for up to six 28-day cycles (PLD on Day 1 and VX-984 on Days 2 to 4). Subjects with tumors responding to treatment may continue on treatment past 6 cycles, with the agreement of the Investigator and medical monitor until disease progression, unacceptable toxicities, withdrawal of consent, or until exposure to PLD exceeds 550 mg/m^2. Part B: Subjects in Part B will receive VX-984 in combination with PLD in 28-day cycles until disease progression, unacceptable toxicity, or withdrawal of consent. Follow-up: All subjects will have a Safety Follow-up Visit 28 (±7) days after the last dose of study drug. For Parts A and B, when possible, a follow-up CT scan will be performed 5 (± 1) weeks after the end of therapy unless the subject had progressive disease at the time of treatment discontinuation or subject has initiated a new treatment in the interim. In Part B, for subjects without disease progression, long-term follow-up, including as indicated staging CT scans and/or follow-up communications, may continue for up to 1 year.
Study Design	This is an open-label, multicenter, single-arm, FIH, dose-escalation study in subjects with solid tumors (Part A) followed by an expansion phase in subjects with recurrent or metastatic endometrial cancer who have progressed on a prior platinum regimen (Part B). **Part A** Part A will be a dose escalation study to evaluate the safety, tolerability, and PK of VX-984 when administered in combination with PLD in subjects with

advanced solid tumors who have progressed through standard therapeutic options and for whom no standard therapy is available or PLD may be considered standard of care. This part will establish the MTD of VX-984 in combination with PLD.

Starting dose and dosing schedule

For each VX-984 dose level tested, subjects will receive VX-984 once daily (qd) alone on Days -14 to -12 of a 14-day Lead-in Period. Following the single agent Lead-in Period, subjects will receive PLD on Day 1 and VX-984 qd on Days 2 to 4 of a 28-day cycle. The starting doses will be 120 mg qd of VX-984 and 40 mg/m^2 of PLD. The Lead-in Period will be required only if the dose of VX-984 is escalated beyond the highest dose of VX-984 previously tolerated in a Lead-in Period.

Guidelines for dose escalation and determination of the MTD:

Three subjects will be enrolled at the starting dose of VX-984 (120 mg) and PLD (40 mg/m^2). If the starting dose of VX-984 is tolerated alone in the 14-day Lead-in Period and in combination with PLD through 1 cycle (28 days) without a DLT or CTCAE Grade 3 or worse toxicities in any of these 3 subjects and without a CTCAE Grade 2 toxicity in 2 subjects, the dose of VX-984 may be increased by up to 100% while holding the dose of PLD constant in a subsequent cohort of 3 subjects. Safety data, including AEs, laboratory values, and ECG results, obtained through the end of Cycle 1, as well as available PK data, will be assessed to determine the dose of VX-984 for the next cohort.

In this way, the dose of VX-984 will be escalated with 40 mg/m^2 of PLD in subsequent cohorts of 3 subjects until 1 subject has a treatment-related or possibly-related DLT or toxicity of CTCAE Grade 3 or worse; or 2 subjects (who may be in different cohorts) have a toxicity of CTCAE Grade 2.

Subsequent dose escalation will proceed depending on the toxicity as described:

- In the event of a treatment-related or possibly-related toxicity of CTCAE Grade 3 or worse in 1 subject (that is not considered a DLT), or treatment-related or possibly-related toxicity of CTCAE Grade 2 or worse (but not a DLT) in 2 subjects (who may be in different cohorts), the dose escalation will continue with a more conservative dose escalation (up to 50%). The dose of VX-984 will continue to be escalated in subsequent cohorts of 3 subjects until there is a DLT through the end of Cycle 1
- In the event of a DLT, an adaptive Bayesian logistic regression model (BLRM) will be used to determine the dose for the subsequent cohorts or determine if the current dose level should be expanded. At each predicted dose, 3 to 6 subjects will be enrolled in each cohort at the discretion of the sponsor and Investigators. If more than 3 subjects are enrolled, the first 3 subjects will receive VX-984 in the Lead-in Period and if no DLT is observed with VX-984 dosing then the additional subjects in the cohort will not have the Lead-in Period. The Lead-in Period will be required only if the dose of VX-984 is escalated beyond the highest dose of VX-984 previously tolerated in a Lead-in Period
- If 2 subjects in a previously untested dose level experience a DLT, enrollment to that cohort will stop, the BLRM will be updated and the next cohort will be opened at a lower dose level or an intermediate dose level that satisfies the escalation overdose control (EWOC) criteria. However, if 2 subjects in a new cohort at a previously tested dose level experience a DLT (e.g., a total of 8 subjects are tested on this dose level with 2 DLTs observed), further enrollment to that cohort will stop, the

BLRM will be updated with this new information and re-evaluation of the available safety, PK and PD data will occur. By incorporating information gained at the preceding dose levels, additional subjects may be enrolled into the current dose level only if the dose still meets the EWOC criteria and as agreed by the sponsor and Investigators.

Subjects will be considered as evaluable for dose determination if they have a DLT during Cycle 1 or the preceding Lead-in Period or meet the minimum treatment and safety evaluation requirements for the first cycle as outline in the protocol.

After completion of Cycle 1 of each cohort (3 to 6 subjects), available safety, PK, and efficacy information as well as recommendations from the Bayesian model will be used to determine the dose for the next cohort. The adaptive BLRM will be guided by the EWOC principle to control the risk of DLT in future subjects (see Statistical Analysis section for details).

After repeating the above steps, the dose escalation of VX-984 will continue with a constant dose of PLD at 40 mg/m^2 until MTD of VX-984 with PLD at 40 mg/m^2 is achieved. The maximum planned dose of VX-984 is 2000 mg; however, higher doses up to 3000 mg may be allowed depending on the observed safety, PK, and PD, and based on recommendation of the BLRM.

If a dose of VX-984 is not tolerated with PLD at 40 mg/m^2, then the VX-984 dose will be reduced by up to 50% with a constant dose of PLD at 40 mg/m^2 or the dose of PLD will be reduced by 25% (30 mg/m^2) or lower with a constant dose of VX-984. These doses will be explored in subsequent cohorts at the discretion of the Investigators and sponsor until the MTD is established with PLD at 30 mg/m^2 or lower. If daily dosing of VX-984 for 3 days after PLD is not tolerated during initial dose escalation, less frequent dosing of VX-984 may be explored in subsequent cohorts.

Treatment duration and disease assessments:

At all dose levels of VX-984, subjects will complete a total of up to six 28-day cycles of VX-984 and PLD combination therapy. Subjects with tumors responding to treatment may continue on treatment past 6 cycles with the agreement of the Investigator and medical monitor until disease progression, unacceptable toxicity, or withdrawal of consent. CT scans will be performed at the end of every 2 cycles (see Table 3-3). If there is evidence of progressive disease as determined using RECIST 1.1, the subject's treatment will be discontinued. In addition, transthoracic echocardiograms will be performed at baseline and at the end of every 2 cycles (see Table 3-3). After 6 cycles, CT scans will be performed at the end of every 2 to 3 cycles (see Table 3-3).

Part B

Part B will be an expanded cohort study to confirm the safety, tolerability, PK, and potential anti-tumor activity of VX-984 in combination with PLD in female subjects with recurrent or metastatic endometrial cancer who have progressed on a prior platinum regimen.

During each cycle, subjects will be administered PLD on Day 1, and VX-984 will be dosed on Days 2 to 4 of a 28-day cycle unless in Part A the number of days was decreased due to tolerability. Approximately 40 subjects will receive VX-984 with PLD at the MTD or lower, as determined during the dose escalation phase.

Subjects will continue to receive treatment until disease progression, unacceptable toxicities, or withdrawal of consent. Subjects will be evaluated by CT scans at the end of every 2 cycles for the first 6 cycles and every 2 to 3 cycles thereafter (see Table 3-3). If there is evidence of progressive disease as determined using RECIST 1.1, treatment will be discontinued. In addition, subjects will be

evaluated by transthoracic echocardiogram at baseline and at the end of every 2 cycles (see Table 3-3).

Pharmacokinetic Assessments

Part A:

Blood samples for measurement of VX-984 PK (in plasma) will be collected during the Lead-in Period Days -12 to -11 and during Cycle 1 on Day 2 and on Days 4 to 5.

Urine samples for measurement of VX-984 PK will be collected during the Lead-in Period on Days -12 to -11.

Blood samples for measurement of PLD PK (in plasma) will be collected at Cycle 1 on Days 1, 2, 4, and 5.

Part B:

Blood samples for measurement of VX-984 PK (in plasma) will be collected during Cycle 1 on Day 4.

Blood sample for measurement of PLD PK (in plasma) will be collected during Cycle 1 on Day 4.

PK sampling may be conducted on Day 2 or Day 3 if subjects are unable to come to the clinic for PK sampling on Day 4.

These PK samples will be required in a minimum of 20 subjects. VX-984 dose will be administered in the clinic on the day of PK sampling.

Efficacy Assessments

CT scans will be performed at Screening and at the end of every 2 cycles for the first 6 cycles and every 2 to 3 cycles thereafter, and at 5 (± 1) weeks after the last dose of study drug (excluding subjects with progressive disease on previous CT scan) (see Table 3-3). For subjects with bony metastases, bone scans will be performed every 4 to 6 cycles or more frequently if clinically indicated.

Safety Assessments

AEs; clinical laboratory values (serum chemistry and hematology studies); standard 12-lead ECGs; echocardiograms; vital signs; and physical examinations.

Exploratory Assessments

CCI [redacted]

Statistical Analyses

Bayesian Adaptive Model:

The adaptive BLRM with EWOC principle will be used, with the following 2 exceptions:

1. For cohorts requiring 3 or more evaluable subjects, if only 2 evaluable subjects are available for assessment (all others drop out), and neither subject has had a treatment-related or possibly-related toxicity greater than CTCAE Grade 1, then 2 subjects will be considered sufficient for decision-making
2. If the first 2 subjects in a cohort have DLTs, no additional subjects will be enrolled into that cohort until the Bayesian model has been updated with this new information. Likewise, the model will be re-evaluated if 2 subjects in a cohort have DLTs before the enrollment of any additional subjects.

Model:

$$logit\{\pi(d_j, x_1, \ldots, x_k)\} = \log(\alpha) + \beta \log\left(\frac{d_j}{d^*}\right) + \sum_{i=1}^{k} \gamma_i x_i$$

Under-dosing: $\pi(d) \in [0.00, 0.166)$

Target toxicity: $\pi(d) \in [0.166, 0.333)$

Excessive toxicity : $\pi(d) \in [0.333, 1.00]$

The recommended dose for the next cohort will fulfill the following 2 criteria:

1. Dose that maximizes probability that true DLT rate is in the target toxicity interval [0.166, 0.333)
2. With overdose control: less than 25% probability of the true DLT rate in the excessive toxicity interval [0.333, 1].

Data Analyses:

Analysis of all data will be performed by the sponsor or designee. The demographics and baseline characteristics will be summarized by dose group, by concurrent regimen and study part, and overall. Baseline characteristics will include but will not be limited to the following variables: type of cancer, tumor stage at baseline, World Health Organization (WHO) performance status at baseline, time elapsed since cancer diagnosis, prior chemotherapy and radiation therapy, and duration of most recent cancer therapy.

The overall safety profile of VX-984 will be assessed in terms of the following primary safety endpoints:

- Incidence of treatment-emergent AEs (TEAEs), including AEs leading to dose modifications or discontinuations
- Incidence of DLTs (Part A)
- Clinical laboratory values
- ECG outcomes
- Echocardiogram outcomes
- Vital signs.

Safety data will be summarized by dose group, by concurrent regimen and study part, and overall. In general, safety analyses will be based on the Safety Set defined as all subjects who have received any study drug.

The summary of DLTs will be based on the DLT Evaluable Set. The BLRM will be used to estimate the posterior distributions for the probabilities of DLT events at various combination dose levels after each cohort of subjects. The MTD is defined as the combination dose associated with the highest probability that DLT events will occur in 16.6% to less than 33.3% subjects and as the combination dose that will not exceed the overdose criterion (< 25% probability that DLT events will occur in ≥ 33% of subjects).

Efficacy data will be summarized by dose group, by concurrent regimen and study part, and overall. For Part B, the proportion of subjects demonstrating ORR, together with exact 90% CI, will be presented.

VX-984 PK data will be analyzed on an ongoing basis during dose escalation in Parts A and B using standard noncompartmental methods. PK data for VX-984 will be reviewed with safety data to inform dose escalation.

3 SCHEDULE OF ASSESSMENTS

Schedules of Assessments are shown in Table 3-1, Table 3-2, and Table 3-3.

Table 3-1 Study VX15-984-001: Screening (Parts A and B)

Assessment	Screening Visit Day -28 to Day -15 (Part A with Lead-in Period) Day -14 to Day -1 (Part A without Lead-in Period and Part B)
Informed consent	X
Demographics	X
Medical history	X
Prior and concomitant medications	X
Height, weight, BMI, and vital signs	X
Physical examination[a]	X
Radiological (CT) disease assessment[b]	X
Bone scan[c]	X
Transthoracic echocardiogram[d]	X
Clinical disease assessment[e]	X
WHO performance status	X
Standard 12-lead electrocardiogram (ECG)	X
Serum FSH (postmenopausal female subjects only)	X
Serum β-HCG (all female subjects)	X
Serum chemistry	X
Hematology	X
Coagulation	X
Urinalysis	X
Thyroid-stimulating hormone	X
CCI [redacted]	

[a] Physical examination of all body systems.

[b] Subjects will have a chest and abdominal CT scan and, if clinically indicated, a pelvic CT scan. Radiologic scans performed within 2 weeks of Screening may substitute for assessment of eligibility; however, for Part B, CT scan must be repeated during Screening according to the Imaging Manual unless discussed with the sponsor.

[c] For all subjects with prostate cancer or for subjects with other malignancies in whom bony metastases have been previously documented or are highly suspected. Results of a bone scan performed within 4 weeks before Screening may substitute for the Screening bone scan. If results from a PET CT scan are available, they may be used to substitute for a bone scan.

[d] If an echocardiogram or nuclear scan has been performed within 1 month before Screening, these results may be used, unless repetition of the assessment is clinically indicated.

[e] Assessment includes tumor staging (I to IV) and Tumor-Node-Metastasis.

[f] CCI [redacted]

Table 3-1 Study VX15-984-001: Screening (Parts A and B)

Assessment	Screening Visit Day -28 to Day -15 (Part A with Lead-in Period) Day -14 to Day -1 (Part A without Lead-in Period and Part B)
Historical CT scans (optional)[g]	X
Adverse events	Continuous from signing of Informed Consent Form (ICF) through Safety Follow-up Visit

[g] If accessible, the last 2 CT scans taken before the Screening scan will be collected from enrolled subjects.

Table 3-2 Study VX15-984-001: Lead-in Period With VX-984 (Part A)

Assessment	Lead-in (Part A)[a]					
	Day -14	Day -13	Day -12	Day -11	Day -10	Day -9
Outpatient Visit	X		X	X		
Safety Assessments						
Physical examination[b]	X					
WHO performance status	X					
Vital signs	X[c]					
12-lead ECG	X[d]					
Serum chemistry[e]	X		X			
Hematology[e]	X		X			
Urine β-hCG[f]	X					
Urinalysis	X					
Concomitant medications and AEs	Continuous from signing of ICF through Safety Follow-up Visit					
Study Drug Administration						
VX-984 dosing[g]	X	X	X			
Pharmacokinetic Assessments						
VX-984 (Plasma PK collection)			X[h]	X[h]		
VX-984 (Urine PK collection)			X[i]	X[i]		
Exploratory Assessments						
CCI [redacted]						

[a] There will be a Lead-in Period of VX-984 monotherapy for all cohorts in Part A in which the administered dose will be higher than any previously evaluated dose of VX-984 as monotherapy in at least 3 subjects.
[b] Symptom-directed physical examinations will be performed as clinically indicated in the Investigator's judgment.
[c] Vital signs will be measured before dosing and 4 (± 1) hours after dosing.
[d] 12-lead ECG will be measured up to 60 minutes before dosing and 2 and 4 hours after dosing (± 60 minutes).
[e] Laboratory results should be reviewed before dosing on days of study drug administration. To facilitate timely administration of study drug, safety labs may be performed the day before dosing. If labs are drawn the evening before, they should be recorded as corresponding to day of planned drug administration. Laboratory values must conform to inclusion/exclusion criteria for study drug administration.
[f] Female subjects of childbearing potential only. Assessment should be performed before dosing.
[g] Subjects will receive study drug in the clinic on Days -14 and -12; and at home on Day -13. Subjects will take study drug at home per instructions provided in Section 10.3.
[h] Plasma PK samples will be collected on Day -12 before dosing (0 hour) and at 0.5, 1, 2, 4, 8, and 24 hours (Day -11) after dosing.
[i] Urine PK samples will be collected before dosing (0 hour) and from 0 to 4, 4 to 8, and 8 to 24 hours (Day -11) after dosing.
[j] CCI [redacted]
[k] CCI [redacted]

Table 3-3 Study VX15-984-001: VX-984 and PLD Combination Therapy and Follow-up (Parts A and B)

Event/Assessment During Each Cycle (Except as Noted)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 15	Follow-up[a]	
								28 days (± 7 days)	5 weeks (± 1 week)
Outpatient visits	X	X[b,c]		X[b]	X[b]	X	X	X	X
Safety Assessments									
Physical examination[d]	X							X	
CT scan disease assessment[e]	At the end of every 2 cycles for first 6 cycles then at the end of every 2 to 3 cycles until disease progression[f]								X
Clinical disease assessment[g]	X								X
Bone scan[h]	At the end of every 4 to 6 cycles until disease progression[f]								
Transthoracic echocardiogram	At the end of every 2 cycles until disease progression[f]								
WHO performance status	X							X	
Weight	X							X	
Vital signs	X[i]	X[b,i]						X	
12-lead ECG	X[j]	X[b,j]						X	
Serum chemistry	X[k]				X[b]	X	X	X	
Hematology	X[k]					X	X	X	
Urine β-hCG[l]	X							X	
Concomitant medications	Continuous from signing of ICF through Safety Follow-up Visit							X	
AEs	Continuous from signing of ICF through Safety Follow-up Visit							X	
Study Drug Administration									
VX-984[m]		X	X	X					
PLD	X								
Pharmacokinetic Assessments									

[a] Follow-up will include a Safety Follow-up Visit 28 (± 7) days after the last dose of study drug and a radiologic Follow-up Visit 5 (±1) weeks after the last cycle of chemotherapy, and survival follow-up assessment at the last subject last visit. In Part B, for subjects without disease progression, long-term follow-up, including as indicated staging CT scans and/or follow-up communications, may continue for up to 1 year. See Section 8.1.4 for additional details.

[b] Cycle 1 only.

[c] Day 2 visit is required for Part A only.

[d] Symptom-directed physical examinations will be performed as clinically indicated in the Investigator's judgment.

Table 3-3 Study VX15-984-001: VX-984 and PLD Combination Therapy and Follow-up (Parts A and B)

Event/Assessment During Each Cycle (Except as Noted)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 15	Follow-up[a]	
								28 days (± 7 days)	5 weeks (± 1 week)
Part A VX-984 (Plasma PK collection)		X[n]		X[n]	X[n]				
Part A PLD (Plasma PK collection)	X[o]	X[o]		X[o]	X[o]				
Part B VX-984 (Plasma PK collection)				X[p]					

[e] CT scan of chest, abdomen, and pelvis should be performed, in addition to CT scan of other body areas, as clinically indicated.
[f] End of cycle assessments may be performed up to 5 days before Day 1 of subsequent cycle.
[g] Assessment includes tumor staging (I to IV) and Tumor-Node-Metastasis.
[h] For all subjects with prostate cancer or for subjects with other malignancies in whom bony metastases have been previously documented or are highly suspected; or if clinically indicated.
[i] Vital signs will be measured on Day 1 up to 60 minutes before administration of PLD and on Day 2 up to 60 minutes before administration of VX-984 and at 2 (± 1) hours after administration of VX-984.
[j] 12-lead ECG will be measured on Day 1 up to 60 minutes before administration of PLD. ECG will be measured on Day 2 only during Cycle 1 and will be measured up to 60 minutes before administration of VX-984, and 2 and 4 hours (± 60 minutes) after administration of VX-984.
[k] To facilitate timely administration of study drug on Day 1, safety lab samples may be collected up to 3 days before Day 1. If safety lab samples are collected before Day 1, they should be recorded as corresponding to Day 1.
[l] Female subjects of childbearing potential only.
[m] For Part A: For Cycle 1, subjects will receive VX-984 in the clinic on Days 2 and 4; and at home on Day 3. After Cycle 1, subjects will be instructed to take all VX-984 doses at home per instructions provided in Section 10.3.
For Part B: For Cycle 1, subjects will receive VX-984 in the clinic on Day 4 or the day subjects come in for PK assessment; and at home on Days 2 and 3. After Cycle 1, subjects will be instructed to take all VX-984 doses at home per instructions provided in Section 10.3.
[n] Cycle 1 only. VX-984 plasma PK samples will be collected on Day 2 before dosing (0 hour) and at 0.5, 1, 2, and 4 hours after dosing; and on Day 4 before dosing (0 hour) and at 0.5, 1, 2, 4, 8, and 24 hours (Day 5) after dosing.
[o] Cycle 1 only. PLD plasma PK samples will be collected on Day 1 before beginning of infusion (BOI) and at 1, 2, 4, 6, 24 hours (Day 2), 72 hours (Day 4) and 96 hours (Day 5) after BOI.
[p] Cycle 1 only. VX-984 plasma PK samples will be collected on Day 4 before dosing (0 hour) and at 0.5, 1, 2, 4, and 8 hours after dosing. PK sampling may occur on Days 2 or 3 if subjects are unable to come to the clinic on Day 4. PK samples are required from a minimum of 20 subjects.

Table 3-3 Study VX15-984-001: VX-984 and PLD Combination Therapy and Follow-up (Parts A and B)

Event/Assessment During Each Cycle (Except as Noted)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 15	Follow-up[a]	
								28 days (± 7 days)	5 weeks (± 1 week)
Part B PLD (Plasma PK collection)				X[q]					
Exploratory Assessments									
CCI [redacted]									

[q] Cycle 1 only. One PLD plasma PK sample will be collected on Day 4 before VX-984 dosing. PK sampling may occur on Days 2 or 3 if subjects are unable to come to the clinic on Day 4. PK samples are required from a minimum of 20 subjects.

CCI [redacted]

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5 INTRODUCTION

DNA-dependent protein kinase (DNA-PK) plays an important role in cellular survival after DNA damage via its activity repairing rare but lethal double strand breaks (DSBs) by non-homologous end joining (NHEJ), as the catalytic subunit of a complex of proteins.[1,2] This activity is crucial because the DSBs rapidly lead to cell death if not quickly and efficiently repaired. Targeting DNA-PK provides a striking opportunity to improve cancer patient outcomes because the majority of cancer patients will receive therapies whose sole objective is to induce DSBs in tumor cells. These therapies include radiation therapy (RT) and certain chemotherapies such as the topoisomerase II inhibitors etoposide and anthracylines such as pegylated liposomal doxorubicin (PLD). While these therapies have achieved some success clinically, ultimately many of these treatments fail due to insufficient local control, local recurrence, and disseminated disease. It is therefore critical to develop new therapeutic strategies to improve loco-regional control as well to impact disseminated disease.

VX-984 (EMD Serono internal compound code: M9831) is a novel potent and selective inhibitor of DNA-PK (median inhibition constant [Ki] = 2 nM) with minimal activity against related and unrelated kinases. This includes 4 highly-related phosphatidylinositol-3-kinase (PI3K) isoforms as well as the other class members ataxia telangiectasia mutated kinase (ATM), ataxia telangiectasia muted and Rad3-related kinase (ATR), and mammalian target of rapamycin (mTor). VX-984 inhibits DNA-PK function in cells with a concentration associated with 50% inhibition [IC_{50}] of 88 nM and sensitizes most cancer cell lines and primary patient derived tumor cells to the lethal effects of RT and to chemotherapies that cause DSBs in DNA. Importantly, additivity to strong synergy is also observed with some DSB-inducing agents such as doxorubicin.[3]

VX-984 is deuterated, which offers the possibility to decrease metabolism by aldehyde oxidase to increase stability in human hepatocytes and, thereby, potentially substantially lowering the required efficacious dose. CCI

In patient-derived xenograft models using ovarian cancer and in multiple cancer cell line models, VX-984 in combination with PLD significantly enhanced the anticancer activity of

PLD when VX-984 was administered 16 hours after PLD, and was generally well-tolerated. VX-984 showed no single-agent efficacy in the tumor models evaluated.[3]

Based on the nonclinical observations, VX-984 had the potential to have a substantial therapeutic impact on malignancies with high unmet need and in which DSB inducers such as PLD is used as standard of care (SOC), such as recurrent or metastatic endometrial cancer.

Endometrial cancer accounts for the 90% of uterine cancers.[4] There are approximately 50,000 newly diagnosed patients in the US and 44,000 in the 5 most populous EU countries (EU5) expected in 2015.[5] Less than a quarter of endometrial cancer presents in an advanced stage, where it is generally treated with platinum-based chemotherapy alone or following surgery.[6] Approximately 60% of these patients ultimately go on to receive subsequent treatment, representing approximately 3,800 patients in the US and 3,100 patients in the EU5 annually.[5] Treatment guidelines recommend single-agent chemotherapy in the second-line setting, though there is no currently approved treatment.[7]

Study VX15-984-001 (Study 001) is an open-label, first-in-human (FIH) study comprised of 2 parts (Part A and Part B). The purpose of Part A is to determine the maximum tolerated dose (MTD) and to characterize the safety, tolerability, and pharmacokinetic (PK) profile of VX-984 administered orally in multiple doses after PLD in adult patients with advanced solid tumors who have progressed through standard therapeutic options and for whom no standard therapy is available or PLD may be considered SOC. After the MTD of VX-984 in combination with PLD has been determined, Part B will evaluate the anti-tumor potential and safety of VX-984 in combination with PLD in subjects with recurrent or metastatic endometrial cancer who have progressed on a prior platinum regimen.

This study will support the development of VX-984 in combination with DNA DSB-inducing agents by providing preliminary safety and efficacy data to guide subsequent development.

6 STUDY OBJECTIVES

6.1 Part A

6.1.1 Primary Objectives

- To evaluate the safety and tolerability of VX-984 administered alone and in combination with PLD in subjects with advanced solid tumors
- To determine the maximum tolerated dose (MTD) of VX-984 in combination with PLD in subjects with advanced solid tumors.

6.1.2 Secondary Objectives

- To evaluate the pharmacokinetics (PK) of VX-984 when administered alone and in combination with PLD in subjects with advanced solid tumors
- To evaluate the PK of PLD when administered in combination with VX-984 in subjects with advanced solid tumors
- To evaluate preliminary anti-tumor activity of VX-984 in combination with PLD in subjects with advanced solid tumors.

6.1.3 Exploratory Objectives

- CCI [redacted]

[redacted]

- To assess tumor response by tumor volume and tumor necrosis in subjects administered VX-984 in combination with PLD
- To assess correlations between prior treatment response and treatment outcome.

6.2 Part B

6.2.1 Primary Objectives

- To evaluate the safety and tolerability of VX-984 administered in combination with PLD in subjects with recurrent or metastatic endometrial cancer who have progressed on a prior platinum regimen
- To assess the overall response to VX-984 administered in combination with PLD in subjects with recurrent or metastatic endometrial cancer who have progressed on a prior platinum regimen.

6.2.2 Secondary Objectives

- To assess progression free survival (PFS) in subjects with recurrent or metastatic endometrial cancer who have progressed on a prior platinum regimen administered VX-984 in combination with PLD
- To assess response duration (RD) in subjects with recurrent or metastatic endometrial cancer who have progressed on a prior platinum regimen administered VX-984 in combination with PLD
- To assess overall survival (OS) in subjects with recurrent or metastatic endometrial cancer who have progressed on a prior platinum regimen administered VX-984 in combination with PLD
- To assess clinical benefit in subjects with recurrent or metastatic endometrial cancer who have progressed on a prior platinum regimen administered VX-984 in combination with PLD as measured by complete response (CR), partial response (PR), or stable disease (SD) of 4 months or greater
- To evaluate the PK of VX-984 when administered in combination with PLD in subjects with recurrent or metastatic endometrial cancer who have progressed on a prior platinum regimen.

6.2.3 Exploratory Objectives

- CCI [redacted]

- To assess tumor response by tumor volume and tumor necrosis in subjects with previously-treated endometrial cancer, administered VX-984 in combination with PLD
- To assess correlations between prior treatment response and treatment outcome
- CCI [redacted]

7 STUDY ENDPOINTS

7.1 Part A

7.1.1 Primary Endpoints

- Safety parameters, including adverse events (AEs), dose-limiting toxicities (DLTs), clinical laboratory values (serum chemistry and hematology), vital signs, echocardiograms, and electrocardiogram (ECG) assessments
- MTD of VX-984 in combination with PLD.

7.1.2 Secondary Endpoints

- Plasma PK parameter estimates of VX-984, administered alone and in combination with PLD, derived from plasma concentration-time data
- Plasma PK parameter estimates of PLD administered in combination with VX-984, derived from plasma concentration-time data
- Preliminary evidence of anti-tumor activity, including tumor response as evaluated by Response Criteria Evaluation RECIST 1.1 and tumor markers.

7.1.3 Exploratory Endpoints

- CCI [redacted]
- Tumor response as assessed by tumor volume and tumor necrosis using 3D computed tomography (CT) scans
- Tumor response as assessed by historical and on-treatment tumor growth dynamics
- CCI [redacted]

[redacted]

7.2 Part B

7.2.1 Primary Endpoints

- Safety parameters, including AEs, clinical laboratory values (serum chemistry and hematology), vital signs, and ECG assessments
- Objective response rate (ORR) as evaluated by CT scan per RECIST 1.1.

7.2.2 Secondary Endpoints

- PFS
- RD as evaluated by CT scan and quantified by RECIST 1.1
- OS
- Clinical benefit (CR + PR + SD of at least 4 months)
- Plasma PK parameter estimates of VX-984 when administered in combination with PLD, derived from plasma concentration-time data.

7.2.3 Exploratory Endpoints

- CCI [redacted]
- Tumor response as assessed by tumor volume and tumor necrosis using 3D CT scans
- Tumor response as assessed by historical and on-treatment tumor growth dynamics
- CCI [redacted]

8 STUDY DESIGN

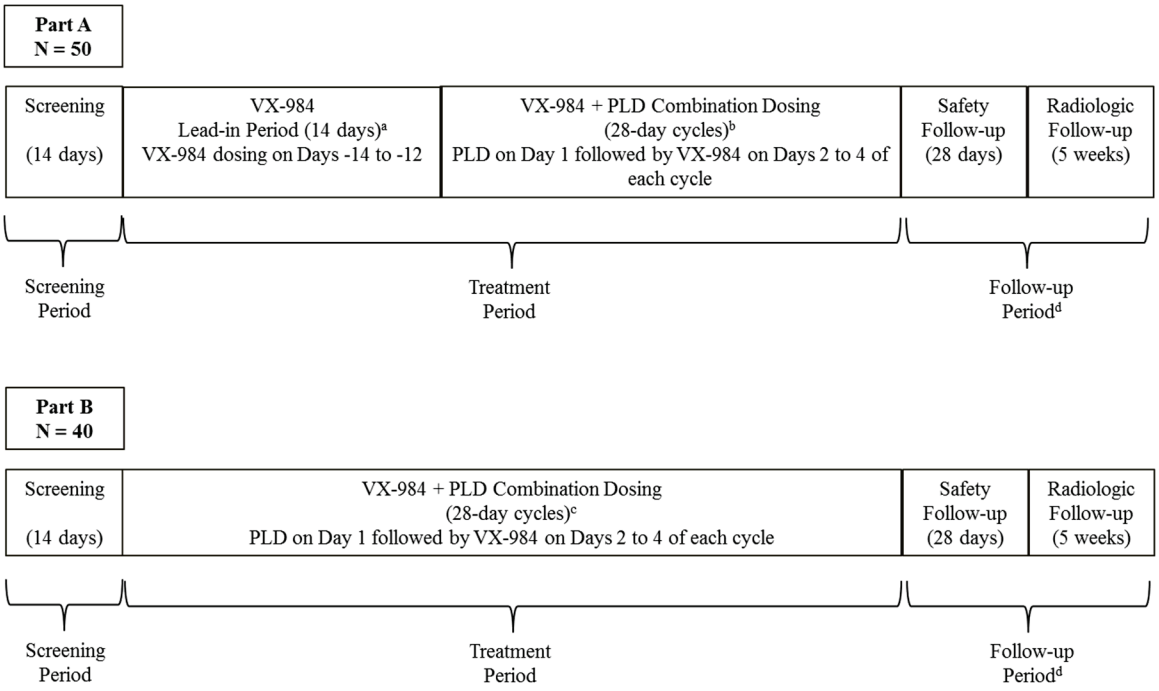
8.1 Overview of Study Design

This is an open-label, multicenter, single-arm, FIH, dose-escalation study in subjects with solid tumors who have progressed through standard therapeutic options and for whom no standard therapy is available or PLD may be considered SOC (Part A) followed by an expansion phase in subjects with recurrent or metastatic endometrial cancer who have progressed on a prior platinum regimen (Part B).

Part A will be a dose escalation study to evaluate the safety, tolerability, and PK of VX-984 when administered in combination with PLD. At each VX-984 dose level tested, subjects will receive VX-984 once daily (qd) alone on Days -14 to -12 of a 14-day Lead-in Period before receiving combination treatment with PLD. Following the single agent Lead-in Period, subjects will receive PLD on Day 1 and VX-984 qd on Days 2 to 4 of a 28-day cycle. The Lead-in Period will be required only if the dose of VX-984 is escalated beyond the highest dose of VX-984 previously tolerated in a Lead-in Period. This part will establish the MTD of VX-984 in combination with PLD (Figure 8-1).

Part B will be an expanded cohort study to confirm the safety, tolerability, PK, and potential anti-tumor activity of VX-984 in combination with PLD at the MTD or lower, as determined during Part A (Figure 8-1).

Figure 8-1 Overview of Study Design



a. The Lead-in Period will be required only if the dose of VX-984 exceeds a dose previously tolerated in a Lead-in Period.
b. Subjects in Part A will receive up to 6 cycles of treatment. Subjects with tumors responding to treatment may continue on treatment past 6 cycles with the agreement of the Investigator and medical monitor.
c. Subjects in Part B will receive treatment until disease progression, unacceptable toxicity, or withdrawal of consent.
d. Follow-up will include a Safety Follow-up Visit 28 (± 7) days after the last dose of study drug and a radiologic follow-up visit 5 (± 1) weeks after the last cycle of chemotherapy, and survival follow-up assessment at the last subject last visit. In Part B, for subjects without disease progression, long-term follow-up, including, as indicated, staging CT scans and/or follow-up communications, may continue for up to 1 year.

8.1.1 Screening (Parts A and B)

Screening Visit assessments are listed in Table 3-1.

Screening will occur within 14 days before administration of study drug. The Investigator (or an appropriate authorized designee at the study site) will obtain informed consent from each subject. If the time between screening and dosing exceeds 14 days as a result of unexpected operational delays (e.g., delayed drug shipment), then subjects do not require re-screening if laboratory results within 7 days of the first dose of study drug meet the eligibility criteria. Subjects who are unable to dose within the screening window because of substantial complications or disease progression will be replaced.

To prepare for study participation, subjects will be instructed on the study restrictions (Section 9.3).

A subject who qualified but did not enroll for an earlier cohort may be enrolled in a subsequent cohort with no required re-screening if predose laboratory results and World

Health Organization (WHO) performance status meet the eligibility criteria. Baseline CT scan will need to be repeated if more than 28 days have passed since most recent CT scan.

Subjects who do not meet the eligibility criteria may not be rescreened, with the following exceptions:

- Subjects who receive red blood cell transfusion or fluid replacement therapy
- In the Investigator's opinion, the reason for initial screen failure is due to a clearly temporary condition (e.g., incomplete recovery from recent surgery; inadequate time frame since prior chemotherapy)
- Subjects who met all eligibility criteria but are not able to obtain required documentation within the allotted screening window
- Subjects who met all eligibility criteria but transiently (for personal reasons) are unable to commit to all study procedures
- Subjects who were screened under a prior version of the protocol and did not meet any exclusion criterion, with the exception of a criterion that was updated in a subsequent version of the protocol.

The medical monitor must authorize re-testing in all cases except when subjects need to receive red blood cell transfusion or fluid replacement therapy. In this case, medical monitor approval is not required for re-testing. Any subject granted approval by the medical monitor for the exceptions listed above may have the screening window extended by 1 week before needing to undergo any rescreening assessments. If more than 35 days have elapsed from screening before first dose of study drug, all screening assessments need to be repeated. Repetition of any screening assessment that did not meet eligibility criteria is not permitted, unless there is clear evidence of a laboratory error (e.g., hemolysis of sample).

8.1.2 Treatment Period

8.1.2.1 Part A

Treatment Period assessments are listed in Table 3-2 for the single agent Lead-in Period and in Table 3-3 for the combination treatment of VX-984 with PLD in Part A.

8.1.2.1.1 Starting Dose and Dosing Schedule

The starting dose of VX-984 will be 120 mg qd and PLD will be 40 mg/m^2. The rationale for selection of the starting dose and dosing schedule for VX-984 and PLD is provided in Section 8.2.2.

For each VX-984 dose level tested, subjects will receive VX-984 qd alone on Days -14 to -12 of a 14-day Lead-in Period. Following the single agent Lead-in Period, subjects will receive PLD on Day 1 and VX-984 qd on Days 2 to 4 of a 28-day cycle. The Lead-in Period will be required only if the dose of VX-984 is escalated beyond the highest dose of VX-984 previously tolerated in a Lead-in Period.

Criteria for study drug administration on Day 1 of Cycle 1 and subsequent cycles are summarized in Section 10.2.

8.1.2.1.2 Guidelines for Dose Escalation

Three subjects will be enrolled at the starting dose of VX-984 and PLD. If the starting dose of VX-984 is tolerated alone in the 14-day Lead-in Period and in combination with PLD through 1 cycle (28 days) without a DLT or Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or worse toxicities in any of these 3 subjects and without a CTCAE Grade 2 toxicity in 2 subjects, the dose of VX-984 may be increased by up to 100% in a subsequent cohort of 3 subjects while holding the dose of PLD constant. Safety data, including AEs, laboratory values, and ECG results, obtained through the end of Cycle 1, as well as available PK data, will be assessed to determine the dose of VX-984 that will be used for the next cohort.

In this way, the dose of VX-984 will be escalated with 40 mg/m^2 of PLD in subsequent cohorts of 3 subjects until:

- 1 subject has a treatment-related or possibly-related DLT or toxicity of CTCAE Grade 3 or worse; or
- 2 subjects (who may be in different cohorts) have a toxicity of CTCAE Grade 2.

Subsequent dose escalation will proceed depending on the toxicity as described:

- In the event of a treatment-related or possibly-related toxicity of CTCAE Grade 3 or worse toxicity in 1 subject (that is not considered a DLT), or treatment-related or possibly-related toxicity of CTCAE Grade 2 in 2 subjects (who may be in different cohorts), the dose escalation will continue with a more conservative dose escalation (up to 50%). The dose of VX-984 will continue to be escalated with 40 mg/m^2 of PLD in subsequent cohorts of 3 subjects until there is a DLT through the end of Cycle 1
- In the event of a DLT, an adaptive Bayesian logistic regression model (BLRM) will be used to determine the dose for the subsequent cohorts or determine if the current dose level should be expanded. The adaptive BLRM will be guided by the escalation overdose control (EWOC) principle to control the risk of DLT in future subjects as described in Section 12.3.3.2. At each predicted dose, 3 to 6 subjects will be enrolled in each cohort at the discretion of the sponsor and Investigators as described in Section 8.1.2.1.8. If more than 3 subjects are enrolled, the first 3 subjects will receive VX-984 in the Lead-in Period and if no DLT is observed with VX-984 dosing then the additional subjects in the cohort will not have the Lead-in Period. The Lead-in Period will be required only if the dose of VX-984 is escalated beyond the highest dose of VX-984 previously tolerated in a Lead-in Period
- If 2 subjects in a previously untested dose level experience a DLT, enrollment to that cohort will stop, the BLRM will be updated and the next cohort will be opened at a lower dose level or an intermediate dose level that satisfies the EWOC criteria. However, if 2 subjects in a new cohort at a previously tested dose level experience a DLT (e.g., a total of 8 subjects are tested on this dose level with 2 DLTs observed), further enrollment to that cohort will stop, the BLRM will be updated with this new information and re-evaluation of the available safety, PK and PD data will occur. By

incorporating information gained at the preceding dose levels, additional subjects may be enrolled into the current dose level only if the dose still meets the EWOC criteria and as agreed by the sponsor and Investigators.

A subject will be considered as evaluable for dose determination if they have a DLT during Cycle 1 or the preceding Lead-in Period, or meet the minimum treatment and safety evaluation requirements for the first cycle as outlined in Subject Evaluability.

After completion of Cycle 1 of each cohort (3 to 6 subjects), available safety, PK, and efficacy information as well as recommendations from the Bayesian model will be used to determine the dose for the next cohort, with the following 2 exceptions:

1. For cohorts requiring 3 or more evaluable subjects, if only 2 evaluable subjects are available for assessment (all others drop out), and neither subject has had a treatment-related or possibly-related toxicity greater than CTCAE Grade 1, then 2 subjects will be considered sufficient for decision-making
2. If the first 2 subjects in a cohort have a DLT, further enrollment to the study will be temporarily suspended and the Bayesian model will be updated with this new information. If the Bayesian model supports enrolling the next cohort at the dose level where 2 DLTs occurred, or at a higher dose level, the relevant data and rationale will be discussed and agreed upon by sponsor and the Investigators of the escalation phase. If sponsor and the Investigators agree that it is medically appropriate to enroll an additional cohort at the dose level where 2 DLTs occurred or at a higher dose, the data and rationale supporting this decision will be documented.

Following the principle of escalation with overdose control (EWOC), after each cohort the recommended dose will be the one with the highest posterior probability of the DLT rate falling in the target toxicity interval [0.166, 0.333) among the doses fulfilling EWOC. Per EWOC, it should be unlikely (< 25% posterior probability) that the DLT rate at the dose will exceed 0.333.

For further understanding of the safety, tolerability, and PK of VX 984 in combination with PLD, additional cohorts of subjects may be enrolled at preceding dose levels, or to intermediate dose levels before or while proceeding with further dose escalation. The maximum planned dose of VX-984 is 2000 mg during escalation, however, higher doses up to 3000 mg may be allowed depending on the observed safety, PK, and PD, and based on recommendation of the BLRM.

After repeating the above steps, the dose escalation of VX-984 will continue with a constant dose of PLD at 40 mg/m^2 until MTD is achieved.

If a dose of VX-984 is not tolerated with PLD at 40 mg/m^2, then the VX-984 dose may be reduced by up to 50% with a constant dose of PLD at 40 mg/m^2 or the dose of PLD will be reduced by 25% (30 mg/m^2) or lower with a constant dose of VX-984. These doses will be explored in subsequent cohorts at the discretion of the Investigators and sponsor. If daily dosing of VX-984 for 3 days after PLD is not tolerated during initial dose escalation, less frequent dosing of VX-984 may be explored in subsequent cohorts.

Details on dose modifications for drug-related toxicity are provided in Section 10.5.

8.1.2.1.3 Dose Escalation Levels

The provisional doses to be administered during dose escalation are listed in Table 8-1.

Table 8-1 Provisional Dose Levels

Dose Level	Proposed VX-984 Dose (mg)[a]	Proposed PLD Dose (mg/m^2)[a]
-1[b]	120	30
1 (Starting Dose)	120	40
2	240	40
3	480	40
4	720	40

a. Proposed dose levels assume 100% escalation will be possible initially followed by up to 50% escalation. Doses beyond these levels are expected to be dictated by the BLRM.

b. Dose level -1 represents a dose that may be evaluated if dose level 1 (starting doses of VX-984 and PLD) is poorly tolerated.

8.1.2.1.4 Treatment Duration and Disease Assessments

At all dose levels of VX-984, subjects will complete a total of up to six 28-day cycles of VX-984 and PLD combination therapy. Subjects with tumors responding to treatment may continue treatment past 6 cycles with the agreement of the Investigator and medical monitor until disease progression, unacceptable toxicity, withdrawal of consent, or until exposure to PLD exceeds 550 mg/m^2. Staging CT scans will be performed at the end of every 2 cycles (see Table 3-3). If there is evidence of progressive disease as determined using RECIST 1.1, the subject's treatment will be discontinued. In addition, transthoracic echocardiograms will be performed at baseline and at the end of every 2 cycles (see Table 3-3). After 6 cycles, CT scans will be performed at the end of every 2 to 3 cycles (see Table 3-3).

8.1.2.1.5 Determination of MTD

Definition of MTD: The MTD is defined as the highest dose combination for a given schedule that causes DLTs in no more than 33.3% of subjects during the first cycle of treatment.

Dose escalation will continue until the identification of MTD or a suitable lower dose for Part B. This will occur when the following conditions are met:

1. at least 6 subjects have been treated at this dose
2. the dose satisfies one of the following conditions:
   a. the posterior probability of targeted toxicity at this dose exceeds 50% and is the highest among potential doses, or
   b. at least 15 subjects have been treated

The DLT Evaluable Set will be used for the determination of the MTD.

8.1.2.1.6 Definition of Dose-Limiting Toxicity

DLTs will be identified throughout the dosing cycles. DLTs will be defined using the National Cancer Institute (NCI) CTCAE (Version 4.0).

Table 8-2 Criteria for Defining Dose-Limiting Toxicities

Toxicity	Any of the Following Criteria

Hematology	• Neutropenia Grade 4 for > 7 days duration[a]
	• Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection)
	• Thrombocytopenia Grade 3:
	  ○ associated with clinically significant bleeding
	  ○ requiring platelet transfusion
	• Thrombocytopenia Grade 4

Cardiac	• QTc prolongation (any QTc interval ≥ 500 msec or any change in QTc interval ≥ 60 msec from baseline) on ECG, unless related to an electrolyte abnormality and prolongation resolves with correction of electrolyte abnormality • Any of the following (CTCAE criteria): Grade 2 or greater ventricular arrhythmia (second or third degree AV block), severe sustained/symptomatic sinus bradycardia less than 45 beats per minute (bpm) or sinus tachycardia > 120 bpm not due to other causes (e.g., fever), persistent supraventricular arrhythmia (e.g., uncontrolled/new atrial fibrillation, flutter, atrioventricular nodal tachycardia, etc.) lasting more than 24 hours, ventricular tachycardia defined as > 9 beats in a row or any length of torsades de pointes (polymorphic ventricular tachycardia with long QTc), or unexplained recurrent syncope • Symptoms suggestive of congestive heart failure with confirmed ejection fraction (EF) < 40% (by 2D-echocardiogram or multiple gated acquisition [MUGA] scan) or a relative decrease > 20% from historical assessment of EF performed within 12 months • Troponin T: level that is confirmed with myocardial infarction
Hepatic	• Any Grade 4 elevation of AST or ALT of any duration • Any Grade 3 elevation of AST or ALT lasting more than 7 days • Any Grade 3 elevation of AST or ALT concomitant with Grade 2 elevation of bilirubin (for subjects with normal baseline bilirubin) or Grade 3 elevation of bilirubin (for subjects with Grade 1 bilirubin abnormality at baseline) • Any Grade 3 elevation in bilirubin
Dermatologic	• Grade 3 rash for > 7 consecutive days, despite skin toxicity treatment (as per local practice) or any Grade 4 rash

Toxicities resulting in treatment interruption	• Any drug-related toxicity that causes interruption of treatment for > 2 weeks (14 successive days)
Other adverse events	• Infection (documented clinically or microbiologically) with Grade 3 or 4 neutropenia (absolute neutrophil count < 1.0×10^9/L) • Grade 3 or 4 toxicity to organs other than the bone marrow, including Grade 3 and 4 biochemical AEs • Death due to drug-related complications
Exceptions to DLT criteria	• Grade 3 nausea • Grade 3 vomiting in subjects who have not received optimal treatment with anti-emetics • Grade 3 diarrhea in subjects who have not received optimal treatment with antidiarrheal • Any Grade 3 elevation of AST or ALT lasting ≤ 7 days[b] • Any elevation of ALP • Acute infusion-related reactions

[a] In the event of a Grade 4 neutropenia, a complete blood count (CBC) must be performed no more than 7 days after the onset of the event to determine if a DLT has occurred. Continue to monitor the subject closely until resolution to Grade 3 or lower.

[b] In the event of a Grade 3 or higher elevation in ALT or AST, follow-up laboratory assessments should be performed every 48 to 72 hours until reduced to Grade 2 or lower.

If any change is made to the grade or causality of an AE during the study that may alter its DLT status, the sponsor must be informed immediately because this may affect dose escalation decisions.

8.1.2.1.7 Subject Evaluability

All subjects who meet the eligibility criteria and receive at least 1 dose of VX-984 will be evaluable for safety.

In order for subjects to be evaluable for dose escalation decisions:

- Subject must receive PLD on Day 1 and receive all 3 doses of VX-984 within 5 days (Days 2 to 6) with the first dose of VX-984 on Day 2; or
- The subject must have had a DLT during Cycle 1.

Subjects who do not fulfill at least 1 of the 2 above criteria will not be evaluable for dose escalation decisions and will be replaced.

8.1.2.1.8 Dose Escalation Process/Decision Making

At the end of each treatment cohort, the sponsor will convene a teleconference with the Investigators of the escalation phase. At the dose escalation teleconference, the clinical course (safety information including both DLTs and all CTCAE Grade ≥ 2 toxicity data during Cycle 1 as well as PK data) for each subject in the current dose cohort will be discussed. Updated safety data on other ongoing subjects, including data in later cycles, will be discussed as well.

Safety laboratory results and AEs occurring up to and including Day 28 of Cycle 1 will be reviewed as soon as they are available for a given cohort. Assessments for Day 28 of Cycle 1 must take place before dosing on Day 1 of Cycle 2. In this case, predose assessments on Day 1 of Cycle 2 will be used for DLT evaluation. DLTs that may have occurred through Day 28 of Cycle 1 of the current cohort, as well as DLTs that have occurred in prior cohorts in later cycles, will be identified.

To determine the dose regimen for the next cohort, the available toxicity information (including DLTs, AEs that are not DLTs, and AE information post-Cycle 1), PK, PD, and anti-tumor activity information, as well as the recommendations from the BLRM will be evaluated by the Investigators and sponsor study personnel (including the sponsor physician and statistician responsible for this study) at the dose decision meeting. The parties must reach a consensus on whether to declare MTD, escalate the dose any further, or whether to de-escalate and/or expand recruitment into particular cohorts.

8.1.2.1.9 Intra-Subject Dose Escalation

Intra-subject dose escalation is not permitted during the first 4 cycles of treatment. After the fourth cycle is completed, individual subjects may be considered for treatment at a dose of VX-984 in combination with PLD higher than the dose to which they were initially assigned. In order for a subject to be treated at a higher dose of VX-984 in combination with PLD, the subject must have received a lower dose for at least 4 cycles without a treatment-related or possibly-related toxicity of CTCAE Grade ≥ 2. Moreover, the new, higher dose with which the subject is to be treated must be a dose that has completed evaluation in a dose escalation meeting and that has not exceeded the MTD estimated by the BLRM. Any further increases after the initial intra-subject dose escalation will follow the same rules as for the initial intra-subject escalation. Consultation with the sponsor must occur before any intra-subject dose escalation decision.

8.1.2.2 Part B

During each cycle, subjects will be administered PLD on Day 1, and VX-984 will be dosed on Days 2 to 4 of a 28-day cycle unless in Part A the number of days was decreased due to tolerability. Treatment Period assessments are listed in Table 3-3. Approximately 40 subjects will receive VX-984 with PLD at the MTD or lower, as determined during the dose escalation phase.

Upon completion of the first cycle of treatment for at least 10 subjects within Part B, if the observed DLT rate exceeds 33.3%, the BLRM will be re-run to confirm that the estimated MTD still satisfies the overdose criteria of the model. If the dose fails to satisfy the criteria, a

change to the dose under study may be made according to the BLRM recommendation after review of the clinical data.

Subjects will continue to receive treatment until disease progression, unacceptable toxicities, or withdrawal of consent. Subjects will be evaluated by CT scans at the end of every 2 cycles for the first 6 cycles and every 2 to 3 cycles thereafter (see Table 3-3). If in the opinion of the Investigators, subjects may benefit with continued treatment with PLD and VX-984, subjects may continue to receive treatment beyond the total exposure of 550 mg/m^2 PLD. If there is evidence of progressive disease as determined using RECIST 1.1, treatment will be discontinued. In addition, subjects will be evaluated by transthoracic echocardiogram at baseline and at the end of every 2 cycles (see Table 3-3).

All subjects who meet the eligibility criteria and are administered at least 1 dose of VX-984 will be evaluable for safety. Subjects who meet the eligibility criteria, are administered at least 1 cycle of study drug, and have a baseline scan will be evaluated for efficacy. For subjects requiring palliative radiotherapy, irradiated lesions will be evaluable for progression, not response.

8.1.3 Stopping Rules (Parts A and B)

Subjects may be discontinued from study drug as follows:

- Subjects experiencing a non-reversible or life-threatening DLT may be discontinued from study drug at the Investigator's discretion, but will continue to complete follow-up assessments until documented progressive disease. Subjects who have a reversible and non-life threatening DLT and, in the judgment of the Investigator, may be exhibiting clinical benefit, may resume therapy after the toxicity has decreased to Grade < 2
- Subjects with progressive disease before the end of Cycle 1 may be discontinued from study drug at the discretion of the Investigator. Subjects with progressive disease beyond Cycle 1 will be discontinued from study drug. In cases where progression is not clear and in the opinion of the Investigator, the subject may be having clinical benefit, at the discretion of the Investigator, the subject may continue treatment but must be reimaged within 2 cycles of treatment
- For dose delays of more than 4 weeks due to drug-related toxicity other than Hand-Foot Syndrome (HFS) and stomatitis: Discontinue treatment, unless in the opinion of the Investigator, the subject is experiencing clinical benefit and it is in their best interest to continue treatment. For these subjects treatment may continue at a reduced dose at the discretion of the Investigator and sponsor
- Part A only: Exposure to PLD exceeds 550 mg/m^2.

8.1.4 Follow-up (Parts A and B)

All subjects, regardless of reason for discontinuation, will have a Safety Follow-up Visit 28 (± 7) days following the last dose of study drug, during which the procedures listed in Table 3-3 will be completed. In addition, all subjects who receive all scheduled study drug doses through Cycle 1, have not had evidence of disease progression, and have not initiated

cancer therapy outside of the study protocol will have radiologic follow-up 5 weeks (± 1 week) after the last cycle of chemotherapy.

A survival follow-up assessment will be performed for all subjects at the last subject last visit for that part. For the survival follow-up assessment, every subject who is not known to have died during the course of the study will be called to ascertain whether the subject is alive, if the subject has initiated another therapy, or if the subject died. If the subject has initiated another therapy or died, the date of initiation of the other therapy or date of death will be confirmed.

Subjects in Part B who complete at least 6 cycles of treatment, discontinue for reasons other than disease progression, and do not have disease progression on the radiologic follow-up visit will be followed by staging CT scan (if possible) approximately every 8 weeks until disease progression, the subject starts a new line of therapy, the subject dies, the study closes, or the subject is at least 12 months from end of treatment, whichever comes first.

Finally, for Part B, regardless of disease progression or initiation of new line of therapy, subjects may be followed by telephone, electronic, or mail communication, or in person, every 3 months for up to 1 year or until the subject is lost to follow-up or dies, whichever occurs first.

8.1.5 Early Treatment Termination (Parts A and B)

Subjects who discontinue study drug will be asked to return to the clinical site for a Safety Follow-up Visit at 28 days after their last dose of study drug. As applicable, subjects who discontinue study drug will be asked to complete all follow-up assessment outlined in Section 8.1.4 as applicable.

8.1.6 Definition of End of Study

Study completion is defined as the time when study drug administration is permanently discontinued due to any reason and the Safety Follow-up Visit or radiologic follow-up (when applicable) after the last dose of study drug has been completed.

The final analysis of study data may be performed when the last subject treated completes at least 6 cycles of treatment or discontinues the study. The additional data for any subjects continuing to receive study treatment after the data cutoff date for the primary clinical study report (CSR) will be further summarized in a report upon completion of the study when all subjects have discontinued study treatment and all required follow-up has been completed or the subject has died, been lost to follow-up, or withdrawn consent to further participation in the study.

8.2 Rationale for Study Design and Study Drug Regimens

8.2.1 Rationale for Study Design

The primary objectives of Part A of the study are to evaluate safety and determine the MTD of VX-984 in combination with PLD in subjects with advanced solid tumors. Three subjects will be enrolled at the starting dose of VX-984 and PLD. In order to limit subjects being treated at a non-efficacious dose, the initial dose escalation will allow for 100% escalation

until 1 subject has a treatment-related or possibly-related DLT or toxicity of CTCAE Grade 3 or worse; or 2 subjects (who may be in different cohorts) have a toxicity of CTCAE Grade 2.

Upon occurrence of a DLT, dose escalation will be guided by BLRM with EWOC principle similar to that proposed by Babb et al.[8] The use of BLRMs for Phase I studies has been advocated by the European Medicines Agency (EMEA) guideline on small populations (2006)[9] and by Rogatko et al.[10]

Subjects enrolled in Part A will have any advanced solid tumor that has failed treatment with at least 1 line of therapy, and have no standard or approved therapy available for treatment of their disease or would potentially be candidates for treatment with PLD. In general, response rates of many advanced solid tumors to second- and third-line therapies are limited. Thus, there is a potential for this population to benefit from the addition of a potential chemotherapy-enhancing agent.

The primary objectives of Part B are to evaluate the safety, tolerability, and OR of VX-984 in combination with PLD in subjects with previously-treated endometrial cancer. There is no approved or standard treatment for advanced recurrent endometrial cancer following a platinum based first-line regimen, and PLD is frequently used as second-line treatment.[11] In xenograft models using cancer cell lines or primary patient tumors, doses of VX-984 combined with PLD significantly enhanced the anti-cancer activity of PLD when VX-984 was administered 16 hours after PLD, and was generally well-tolerated.[3] The trigger for the initiation of the expansion cohort will be achieving a tolerated dose of PLD at or near SOC doses in combination with PLD at doses above the predicted efficacious dose in Part A.

8.2.2 Rationale for Study Drug Starting Dose and Duration

The selection of a starting dose of orally-administered VX-984 was made in accordance with the ICH S9 Guidance for Industry.[12] CCI

The approved single-agent dose of DOXIL®/CAELYX® is 50 mg/m^2 for ovarian cancer.[13,14] To reduce the potential of increased toxicities of PLD when dosed in combination with VX-984, PLD will be administered at 40 mg/m^2, which is frequently used in the clinic.

The dosing schedule for VX-984 is based on optimal timing of DNA-PK inhibition in relation to DNA-damaging drug exposure. Nonclinical data supports administration of VX-984 for 3 days starting 12 to 24 hours after the initial PLD dose. This schedule will minimize the potential for toxicity and is expected to cover time of the maximum concentration (t_{max}) and at least one terminal phase half-life ($t_{1/2}$) of PLD in tumors. [3]

8.2.3 Rationale for Study Assessments

Subjects will be monitored frequently for AEs that may be of potential consequences, based on nonclinical toxicology of VX-984 or based on prior experience in patients treated with PLD, using labs, ECGs, and echocardiograms.

CT scans will be used periodically to monitor tumor response to treatment, and response will be judged using RECIST 1.1. Subjects who do not demonstrate response to therapy will discontinue treatment.

9 STUDY POPULATION

Eligibility will be reviewed and documented by an appropriately qualified member of the Investigator's team before subjects are enrolled.

9.1 Inclusion Criteria

Subjects who meet all of the following inclusion criteria will be eligible.

1. Subjects (male and female for Part A and female for Part B) will be at least 18 year of age
2. Disease status

   Part A

   Subjects with histologically or cytologically confirmed malignant advanced solid tumors who have progressed on at least 1 prior chemotherapy, and for whom either

   - no standard therapy is available, or
   - PLD at the dose and schedule being used might be considered standard of care

   Part B

   - Subjects with histologically confirmed advanced primary endometrial cancer (locally advanced and incurable endometrial cancer that has been treated with surgery and/or radiation or is ineligible for such treatment), or recurrent or metastatic endometrial cancer, and
   - Completed 1 line of chemotherapy treatment with a platinum-containing regimen in the advanced setting
3. Measurable disease according to RECIST criteria (Version 1.1)
4. WHO performance status of 0 or 1
5. Life expectancy of at least 12 weeks

6. Hematological and biochemical indices within the ranges shown below at screening. These values must be confirmed within 3 days before the first day of dosing, before study drug administration:
    a. Hemoglobin: ≥ 9.0 g/dL
    b. Absolute neutrophil count: ≥ 2.5×10^9/L
    c. Platelet count: ≥ 125×10^9/L
    d. Serum bilirubin: ≤ 1.5 × upper limit of normal (ULN)
    e. ALT, AST: ≤ 2 × (ULN)
    f. Estimated glomerular filtration rate: ≥ 50 mL/min
    g. Prothrombin time: < 1.25 × ULN unless on anticoagulant therapy and discussed with the medical monitor

    In addition, there should not be other clinically significant metabolic or hematologic abnormalities that are uncorrectable or that require ongoing, recurrent pharmacologic management (except subjects who are receiving potassium, magnesium, or other supplementation for an otherwise controlled condition)
7. Normal left ventricular ejection fraction on screening assessed by transthoracic echocardiogram or MUGA scan
8. Subject will sign and date an informed consent form (ICF)
9. Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines, and other study procedures.

9.2 Exclusion Criteria

Subjects who meet any of the following exclusion criteria will **not** be eligible.

1. Previous radiotherapy (unless brachytherapy), endocrine therapy, chemotherapy, or exposure to investigational medicinal products during the 4 weeks (6 weeks for nitrosoureas and Mitomycin-C) or 4 drug half-lives before the planned administration of the first dose of study drug, whichever is greater. Previous immunotherapy during the 4 weeks before the planned administration of the first dose of study drug
2. For Part B only:
    - Subjects with uterine carcinosarcoma
    - Prior anthracycline therapy
    - More than 1 prior chemotherapy regimen (a subject who received first-line carboplatin and taxane and then receives the same taxane second-line will be considered to have had 1 prior chemotherapy regimen)
3. Unresolved toxicity of CTCAE Grade 2 or greater from previous anti-cancer therapy or radiotherapy, excluding
    - Alopecia

- Anemia or leukopenia if absolute neutrophil counts fall within limits specified in Inclusion Criterion 6 and is not decreasing at the time of treatment
- Other toxicities that in the opinion of the Investigator and the sponsor should not exclude the subject

4. History of spinal cord compression or brain metastases, unless asymptomatic, treated, stable, and not requiring treatment with steroids for at least 4 weeks before the planned administration of the first dose of study drug. Any history of leptomeningeal metastases
5. Female subjects who are pregnant or lactating at Screening, or plan to become pregnant while on study or within 6 months after the last dose of study drug
6. Female subjects of childbearing potential must adhere to contraception guidelines as outlined in the protocol. Female subjects will be considered to be of nonchildbearing potential if they have undergone surgical hysterectomy or bilateral oophorectomy or have been amenorrheic for more than 2 years with a screening serum follicle-stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal females
7. Male subjects with partners of childbearing potential must agree to adhere to contraception guidelines
8. Male subjects with pregnant or lactating partners or partners who plan to become pregnant while on study or within 6 months after the planned administration of the last dose of study drug
9. Major surgery ≤ 4 weeks before first dose of study drug, or incomplete recovery from a prior major surgical procedure
10. Cardiac conditions as follows:
    - Clinically significant cardiovascular event within 6 months before Screening:
        - congestive heart failure
        - unstable angina pectoris
        - myocardial infarction
        - Class II/III/IV cardiac disease (New York Heart Association functional classification)
        - presence of severe valvular heart disease
        - presence of a ventricular arrhythmia requiring treatment
    - History of arrhythmia that is symptomatic or requires treatment (CTCAE 3), symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia. Subjects with atrial fibrillation controlled by medication are permitted
    - Uncontrolled hypertension (blood pressure ≥ 160/100 despite optimal therapy)
    - Second- or third-degree heart block with or without symptoms

- QTc > 450 msec (by either Fridericia's or Bazett's correction) not due to electrolyte abnormality and that does not resolve with correction of electrolytes
- History of congenital long QT syndrome
- History of torsades de pointes (or any concurrent medication with a known risk of inducing torsades de pointes)

11. Clinically-significant abnormality, including ejection fraction below normal institutional limits, present on transthoracic echocardiogram performed at Screening
12. Prior bone marrow transplant
13. Extensive radiotherapy (to greater than 15% of bone marrow)
14. Participation or plan of participation in another interventional clinical study while taking part in this study. Participation in an observational study would be acceptable
15. Any other condition that in the Investigator's opinion would not make the subject a good candidate for the clinical study, including
    a. History of human immunodeficiency virus-1 (HIV-1), HIV-2, or unresolved hepatitis B or unresolved hepatitis C infection
    b. High medical risk because of non-malignant systemic disease including active uncontrolled infection
16. Part B: Current active malignancies of other types, with the exception of adequately treated cone-biopsied in situ carcinoma of the cervix uteri and basal or squamous cell carcinoma of the skin. Prior cancer in remission for 2 years or more would not be excluded
17. Current therapy:
    - Subjects receiving treatment with medications that are known to be moderate to strong inhibitors or inducers of cytochrome P450 3A4 (CYP3A4) that cannot be discontinued at least 1 week before first dose of study drug and for the duration of the study
    - Subjects receiving treatment with medications that are mainly metabolized by CYP3A4 and have a low therapeutic index that cannot be discontinued at least 1 week before first dose of study drug and for the duration of the study.

9.3 Study Restrictions

Study restrictions are summarized in Table 9-1.

Table 9-1 Study VX15-984-001: Study Restrictions

	Study Period	
Restricted Medication/Food/Activity	**Screening Period**	**Treatment Period**
Food Grapefruit/grapefruit juice Seville or blood oranges	None allowed within 7 days before the first dose of study drug	None allowed through the Safety Follow-up Visit
Moderate and Strong CYP3A4 inhibitors or inducers	None allowed within 7 days before the first dose of study drug	None allowed through the Safety Follow-up Visit
Anti-emetics	Allowed for symptom management	Prophylactic use not allowed during Lead-in Period of Part A. Allowed beyond Lead-in Period in Part A and throughout Part B.
Antidiarrheals	Allowed for symptom management	Prophylactic use not allowed during Lead-in Period and Cycle 1 of Part A. Allowed beyond Cycle 1 in Part A and throughout Part B.
Hematopoietic growth factors	Not allowed	Prophylactic use not allowed during Lead-in Period and Cycle 1 of Part A. Allowed beyond Cycle 1 in Part A and throughout Part B.

Note: Refer to the study reference manual for a complete list of medications prohibited in this study.

9.3.1 Additional Dietary Restrictions

- There are no restrictions on food and non-alcoholic beverages, except restrictions mentioned in Table 9-1.

9.3.2 Activity

- Subjects will abstain from strenuous exercise (e.g., heavy lifting, weight training, and aerobics) for at least 48 hours before each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted.
- Subjects should avoid prolonged or intense sun exposure, sunlamps, and tanning beds. Use of sunscreen, clothing, and eyewear that decrease sun exposure is recommended.

9.4 Prior and Concomitant Medications

In vitro drug metabolism studies suggest that VX-984 is a substrate of CYP3A4 and its systemic exposure may be affected by concomitant medications that are moderate or strong CYP3A4 inhibitors or inducers. Restrictions for prior and concomitant medications that are moderate or strong inhibitors and inducers of CYP3A4 are provided in the Study Reference Manual. Based upon in vitro data, VX-984 is a weak to moderate inhibitor of CYP3A. Therefore, use of drugs that are metabolized mainly by CYP3A and have a low therapeutic

index is not allowed in the study. Investigators should use standard precautions when prescribing medications, as with any novel therapeutic for which there is limited clinical experience.

- Subjects will abstain from concomitant medications as described in Table 9-1. If a prohibited medication is considered medically necessary for a subject, the subject will be withdrawn from the study
- Subjects should not receive prophylactic treatment with hematopoietic growth factors and antidiarrheal medications during the Lead-in Period and Cycle 1 of Part A. These treatments may be used to specifically address subject symptoms, per institutional practice, as long they adhere to restrictions listed in Table 9-1
- The Investigator should refer to the package inserts for PLD for guidance on prohibited medications during treatment with this agent. Subjects should not use nephrotoxic or ototoxic medications from 7 days before the first dose of study drug through the Safety Follow-up Visit. Inadvertent or short-term use while in the study will not cause a subject to be ineligible
- Medications taken from 28 days before the first dose of study drug will be documented as a prior medication. Medications taken after the first dose of study drug through the end of the study will be documented as concomitant medications. All medications must be recorded with indication, route of administration, and start and stop dates of administration. All subjects will be questioned about concomitant medication at each clinic visit.

9.5 Removal of Subjects

Subjects may withdraw from the study at any time at their own request. Subjects may be withdrawn from study drug treatment at any time at the discretion of the Investigator or EMD Serono Research & Development Institute (the Sponsor) for safety, behavior, noncompliance with study procedures, or administrative reasons. If a subject has been withdrawn from study drug treatment, the subject will continue to be followed, provided the subject has not withdrawn consent.

If a subject does not return for a scheduled visit, reasonable effort will be made to contact the subject. In any circumstance, reasonable effort will be made to document subject outcome. The Investigator will inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for a Safety Follow-up Visit, if applicable (see Section 8.1.5), and follow up with the subject regarding any unresolved AEs.

If the subject withdraws consent for the study, no further evaluations will be performed and no additional data will be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent.

Subjects may be discontinued from study drug for toxicity or lack of efficacy, as specified in Section 8.1.3.

9.6 Replacement of Subjects

In Part A, subjects who withdraw or are withdrawn from treatment for reasons other than DLT before the Cycle 1 Day 28 assessment and who have not had the minimum exposure to study drugs described in Subject Evaluability will be replaced. Subjects who withdraw or are withdrawn from treatment beyond Cycle 1 will not be replaced.

For Part B, subjects who discontinue for reasons other than disease progression or are non-evaluable for efficacy analysis may be replaced. Subjects who discontinue for disease progression before the completion of Cycle 1 may also be replaced.

10 STUDY DRUG ADMINISTRATION AND MANAGEMENT

10.1 Preparation and Dispensing

Study drug may be dispensed only under the supervision of the Investigator or an authorized designee and only for administration to the study subjects.

Study drug will be supplied to sites as individual dosing containers of VX-984 adipic acid cocrystal powder (drug product intermediate) with additional adipic acid.

The final suspension will be prepared using a vehicle containing 0.5% methylcellulose, 0.1% sodium benzoate, 0.1% benzoic acid, and adipic acid (amount varies with dose). Details of dose preparation, including constitution, will be given in a separate document (Formulation Preparation Instructions).

Individual dose concentrations of VX-984 will be bracketed between 8 mg/g and 50 mg/g in the suspending vehicle.

The subjects will be provided with 3 containers per dose:

- VX-984 adipic acid cocrystal powder,
- dosing vehicle, and
- vehicle to be used as rinsate.

All 3 containers will be labelled appropriately for easy administration.

10.2 Criteria for Study Drug Administration

When clinical chemistry and/or hematology laboratory testing is required as described in the Schedule of Assessments (Table 3-1, Table 3-2, and Table 3-3) before administration of chemotherapy or VX-984, the laboratory criteria specified in Table 10-1 must be met before dosing. To facilitate timely administration of study drug, this laboratory testing may be performed up to 3 days before dosing.

Table 10-1 Laboratory Values Required for Administration of Chemotherapy or VX-984

Laboratory Parameter	Cycle 1, Day 1	Day 1 of Subsequent Cycles
Hemoglobin	≥ 9.0 g/dL	≥ 7.0 g/dL (if asymptomatic)
Absolute neutrophil value	≥ 2.5×10^9/L	≥ 1.5×10^9/L
Platelet count	≥ 125×10^9/L	≥ 100×10^9/L
AST, ALT	≤ 2 × ULN	≤ 2 × ULN
Estimated glomerular filtration rate	≥ 50 mL/min	≥ 45 mL/min (if no more than 20% decrease from prior cycle)
Total bilirubin (serum)	≤ 1.5 × ULN[a]	≤ 1.5 × ULN[a]

a. Unless subject has known or suspected Gilbert's syndrome

10.3 Administration

VX-984, On-site and In-home:

When on-site at the clinic, subjects may receive either the suspension already mixed or subjects will prepare their dose in the presence of a nurse or other authorized designee. Subjects will also receive a rinsate container containing vehicle.

Steps for mixing and consuming the study drug are as follows:

- The contents of the dosing vehicle will be added to the VX-984 adipic acid cocrystal powder. The container will be sealed, and the contents will be shaken to mix and consumed immediately
- The contents of the second vehicle container will be used as a rinsate and added to the residual material. The container will be sealed, and the contents will be shaken to ensure that no powder is left behind. The contents will be consumed immediately.

For in-home administration by the subject, a kit will be provided that contains 3 containers per dose needed for in-home administration. For example, if a subject will take the next 2 doses at home, a total of 6 containers will be provided.

PLD, On-site:

PLD, supplied as single use vial: 20 mg/10 mL or 50 mg/25 mL. PLD doses up to 90 mg will be diluted in 250 mL of 5% Dextrose Injection, USP before administration. PLD doses exceeding 90 mg will be diluted in 500 mL of 5% Dextrose Injection, USP before administration. Diluted PLD must be refrigerated at 2° to 8°C and administered within 24 hours.

The Investigator should refer to the DOXIL®/CAELYX® label for administration guidelines of PLD. Precautionary preparations should be made to prepare for serious and sometimes life-threatening infusion-related reactions that may occur most commonly during the first infusion of PLD, but may also occur in subsequent cycles. Acceptable window for infusion: ± 25% of the planned infusion time.

10.4 Method of Assigning Subjects to Treatment Groups

This is an open-label study.

10.5 Dose Modification and Dose Delay for Toxicity

Part A:

Doses of VX-984 or PLD may be reduced beyond Cycle 1 for toxicity using the following guidelines:

- For Grade 4 neutropenia or thrombocytopenia: Delay dosing until absolute neutrophil count ≥ 1500 and platelets ≥ 75000. The dose of VX-984 will be reduced to previous tolerated dose level and PLD will be reduced by 25% when dosing resumes
- For HFS and stomatitis, modify PLD doses according to DOXIL package insert[13]
    - For Grade 1 HFS and stomatitis: if no previous Grade 3 or 4 HFS, no dose adjustment. If previous Grade 3 or 4 HFS, delay dose for up to 2 weeks, then decrease PLD dose by 25%
    - Grade 2, 3 and 4 HFS and stomatitis: delay dosing up to 2 weeks or until resolved to Grade 0 or 1, then decrease PLD dose by 25%. Discontinue treatment if no resolution after 2 weeks
- For other Grade 3 non-hematologic toxicity: Do not dose until recovered to Grade < 2, then reduce the dose of VX-984 to the previous tolerated dose level and PLD by 25%
- For Grade 4 non-hematologic toxicity: Do not dose until recovered to Grade < 2, then reduce the dose of VX-984 to the previous tolerated dose level and PLD by 25% or discontinue treatment
- For dose delays of more than 1 week due to toxicity: Reduce VX-984 dose to the previous tolerated dose level
- For dose delays of more than 4 weeks due to drug-related toxicity other than HFS and stomatitis: Discontinue treatment, unless in the opinion of the Investigator, the subject is experiencing clinical benefit and it is in their best interest to continue treatment. For these subjects treatment may continue at a reduced dose, at the discretion of the Investigator and sponsor.

Part B:

For drug-related toxicity, the following modifications of drug dose and schedule will be made:

- In case of non-hematologic Grade 3 or higher toxicity (excluding fatigue or nausea/vomiting/diarrhea adequately managed by supportive care), treatment will be interrupted and may be resumed when all toxicities have returned to Grade < 2, at the discretion of the Investigator
- For the following hematologic toxicities, once the toxicity has returned to Grade < 2, dosing can be resumed with a 25% reduction in VX-984 dose. If, after 25% reduction of

VX-984 dose, any of the below drug-related hematologic toxicities are subsequently observed, then, the dose of PLD will be reduced by 25%

  - Grade 4 thrombocytopenia
  - Febrile neutropenia (growth factor support, per site protocol, may be used in lieu of dose reduction)
  - Grade 4 neutropenia lasting more than 7 days (growth factor support, per site protocol, may be used in lieu of dose reduction)

- For the following non-hematologic toxicities, once the toxicity has returned to Grade < 2, dosing can be resumed at a lower dose of chemotherapy. PLD dose will be reduced by 25%. If any of the below drug-related toxicity is subsequently observed with the reduced dose of chemotherapy, VX-984 dose will be reduced by 25%
  - Grade 3 non-hematologic toxicity (Except for fatigue or nausea, vomiting, or diarrhea adequately controlled by medication)
  - Any non-hematologic toxicity requiring dose delay of more than 2 weeks.
- For Grade 4 non-hematologic toxicity, treatment will be interrupted and may be resumed at a lower dose when toxicity has returned to Grade < 2 or subjects may be removed from the study. VX-984 dose will be reduced by 25%. In addition, the PLD dose will be reduced by 25%
- For HFS and stomatitis, modify PLD doses according to DOXIL package insert[13]
  - For Grade 1 HFS and stomatitis: if no previous Grade 3 or 4 HFS, no dose adjustment. If previous Grade 3 or 4 HFS, delay dose for up to 2 weeks, then decrease PLD dose by 25%
  - Grades 2, 3 and 4 HFS and stomatitis: delay dosing up to 2 weeks or until resolved to Grade 0 or 1, then decrease PLD dose by 25%. Discontinue treatment if no resolution after 2 weeks
- For dose delays of more than 4 weeks due to drug-related toxicity other than HFS and stomatitis: Discontinue treatment, unless in the opinion of the Investigator, the subject is experiencing clinical benefit and it is in their best interest to continue treatment. For these subjects treatment may continue at a reduced dose, at the discretion of the Investigator and sponsor.

If any toxicity not described above results in delay in dosing in any part of the study and the subject may be benefitting from therapy, then at the discretion of the Investigator, the dose of VX-984 or chemotherapy may be reduced by 25%.

10.6 Missed Doses and Study Visits

Treatment will be interrupted because of Grade 3 or higher toxicity during any cycle beyond Cycle 1. Treatment may be resumed as described in Section 10.5.

Study visits that are missed because of clinic or subject unavailability (e.g., for reasons of public holiday, clinic closure, urgent personal matter, transportation problems), should be

made up when and if reasonably possible. For delayed doses, the dosing schedule should continue from the date of the delayed dose without omitting any doses of chemotherapy or any rest intervals between chemotherapy, if possible. Whenever possible, subsequent doses of chemotherapy should be advanced in time to synchronize with the actual date of administration of the delayed dose.

The relative timings of all other assessments and drug dosing may be moved to accommodate subject and clinic availability. Delays between sequential cycles in therapy, other than for reasons of toxicity, should not exceed 7 days, except as approved by the Sponsor medical monitor.

10.7 Stopping Rules

Stopping rules for this study are described in Section 8.1.3.

10.8 Packaging and Labeling

The Sponsor will supply the VX-984 as powder in high density polyethylene (HDPE) bottles with induction-sealed polypropylene caps. Study drug labeling will be in compliance with applicable local and national regulations. Additional details regarding packaging, labeling, and dispensing for VX-984 will be included in the Pharmacy Manual.

10.9 Study Drug Supply, Storage, and Handling

The Investigator, or an authorized designee (e.g., a licensed pharmacist), will ensure that all investigational product is stored in a secured area, under recommended storage conditions as outlined in the Pharmacy Manual, and in accordance with applicable regulatory requirements. To ensure adequate records, all study drugs will be accounted for as described in Section 10.10 or via the drug accountability forms as instructed by the Sponsor.

Drug supply will be sent to the site in the form of bulk bottles, with pharmacist or designated study staff allocating the necessary units to a subject-specific bottle. Empty bottles and caps will be provided by the sponsor. If a site needs to use a bottle other than those provided by the sponsor, the site should request prior approval from the sponsor. The site will apply a label to the bottles.

10.10 Drug Accountability

The pharmacist or designated study site staff will maintain information regarding the dates and amounts of (1) study drug received, (2) study drug dispensed to the subjects, and (3) study drug returned by the subjects. Subjects will be instructed to return all used and unused materials associated with the study drug to the site. These materials will be retained at the site according to instructions provided by the Sponsor or its designee until inventoried by the study monitor. The study monitor will review study drug records and inventory throughout the study.

10.11 Disposal, Return, or Retention of Unused Drug

The study site staff or pharmacy personnel will retain all materials returned by the subjects until the study monitor has performed drug accountability. At the end of the study, the study monitor will provide instructions as to the disposition of any unused investigational product. If the study monitor authorizes destruction at the study site, the Investigator will ensure that

the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by the Sponsor. Destruction will be adequately documented.

10.12 Compliance

For study drug doses administered when on-site at the clinic, doses will be administered under the direct supervision of the Investigator or designee. A hand-and-mouth check will be done after each dose administration in the clinical research unit to ensure 100% study treatment compliance.

For study drug doses administered during the outpatient periods of the study, drug accountability will be assessed at each visit by counting returned dosage units. Discrepancies will be discussed with the subject and recorded in the source documents. If subjects demonstrate continued noncompliance of study drug dosing despite educational efforts, the Investigator will contact the medical monitor to discuss discontinuing the subject from the study.

10.13 Blinding and Unblinding

This will be an open-label study.

11 ASSESSMENTS

11.1 Timing of Assessments

The timing of assessments is shown in Table 3-1, Table 3-2, and Table 3-3.

11.2 Subject and Disease Characteristics

Subject and disease characteristics include the following: demographics, medical history, height, weight, type of cancer (including histologic subtype), tumor stage at baseline, date of cancer diagnosis, prior chemotherapy and radiation therapy, date and duration of most recent cancer therapy, and WHO performance status at baseline.

11.3 Pharmacokinetics

11.3.1 Blood Sampling

For the evaluation of plasma concentrations of VX-984 and PLD, plasma samples will be collected according to the Schedule of Assessments (Table 3-2 and Table 3-3). These samples may also be used for evaluations of metabolites of VX-984, for further evaluation of the bioanalytical method, and for analyses that provide information on the metabolic pathways used by or affected by VX-984.

Actual sampling times may change upon agreement of the clinical pharmacologist and Investigator, but the number of samples will remain the same. All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. Acceptable windows for sampling times are shown in Table 11-1. Samples collected outside of these acceptable windows will be considered protocol deviations. The exact time of the sample collection will be noted.

Table 11-1 Acceptable Pharmacokinetic Sampling Windows

Sampling Time	Time From Scheduled Sampling Allowed
Predose	- 120 minutes
From 0.5 up to ≤ 4 hours after study drug dosing	± 15 minutes
From > 4 up to ≤ 72 hours after study drug dosing	± 120 minutes

11.3.2 Urine Sampling

Urine will be collected for measurement of VX-984 PK in the Lead-in Period according to the Schedule of Assessments (Table 3-1).

Detailed instruction for urine PK sample collection, processing, handling, and storage will be provided in the Laboratory Manual.

11.3.3 Processing and Handling of Pharmacokinetic Samples

Detailed procedures for the collection of blood and urine samples and further procedures for processing and handling of samples for PK analysis will be provided in the Laboratory Manual. The shipment address and assay laboratory contact information will be provided to the investigational site before initiation of the study.

11.3.4 Bioanalysis

Samples will be analyzed using a validated analytical method in compliance with the Sponsor or designee standard operating procedures. A description of the assay and validation data will be provided in separate reports.

11.4 CCI [redacted]

[redacted]

(Table 3-1, Table 3-2, and Table 3-3).

11.5 Exploratory

CCI [redacted]

[redacted]

CCI
CCI

[redacted]

11.5.2 CCI

CCI

[redacted]

11.6 Efficacy

Subjects with measurable disease will be assessed by standard criteria (RECIST 1.1). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria. Refer to the RECIST 1.1 publication for additional information.[15]

CT scans will be read locally for all parts of the study. The applicable overall response category for each visit that includes disease assessment, based on evaluation of CT scan by a qualified radiologist local to the Investigator, will be recorded in the electronic case report form (eCRF). Determination of subject study disposition (i.e., discontinuation or extension of therapy) will be based on the interpretation of disease progression from the local evaluation of the CT scan.

Information regarding anatomical imaging (CT scans) will be collected according to the Imaging Manual. The sponsor will engage an imaging contract research organization to facilitate acquisition and potential interpretation of images.

In addition to the standard RECIST 1.1 assessments, anatomical images collected may be analyzed using image analysis techniques that enable additional insights into tumor changes following treatment, including, but not limited to, assessments of 3D-tumor volumes and

tumor necrosis (for tumors amenable to volume and necrosis assessment). Additional information will be provided in the Imaging Manual. These additional imaging analyses will be exploratory in nature and will not be used to make subject treatment decisions or as a replacement of standard RECIST 1.1.

Historical CT scans may be collected and analyzed to enable assessment of historical and on-treatment tumor growth dynamics.

CT scans expose patients to medical radiation. The scans performed in this study should be considered within the standard of care for the subject. It is important that all scans performed on a subject should be consistent. This includes use of the same scanner, acquisition parameters, and administration of contrast agents (to the extent it is clinically feasible).

11.7 Safety

Safety evaluations will include AEs, clinical laboratory assessments, clinical evaluation of vital signs, ECGs, echocardiograms, and PEs.

11.7.1 Adverse Events

All AEs will be assessed, documented, and reported in accordance with ICH GCP guidelines. Section 13.1 outlines the definitions, collection periods, criteria, and procedures for documenting, grading, and reporting AEs. A separate document that details AE CRF completion guidelines for Investigators as well as training will be provided.

11.7.2 Clinical Laboratory Assessments

Blood and urine samples will be analyzed at a local or central laboratory. At the Screening Visit, blood specimens will be collected for safety laboratory tests. Samples will be collected as specified in the Schedule of Assessments (Table 3-1, Table 3-2, and Table 3-3).

To facilitate timely administration of study drug, safety labs may be obtained up to 3 days before dosing. If labs are drawn before the day of dosing, they should be recorded as corresponding to the day of dosing.

Laboratory test results that are abnormal and considered clinically significant will be reported as AEs (see Section 13.1).

The safety laboratory test panels are shown in Table 11-2.

Table 11-2 Safety Laboratory Test Panels

Serum Chemistry	Hematology	Urinalysis[a]
Glucose	Hemoglobin	Leukocyte esterase
Blood urea nitrogen[b]	Erythrocytes:	Nitrite
Creatinine	Mean corpuscular volume	Urobilinogen
Sodium	Platelets	Urine protein
Potassium	Reticulocytes (absolute)[c]	pH
Calcium	Leukocytes	Urine blood
Chloride	Differential (absolute and percent):	Specific gravity
Magnesium	Eosinophils	Urine ketones
Bicarbonate	Basophils	Urine bilirubin
Inorganic phosphate	Neutrophils	Urine glucose
Total bilirubin, direct bilirubin	Lymphocytes	
ALP	Monocytes	
AST	**Coagulation[c]**	
ALT	Activated partial thromboplastin time	
Total protein	Prothrombin time	
Albumin	Prothrombin time International Normalized Ratio	
Creatine kinase[c]		
Uric acid[c]		

[a] If urinalysis results are positive for leukocyte esterase, nitrite, protein, or blood, microscopic examination of urine will be performed and results for provided for leukocytes, erythrocytes, crystals, bacteria, and casts.
[b] If blood urea nitrogen cannot be collected, urea may be substituted.
[c] Creatine kinase, uric acid, and reticulocytes (absolute) parameters will be tested only at Screening and Safety Follow-up. Coagulation parameters will be tested only at Screening.

Additional tests at screening: The following additional tests will be performed during screening to assess eligibility:

- Serum beta-human chorionic gonadotropin (β-hCG) for all female subjects
- Serum FSH for suspected postmenopausal female subjects only. Levels will be within the laboratories range for postmenopausal for subjects to be considered of non-childbearing potential.

Clinical laboratory assessments from screening will have no clinically significant findings that preclude participation in the study, as judged by the Investigator, for a subject to receive study drug.

Pregnancy testing for female subjects of childbearing potential (as defined in Section 11.7.6.1):

- Subjects in Part A receiving VX-984 with Lead-in Period will have a urine β-hCG test on Day -14, Day 1 of VX-984 and PLD combination therapy, and every 4 weeks thereafter through the Safety Follow-up Visit
- Subjects in Part A receiving VX-984 without Lead-in Period and subjects in Part B will have a urine β-hCG test on Day 1 of VX-984 and PLD combination therapy, and every 4 weeks thereafter through the Safety Follow-up Visit.

When there are no scheduled study visits, pregnancy testing will be performed using a urine home pregnancy test kit provided by the study site.

If a urine pregnancy test is positive, all study drug dosing will stop and the pregnancy will be confirmed with a serum β-hCG test. If confirmed, the pregnancy will be reported and the subject will be permanently withdrawn from study drug dosing as discussed in Section 11.7.6.2. If a pregnancy test is positive, the procedures outlined in Section 11.7.6.2 will be followed.

Additional Evaluations: Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate.

11.7.3 Physical Examinations and Vital Signs

A PE of all body systems and vital signs assessment will be performed at screening and select study visits (Table 3-1, Table 3-2, and Table 3-3). At other visits, symptom-directed PEs and symptom-directed vital sign assessments can be performed at the discretion of the Investigator.

A PE includes a review of the following systems: head/neck/thyroid; eyes/ears/nose/throat (EENT); respiratory; cardiovascular; lymph nodes; abdomen; skin; musculoskeletal; and neurological. Breast, anorectal, and genital examinations will be performed when medically indicated. After screening, any clinically significant abnormal findings in PEs will be reported as AEs.

Vital signs include blood pressure (systolic and diastolic), temperature, pulse rate, and respiration rate. These will be assessed following a 5-minute rest in the supine position.

11.7.4 Electrocardiograms

Standard 12-lead ECGs will be performed using a machine with printout according to the Schedule of Assessments (Table 3-1, Table 3-2, and Table 3-3). Additional standard 12-lead ECGs will be performed at any other time if clinically indicated. The performance of all ECGs will adhere to the following guidelines:

- The subject will be instructed to rest in the supine position for at least 5 minutes before having an ECG performed
- The ECG will be performed before any other procedures that may affect heart rate, such as blood draws.

The ECG traces will be manually read at the study site at the Screening and Safety Follow-up Visits. A printout of the ECG traces will be made for safety review by the Investigator and maintained with source documentation. Clinically significant ECG abnormalities occurring during the study through the Safety Follow-up Visit will be recorded as AEs.

11.7.5 Echocardiogram

Echocardiograms will be collected from all subjects according to the Schedule of Assessments (Table 3-1, Table 3-2, and Table 3-3).

11.7.6 Contraception and Pregnancy

11.7.6.1 Contraception

Male Subjects:

Acceptable contraceptive methods must be used from the Screening Visit through 6 months after the last dose of study drug, and include the following:

- True abstinence (absence of any sexual intercourse), when in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods), and withdrawal are not acceptable methods of contraception
- Condom with spermicide and the female partner must use an acceptable method of contraception, such as an oral, transdermal, injectable, or implanted steroid-based contraceptive, or a diaphragm or cervical cap with spermicide
- Vasectomy (with a negative sperm postvasectomy semen analysis) at least 6 months before first dose of study drug and 1 additional acceptable contraception method.

Male subjects must not donate sperm from the Screening Visit through 6 months after the last dose of study drug.

Note 1: Male condom cannot be used with female condom due to risk of tearing.

Note 2: The use of birth-control methods does not apply if the female partner has a bilateral oophorectomy, hysterectomy, or is postmenopausal (as defined below).

Female Subjects of Nonchildbearing Potential:

Female subjects of non-childbearing potential must meet at least 1 of the following criteria:

- Postmenopausal: Female subjects, less than 60 years of age, who have been amenorrheic for at least 2 years and have a serum FSH level within the laboratory's reference range for postmenopausal females. Female subjects who are 60 years of age or older and who have been amenorrheic for greater than 2 years will be assumed to be postmenopausal
- Documented hysterectomy or bilateral oophorectomy or both.

All other female subjects (including subjects with tubal ligations and subjects who do not have a documented hysterectomy) will be considered to be of childbearing potential.

Female Subjects of Childbearing Potential:

Acceptable nonhormonal, contraceptive methods must be used from the 28 days before first dose of study drug through 6 months after the last dose of study drug and include the following:

- True abstinence (absence of any sexual intercourse), when in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception

- Double barrier contraception such as diaphragm or cervical cap with spermicide and the male partner must use a condom with spermicide
- Intrauterine device (nonhormone-releasing) in place for at least 90 days previously and the male partner must use a condom with spermicide
- Bilateral tubal ligation at least 6 months previously and 1 additional acceptable contraception method
- Vasectomy of the male partner (with a negative sperm postvasectomy semen analysis) at least 6 months before first dose of study drug and 1 additional acceptable contraception.

11.7.6.2 Pregnancy

Subjects will be counseled to inform the Investigator of any pregnancy that occurs during study treatment and for 90 days after the last dose of study drug(s).

If a subject or the female partner of a male subject becomes pregnant while participating in the study, study drug will be permanently discontinued immediately. The Investigator will notify the medical monitor and the Sponsor Global Patient Safety (GPS) within 24 hours of the site's knowledge of the subject's (or partner's) pregnancy using the Pregnancy Information Collection Form. The subject or partner will be followed until the end of the pregnancy and the infant will be followed for 1 year after the birth, provided informed consent is obtained. A separate ICF will be provided to explain these follow-up activities. Pregnancy itself does not constitute an AE.

12 STATISTICAL AND ANALYTICAL PLANS

Analysis of all data, including safety, efficacy, and PK profiles, will be performed by the Sponsor or its designee. The results of all parts of the study will be reported in the clinical study report.

The final analysis of study data will be based on all subject data of the escalation and expansion phases up to the time when all subjects have completed at least 6 cycles of treatment or discontinued the study. Within this analysis, subjects treated during the escalation phase will be pooled with those receiving the same dosing regimen during expansion phase.

The additional data for any subjects continuing to receive study treatment after the data cutoff date for the primary CSR will be further summarized in a report upon completion of the study (see Section 8.1.6) when all subjects have discontinued study treatment and all required follow-up has been completed or the subject has died, been lost to follow-up, or withdrawn consent to further participation in the study.

For subjects undergoing intra-subject escalation to doses other than their initially received dose level, their post-escalation data will be listed.

A detailed analysis plan for the analysis of safety and efficacy data, and PK profiles will be presented in a statistical analysis plan (SAP) before the database is locked for analysis.

12.1 Sample Size and Power

For Part A, no formal statistical power calculations were performed to determine sample size. It is estimated that 50 subjects will be enrolled in Part A including at least 6 subjects treated at the MTD level. The actual number of subjects will depend on the number of dose levels/cohorts that are tested.

For Part B, assuming a historical ORR of 10% among subjects with endometrial cancer treated with PLD as second-line therapy, [16] a sample size of 40 subjects treated with VX-984 in combination with PLD in Part B will provide a power of 41% and 90% CI of (10.4%, 33.2%) with a target ORR of 20% and a power of 70% and 90% CI of (14.2%, 38.7%) with a target ORR of 25%, assuming an exact binomial test and an actual 2-sided significance level of 0.03.

Table 12-1 Power Consideration With Historical Response Rate of 10%

N	Treatment Response Rate	Power (%)
40	20%	40.7
	25%	70.0
	30%	88.9

12.2 Analysis Sets

For Part A:

- The DLT Evaluable Set is defined as all subjects in the Safety Set of Part A who either meet the minimum exposure criterion and have sufficient safety evaluations (as determined by the Investigators and sponsor), or have had a DLT during Cycle 1 (including the Lead-in Period)

  A subject is considered to have met the minimum exposure criterion at a dose level if the subject received PLD on Day 1 and 3 doses of VX 984 within 5 days with the first dose of VX-984 on Day 2. Subjects who do not have a DLT during Cycle 1 are considered to have sufficient safety evaluations if they have been observed through the end of Cycle 1 following the administration of PLD and VX-984, and are considered by both the sponsor and Investigators to have enough safety data to conclude that a DLT did not occur
- The Safety Set is defined as all subjects who received at least 1 dose of study drug. The Safety Set will be used for safety analyses
- The Full Analysis Set is defined as all subjects who received at least 1 cycle of study drug and have a baseline scan. The Full Analysis Set will be used for efficacy analyses.

For Part B:

- The Safety Set is defined as all subjects who received at least 1 dose of study drug. The Safety Set will be used for safety analyses
- The Full Analysis Set is defined as all subjects who received at least 1 cycle of study drug and have a baseline scan. The Full Analysis Set will be used for the primary and secondary efficacy analyses.

12.3 Statistical Analysis

The primary objective of this study is evaluation of safety (Parts A and B) and assessment of ORR in subjects with advanced endometrial cancer (Part B). The secondary objective is evaluation of anti-tumor activity based on radiological assessments of subjects.

The Sponsor Biometrics Department or designee will analyze the safety and efficacy data.

Methodological and related details (e.g., missing data) will be provided in the SAP.

This section presents a summary of the planned statistical analyses of efficacy and safety for this study. Statistical analysis details will be provided in the SAP for this study, which will be finalized before clinical database lock.

12.3.1 General Considerations

Continuous data will be summarized (by dose group and by nominal study day, if applicable) using the following descriptive summary statistics: the number of subjects (n), mean, standard deviation (SD), standard error (SE), median, minimum value (min), and maximum value (max). Categorical data will be summarized using counts and percentages. All subject data, including those derived, will be presented in the subject data listings; listings will display all subjects who were enrolled, regardless of whether or not they received study drug.

Analysis details will be presented in the study SAP.

12.3.2 Background Characteristics

12.3.2.1 Subject Disposition

The number and percentage of subjects in each disposition category (e.g., enrolled, included in Safety Set, included in DLT Evaluable Set, included in Full Analysis Set, discontinuing treatment, and discontinuing study, with a breakdown of the reasons for discontinuation) will be summarized by dose group, by concurrent regimen and study part, and overall.

12.3.2.2 Demographics and Baseline Characteristics

The following demographics and baseline characteristics will be summarized by dose group, by concurrent regimen and study part, and overall for the Safety Set: sex, race, age, weight, height, body mass index (BMI), type of primary malignancy, tumor stage (tumor-node-metastases), WHO performance status, time elapsed since cancer diagnosis, prior treatment with chemotherapy, prior treatment with radiation, duration of most recent cancer therapy, and medical history.

No statistical tests will be carried out to evaluate any baseline imbalance between dose groups.

12.3.2.3 Prior and Concomitant Medications

Medications taken 14 days before the Screening Visit and up to the Safety Follow-up Visit will be summarized by preferred term using the World Health Organization-Drug Dictionary Enhanced (WHO-DDE) for the Safety Set as frequency tables in 2 parts:

1. Prior medication: medication that started before the first dose of study drug, regardless of when dosing of the medication ended

2. Concomitant medication: medication received at or after the first dose of study drug, medication that was received before initial dosing and continued after initial dosing of study drug, or medication with missing stop date.

Medication that started before the first dose of study drug and continued after the first dose of study drug will be summarized as prior medication and separately as concomitant medication. Medications with a missing start date will be considered to have a start date before the first dose of study drug.

12.3.2.4 Study Drug Exposure and Compliance

Total number of cycles is defined as the maximum number of treatment cycles that a subject receives. Total cumulative dose (mg) is the sum of the actual doses that the subject receives across cycles. Total planned dose (mg) is the sum of the planned doses. The total number of cycles, total cumulative dose (mg), and total planned dose (mg) will be summarized. The study drug exposure will be summarized based on the Safety Set.

12.3.3 Determination of the MTD

The determination of the MTD is based on an adaptive BLRM guided by the EWOC principle using the methodology described in detail in Section 12.3.3.2. The MTD will be further evaluated for anti-tumor activity and overall tolerability during the dose expansion phase of the trial.

After the dose expansion phase (Part B), the final recommended dose for future development will be based on considerations of the MTD estimated by the BLRM, and on an overall clinical assessment of all available safety, tolerability, PK, and PD data from all cycles at all different dose levels tested, in both phases of the study. If it is determined that treatment at a dose of VX-984 in combination with PLD lower than the MTD established during the dose escalation of the study is better tolerated, and has a better PK/PD or efficacy profile based on clinical considerations, then that dose may be used in further development.

12.3.3.1 MTD

The MTD is defined as the highest dose combination for a given schedule that causes DLTs in no more than 33.3% of subjects during the first cycle of treatment. Estimation of the MTD during the dose escalation phase of the study will be based upon the posterior distribution of the incidence of DLT in Cycle 1 in subjects in the DLT Evaluable Set. The corresponding methodology is described in Section 12.3.3.2.The variable of interest for the determination of MTD is the frequency of DLTs associated with the administration of VX-984 in combination with PLD during the first cycle of treatment.

12.3.3.2 Statistical Model and Method of Analysis

An adaptive BLRM with ≥ 2 parameters, guided by the EWOC principle, will be used to make dose recommendations and estimate the MTD during the escalation phase of the study, with the following 2 exceptions:

- For cohorts requiring 3 or more evaluable subjects, if only 2 evaluable subjects are available for assessment (all others drop out), and neither subject has had a

treatment-related or possibly-related toxicity greater than CTCAE Grade 1, then 2 subjects will be considered sufficient for decision-making

- If the first 2 subjects in a cohort have DLTs, no additional subjects will be enrolled into that cohort until the Bayesian model has been updated with this new information. Likewise, the model will be re-evaluated if 2 subjects in a cohort have DLTs before the enrollment of any additional subjects.

The DLT relationship in the escalation part of the study will be described by the following BLRM**:**

$$logit\{\pi(d_j,\ x_1, \ldots,\ x_k)\} = \log(\alpha) + \beta \log\left(\frac{d_j}{d^*}\right) + \sum_{i=1}^{k} \gamma_i\, x_i$$

Under-dosing: $\pi(d) \in [0.00,\ 0.166)$

Target toxicity: $\pi(d) \in [0.166,\ 0.333)$

Excessive toxicity: $\pi(d) \in [0.333,\ 1.00]$

where logit(π) = ln(π/(1 - π)), where π is the probability of a DLT.

Prior specifications

Prior for (log(α), log(β)): A vague bivariate normal prior for the model parameters (log(α),log(β)) is elicited based on prior guesses (medians) from nonclinical data and wide confidence intervals for the probabilities of a DLT at each dose.

12.3.3.3 Dose Recommendation

Part A

After each cohort of subjects the posterior distribution for the model parameters will be obtained through Gibbs' sampling procedures by updating the prior distribution with the most up-to-date DLT information. Based on the posterior distribution of all model parameters, the corresponding posterior distributions for the probabilities of DLT at different dose levels are obtained. The results of this analysis are summarized in terms of the estimated probabilities that the true rate of DLT at each dose level will have of lying in each of the following intervals:

- [0, 0.166) under-dosing
- [0.166, 0.333) targeted toxicity
- [0.333, 1.00] excessive toxicity

Following the principle of EWOC, after each cohort of subjects the recommended dose is the one with the highest posterior probability of the DLT rate falling in the target interval [16.6%, 33.3%) among the doses fulfilling EWOC, i.e., it is unlikely (< 25% posterior probability) that the DLT rate at the dose falls in the excessive toxicity interval.

Note that the dose that maximizes the posterior probability of targeted toxicity is the best estimate of the MTD, but it may not be an admissible dose according to the overdose criterion if the amount of data is insufficient. If vague prior information is used for the

probabilities of DLT in the early stages of the study, this escalation procedure will reflect a conservative strategy.

The dose recommended by the adaptive BLRM may be regarded as guidance and information to be integrated with a clinical assessment of the toxicity profiles observed at the time of the analysis in determining the next dose level to be investigated.

The final recommended dose will be based on considerations of the MTDs estimated by the BLRM and on an overall clinical assessment of all available safety, tolerability, PK, and PD data from all cycles at all different dose levels tested.

Part B

Upon completion of the first cycle of treatment for at least 10 subjects within the dose expansion phase (Part B), if the observed DLT rate exceeds 33.3%, the BLRM will be re-run to confirm that the estimated MTD still satisfies the overdose criteria of the model. If the dose fails to satisfy the criteria, a change to the dose under study may be made according to the BLRM recommendation after review of the clinical data.

12.3.4 Efficacy Analysis

Efficacy data will be summarized by dose group, by concurrent regimen and study part, and overall. Efficacy data may also be summarized by type of primary malignancy.

12.3.4.1 Analysis of Primary Variables

For Part B, the primary approach to analyze the best overall response and overall response at each scheduled assessment will be based on the Full Analysis Set. The proportion of subjects achieving best overall response of (CR or PR), with exact 90% CI, will be provided. Also, the overall response at each scheduled assessment visit will be summarized.

Methodological details will be provided in the study SAP.

12.3.4.2 Analysis of Secondary Efficacy Variables

The proportion of subjects achieving a given categorical efficacy endpoint will be summarized by dose group, by concurrent regimen and study part, and separately for all subjects combined. For each proportion, a 90% CI will be reported using the exact method.

- Tumor response at scheduled assessment visit
- Disease control at scheduled assessment visit: disease control is defined as having CR, PR, or SD.

A supportive analysis will depict maximum percent decrease of the sum of target tumor length using a waterfall plot. The waterfall plot will show the bar for the subject with the largest positive change on the left, and the bar for the subject with the largest negative change on the right.

Time-to-event endpoints, such as PFS and OS, will be estimated via the Kaplan-Meier method if the number of events is adequate. For subjects achieving objective response (CR or PR), the response duration will be estimated. Methods that accommodate different censoring approaches will be specified with details in the SAP for the study.

Overall tumor response, target tumor, and non-target tumor assessment over time will be presented in an individual subject data listing.

12.3.4.3 Analysis of Other Variables

Not applicable

12.3.5 Safety Analysis

The overall safety profile of VX-984 will be assessed in terms of the following primary (safety) endpoints:

- Incidence of treatment-emergent adverse events (TEAEs)
- Incidence of DLTs (Part A)
- Clinical laboratory values
- ECG outcomes
- Echocardiogram outcomes
- Vital signs.

Safety data will be summarized by dose group, by concurrent regimen and study part, and overall. In general, safety analyses will be based on the Safety Set. The summary of DLTs will be based on the DLT Evaluable Set.

For safety variables, the scheduled Day 1, predose measurement will be used as the baseline value, when available; otherwise, the baseline value will be defined as the Day -1 measurement. If none of these values is available, the baseline value will be defined as the value at the Screening Visit.

All safety data will be presented in individual subject data listings.

12.3.5.1 Adverse Events

AEs will be coded according to MedDRA. The number and percentage of subjects experiencing an AE will be summarized by the MedDRA system organ class and preferred term, as well as by dose group, concurrent regimen and study part, and overall. AEs will be classified as pre-treatment or treatment-emergent.

Pre-treatment AEs are defined as AEs that were reported or worsened after signing the ICF up to the start of study drug dosing.

Treatment-emergent AEs are defined as AEs that were reported or worsened on or after the start of study drug dosing through the 28-day Safety Follow-up Visit.

Only TEAEs will be summarized in tables. All summaries of TEAEs will be presented by the severity of the AE and relationship to the study drug. Some rules that will apply to the summarization of AEs are (1) a subject with multiple occurrences of the same AE or a continuing AE will only be counted once; (2) only the maximum severity level will be presented in the severity summary; and (3) only the worst relationship level will be presented in the relationship summary.

AEs leading to death, serious adverse events (SAEs), dose interruption, and permanent discontinuation will be listed separately. All AEs through the Safety Follow-up Visit will be listed in an individual subject data listing, including pre-treatment AEs.

12.3.5.2 Clinical Laboratory Assessments

All statistical analyses of laboratory values will be performed using SI units. Hematology and clinical chemistry results will be summarized by dose group, concurrent regimen and study part, and overall at each scheduled time point. The number and percentage of subjects with shift changes from baseline based on the CTCAE toxicity grades will be tabulated. A listing of abnormal individual subject hematology and clinical chemistry values from scheduled and unscheduled time points will be provided. Grade 3 or higher toxicity laboratory values will be provided in an individual subject data listing. Urinalysis results will be listed only in individual subject data listings. These results will not be summarized. Clinically significant abnormal laboratory findings will be reported as AEs.

12.3.5.3 Electrocardiogram

A summary of raw values and change from baseline values will be provided by dose group, concurrent regimen and study part, and overall at each scheduled visit for the following ECG measurements: PR, QT, QRS, and QTc intervals and heart rate. In addition, the number and percentage of subjects by maximum on-treatment value of QT/QTc intervals, categorized as $\leq$ 450 msec, > 450 msec and $\leq$ 480 msec, > 480 msec and $\leq$ 500 msec, and > 500 msec, as well as maximum on-treatment change from baseline value of QT/QTc intervals, categorized as $\leq$ 30 msec, > 30 msec and $\leq$ 60 msec, and > 60 msec, will be provided. Clinically significant abnormal findings will be reported as AEs.

12.3.5.4 Echocardiogram

A summary of raw values and change from baseline values will be provided by dose group, concurrent regimen and study part, and overall at each scheduled visit for echocardiogram measurements (including left ventricular ejection fraction [LVEF]). In addition, the number and percentage of subjects by maximum on treatment decrease from baseline value in LVEF, categorized as 0 to $\leq$ 10%, > 10% and $\leq$ 20%, and > 20%, will be provided. Clinically significant abnormal findings will be reported as AEs.

12.3.5.5 Vital Signs

The following vital signs will be summarized by dose group, concurrent regimen and study part, and overall at each scheduled time point: systolic and diastolic blood pressure (mmHg), body temperature, pulse rate (bpm), and respiratory rate (breaths per minute). Clinically significant abnormal findings in vital signs will be reported as AEs.

12.3.5.6 Physical Examination

PE results will be presented in individual subject data listings only. Clinically relevant results identified after screening will be reported as AEs.

12.3.5.7 Other Safety Analysis

For Part A, incidence of DLTs will be presented by dose cohort.

12.3.6 Handling of Missing Values/Censoring/Discontinuations

- Subjects continuing to receive treatment will have time-to-event data (e.g., PFS) censored at the date of last radiological disease assessment before the cutoff date
- Partial or complete responses reported before any additional anti-cancer therapy will be considered as responses in the calculation of the ORR irrespective of the number of missed assessments before response
- Subjects with a best overall response of "Unknown" or "Not Assessed" per RECIST 1.1 will be considered as non-responders in estimating the ORR
- Continuing events (e.g., AEs, concomitant medication, etc.) will be summarized using the data cut-off date as the date of completion, with an indication within listings that the event is continuing
- For subjects who discontinue the study with ongoing events, the discontinuation date will be used as the completion date of the event with the appropriate censoring as described in the above bullet
- The reason for discontinuation from study will be summarized and listed, along with dates of first and last study drug, duration of exposure to study drug, and date of discontinuation for each subject, by dose group and expansion arm. Other missing data will be noted as missing in appropriate tables/listings.

12.3.7 Interim and IDMC Analyses

12.3.7.1 Interim Analysis

Interim analyses may be conducted for the purpose of data review and regulatory updates.

12.3.7.2 IDMC Analysis

Not applicable

12.4 Clinical Pharmacology Analysis

12.4.1 Pharmacokinetic Analysis

Upon receipt of bioanalytical data, VX-984 PK will be assessed on an ongoing basis during the dose escalation phase in Part A using standard noncompartmental analysis methods. When possible, PK results for VX-984 will be reviewed along with safety data to inform dose escalation.

Details of the analyses will be provided in a SAP.

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

13 PROCEDURAL, ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

13.1 Adverse Event and Serious Adverse Event Documentation, Severity Grading, and Reporting

13.1.1 Adverse Events

13.1.1.1 Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a subject during the study; the event does not necessarily have a causal relationship with the treatment. This includes any newly occurring event or worsening of a preexisting condition (e.g., increase in its severity or frequency) after the ICF is signed.

An AE is considered serious if it meets the definition in Section 13.1.2.1.

13.1.1.2 Clinically Significant Assessments

Study assessments including laboratory tests, ECGs, PEs, and vital signs, will be assessed and those deemed a clinically significant worsening from baseline documented as an AE. When possible, a clinical diagnosis for the study assessment will be provided, rather than the abnormal test result alone (e.g., urinary tract infection, anemia). In the absence of a diagnosis, the abnormal study assessment itself will be listed as the AE (e.g., bacteria in urine or decreased hemoglobin).

An abnormal study assessment is considered clinically significant if the subject has 1 or more of the following:

- Concomitant signs or symptoms related to the abnormal study assessment
- Further diagnostic testing or medical/surgical intervention
- A change in the dose of study drug or discontinuation from the study.

Repeat testing to determine whether the result is abnormal, in the absence of any of the above criteria, does not necessarily meet clinically significant criteria. The determination of whether the study assessment results are clinically significant will be made by the Investigator.

A laboratory value that is Grade 4 will not automatically be an SAE. A Grade 4 laboratory value will be an SAE if the clinical status of the subject indicates a life-threatening AE.

13.1.1.3 Documentation of Adverse Events

All AEs will be collected from the time ICF is signed until the following time points:

- For subjects who do not enroll: until time of screen failure (e.g., screen failure, withdrawal of consent)
- For enrolled subjects who have a Safety Follow-up Visit: through the Safety Follow-up Visit
- For enrolled subjects who do not have a Safety Follow-up Visit, the **earliest** of 28 days after the last dose of study drug.

All subjects will be queried, using non-leading questions, about the occurrence of AEs at each study visit. When possible, a constellation of signs and/or symptoms will be identified as 1 overall event or diagnosis. All AEs for enrolled subjects will be recorded in the CRF and source document. AEs for subjects who are screened but not subsequently enrolled in the study will be recorded only in the subject's source documents. The following data will be documented for each AE:

- Description of the event
- Classification of "serious" or "nonserious"
- Date of first occurrence and date of resolution (if applicable)
- Toxicity grade
- Causal relationship to study drug(s)
- Action taken
- Outcome
- Concomitant medication or other treatment given
- Indication of DLT (Part A).

13.1.1.4 Adverse Event Severity

The Investigator will determine and record the severity of all serious and non-serious AEs. The guidance available at the following website will be consulted: CTCAE, Version 4.0, Cancer Therapy Evaluation Program, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (Accessed August 2012). The severity of an AE that does not appear in the CTCAE will be determined according to the definitions in Table 13-1.

Table 13-1 Grading Scale for AEs That Are Not in CTCAE Scale

Classification	Definition
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)[a]
Grade 3	Severe or medical significant but not immediately life-threatening; hospitalization of prolongation of hospitalization indicated; disabling; limiting self-care ADL[b]
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

Note: A semi-colon indicates 'or' within the description of the grade.

[a] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

13.1.1.5 Adverse Event Causality

Every effort will be made by the Investigator to assess the relationship of the AE, if any, to the study drug(s). Causality will be classified using the categories presented in Table 13-2.

Table 13-2 Classifications for AE Causality

Classification	Definition
Related	There is an association between the event and the administration of investigational study drug, a plausible mechanism for the event to be related to the investigational study drug and causes other than the investigational study drug have been ruled out, and/or the event re-appeared on re-exposure to the investigational study drug.
Possibly related	There is an association between the event and the administration of the investigational study drug and there is a plausible mechanism for the event to be related to investigational study drug, but there may also be alternative etiology, such as characteristics of the subject's clinical status or underlying disease.
Unlikely related	The event is unlikely to be related to the investigational study drug and likely to be related to factors other than investigational study drug.
Not related	The event is related to an etiology other than the investigational study drug (the alternative etiology will be documented in the study subject's medical record).

13.1.1.6 Study Drug Action Taken

The Investigator will classify the study drug action taken with regard to the AE. The action taken will be classified according to the categories shown in Table 13-3.

Table 13-3 Classifications for Study Drug Action Taken With Regard to an AE

Classification	Definition
Dose not changed	Study drug dose not changed in response to an AE
Dose reduced	Study drug dose reduced in response to an AE
Drug interrupted	Study drug administration interrupted in response to an AE
Drug withdrawn	Study drug administration permanently discontinued in response to an AE
Not applicable	Action taken regarding study drug administration does not apply. "Not applicable" will be used in circumstances such as when the investigational treatment had been completed before the AE began and no opportunity to decide whether to continue, interrupt, or withdraw treatment is possible.

13.1.1.7 Adverse Event Outcome

An AE will be followed until the Investigator has determined and provided the final outcome. The outcome will be classified according to the categories shown in Table 13-4.

Table 13-4 Classifications for Outcome of an AE

Classification	Definition
Recovered/Resolved	Resolution of an AE with no residual signs or symptoms
Recovered/ Resolved With Sequelae	Resolution of an AE with residual signs or symptoms
Not Recovered/Not Resolved (Continuing)	Either incomplete improvement or no improvement of an AE, such that it remains ongoing
Fatal	Outcome of an AE is death. "Fatal" will be used when death is at least possibly related to the AE.
Unknown	Outcome of an AE is not known (e.g., a subject lost to follow-up)

13.1.1.8 Treatment Given

The Investigator ensures adequate medical care is provided to subjects for any AEs, including clinically significant laboratory values related to study drug. In addition, the Investigator will describe whether any treatment was given for the AE. "Yes" is used if any treatment was given in response to an AE, and may include treatments such as other medications, hospitalization, surgery, or physical therapy. "No" indicates the absence of any kind of treatment for an AE.

13.1.2 Serious Adverse Events

13.1.2.1 Definition of a Serious Adverse Event

An SAE is any AE that meets any of the following outcomes:

- Fatal (death, regardless of cause, that occurs during participation in the study or occurs after participation in the study and is suspected of being a delayed toxicity due to administration of the study drug)
- Life-threatening, such that the subject was at immediate risk of death from the reaction as it occurred

- Inpatient hospitalization or prolongation of hospitalization
- Persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- Congenital anomaly or birth defect
- Important medical event that, based upon appropriate medical judgment, may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above (e.g., an allergic bronchospasm requiring intensive treatment in an emergency room or at home).

If a subject has a hospitalization or procedure (e.g., surgery) for an event or condition that occurred before the subject signed the ICF, and the hospitalization or procedure was planned before the subject signed the ICF, the hospitalization or procedure will not be considered to indicate an SAE, unless an AE caused the hospitalization or procedure to be rescheduled sooner or to be prolonged relative to what was planned. In addition, hospitalizations clearly not associated with an AE (e.g., social hospitalization for purposes of respite care) will not be considered to indicate an SAE.

Clarification will be made between the terms "serious" and "severe," because they are not synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event, as in mild, moderate, or severe myocardial infarction. The event itself, however, may be of relatively minor medical significance, such as a severe headache. This is not the same as "serious," which is based on subject/event outcome or action described above, and is usually associated with events that pose a threat to a subject's life or functioning. Seriousness, not severity, serves as a guide for defining expedited regulatory reporting obligations.

13.1.2.2 Documentation of Serious Adverse Events

All SAEs that occur after obtaining informed consent and assent (where applicable) through the Follow-up Visit, regardless of causality, will be reported by the Investigator to the Sponsor GPS. In addition, all SAEs that occur after the Safety Follow-up Visit and are considered related to study drug(s) will be reported to the Sponsor GPS **within 24 hours**.

SAEs will be recorded on the Sponsor Organized Safety Information Collection Form (hereafter referred to as the "SAE Form") using a recognized medical term or diagnosis that accurately reflects the event. SAEs will be assessed by the Investigator for relationship to the investigational study drug(s) and possible etiologies. On the Clinical Trials SAE Form, relationship to study drug(s) will be assessed only as related (includes possibly related) or not related (includes unlikely related), and severity assessment will not be required. For the purposes of study analysis, if the event has not resolved at the end of the study reporting period, it will be documented as ongoing. For purposes of regulatory safety monitoring, the Investigator is required to follow the event to resolution and report to the Sponsor the outcome of the event using the Sponsor Clinical Trials SAE Form.

13.1.2.3 Reporting Serious Adverse Events

The Investigator is responsible for notifying the sponsor or designee in writing within 24 hours of identifying an SAE, regardless of relationship to the investigational study drug,

using the SAE Report Form following specific completion instructions. Names, addresses, and telephone and fax numbers for SAE reporting will be included in the study specific SAE Report Form. Investigators are asked to report any new information on previously reported SAEs as follow-up report as soon as it becomes available to ensure timely reporting to health authorities.

In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone; in these cases, a written report must be sent immediately thereafter by fax or e-mail.

Relevant pages from the eCRF may be provided in parallel (for example, medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (for example, laboratory results, hospital report, autopsy report). In all cases, the information provided on the SAE Report Form must be consistent with the data about the event recorded in the eCRF.

The Investigator must respond to any request for follow-up information (eg, additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor/designee may have on the AE within the same timelines as those noted above for initial reports. This is necessary to ensure prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made via the responsible monitor, although in exceptional circumstances the Global Patient Safety department may contact the Investigator directly to obtain further information or to discuss the event.

13.1.2.4 Expedited Reporting and Investigator Safety Letters

The Sponsor is responsible for reporting suspected, unexpected, serious adverse reactions (SUSARs) involving the study drug(s) to all regulatory authorities and participating Investigators in accordance with ICH Guidelines and/or local regulatory requirements, as applicable. In addition, the Sponsor, or authorized designee, will be responsible for the submission of safety letters to central independent ethics committees (IECs).

It is the responsibility of the Investigator or designee to promptly notify the local institutional review board (IRB)/local IEC of all unexpected serious adverse drug reactions involving risk to human subjects.

13.2 Administrative Requirements

13.2.1 Ethical Considerations

The study will be conducted in accordance with the current ICH GCP Guidelines, which are consistent with the ethical principles founded in the Declaration of Helsinki, and in accordance with local applicable laws and regulations. The IRB/IEC will review all appropriate study documentation to safeguard the rights, safety, and well-being of the subjects. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, sample ICF, advertisements (if applicable), written information given to the subjects (including diary cards), safety updates, annual

progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator or the Sponsor, as allowable by local applicable laws and regulations.

13.2.2 Subject Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from the subject or legal representative or guardian (if applicable), before study participation. The method of obtaining and documenting the informed consent and assent (if applicable) and the contents of the consent will comply with ICH GCP and all applicable laws and regulations and will be subject to approval by the Sponsor or its designee.

13.2.3 Investigator Compliance

No modifications to the protocol will be made without the approval of both the Investigator and the Sponsor. Changes that significantly affect the safety of the subjects, the scope of the investigation, or the scientific quality of the study (i.e., efficacy assessments) will require IRB/IEC notification before implementation, except where the modification is necessary to eliminate an apparent immediate hazard to human subjects. The Sponsor will submit all protocol modifications to the required regulatory authorities.

When circumstances require an immediate departure from procedures set forth in the protocol, the Investigator will contact the Sponsor to discuss the planned course of action. If possible, contact will be made before the implementation of any changes. Any departures from protocol will be fully documented in the source documentation and in a protocol deviation log.

13.2.4 Access to Records

The Investigator will make the office and/or hospital records of subjects enrolled in this study available for inspection by the Sponsor or its representative at the time of each monitoring visit and for audits. The records will also be available for direct inspection, verification, and copying, as required by applicable laws and regulations, by officials of the regulatory health authorities (FDA and others). The Investigator will comply with applicable privacy and security laws for use and disclosure of information related to the research set forth in this protocol.

13.2.5 Subject Privacy

To maintain subject confidentiality and to comply with applicable data protection and privacy laws and regulations, all CRFs, study reports, and communications relating to the study will identify subjects by assigned subject numbers and access to subject names linked to such numbers shall be limited to the site and the study doctor and shall not be disclosed to the Sponsor. As required by applicable laws and regulations in the countries in which the study is being conducted, the Investigator will allow the Sponsor and/or its representatives access to all pertinent medical records to allow for the verification of data gathered in the CRFs/SAE forms and the review of the data collection process. The FDA and regulatory authorities in other jurisdictions, including the IRB/EC, may also request access to all study records, including source documentation, for inspection.

For sites participating in the study in the US, and in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and associated regulations, an executed HIPAA

authorization shall be obtained by the site from each subject (or the legal representative of the subject) before research activities may begin. Each HIPAA authorization shall comply with all HIPAA requirements including authorization allowing the site access to and use of the subject's personally identifiable health information, authorization for the site to disclose such information to the Sponsor, the FDA, and other parties requiring access under the protocol, and statements as to the purpose for which such information may be used and for how long.

13.2.6 Record Retention

The Investigator will maintain all study records according to ICH GCP guidelines and/or applicable local regulatory requirement(s), whichever is longest, as described in the Clinical Trial Agreement. If the Investigator withdraws from the responsibility of keeping the study records, custody will be transferred to a person willing to accept the responsibility and the Sponsor will be notified.

13.2.7 Study Termination

At any time, the Sponsor may terminate this study in its entirety or may terminate this study at any particular site. In addition, for reasonable cause, either the Investigators or their IRBs/IECs may terminate the study at their center.

Conditions that may lead to reasonable cause and warrant termination include, but are not limited to:

- Subject or Investigator noncompliance
- Unsatisfactory subject enrollment
- Lack of adherence to protocol procedures
- Lack of evaluable and/or complete data
- Potentially unacceptable risk to study subjects
- Decision to modify drug development plan
- Decision by the FDA or other regulatory authority.

Written notification that includes the reason for the clinical study termination is required.

13.3 Data Quality Assurance

The Sponsor or its designated representative will conduct a study site visit to verify the qualifications of each Investigator, inspect clinical study site facilities, and inform the Investigator of responsibilities and procedures for ensuring adequate and correct study documentation.

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. Study data for each enrolled subject will be entered into a CRF by study site personnel using a secure, validated web-based electronic data capture (EDC) application. The Sponsor will have read-only access to site-entered clinical data in the EDC application.

Instances of missing, discrepant, or uninterpretable data will be queried with the Investigator for resolution. Any changes to study data will be made to the CRF and documented in an audit trail, which will be maintained within the clinical database.

13.4 Monitoring

Monitoring and auditing procedures developed or approved by the Sponsor will be followed to comply with GCP guidelines. On-site checking of the CRFs/SAE Forms for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

The study will be monitored by the Sponsor or its designee. Monitoring will be done by personal visits from a representative of the Sponsor, or designee (study site monitor), who will review the CRFs/SAE Forms and source documents. The study site monitor will ensure that the investigation is conducted according to the protocol design and regulatory requirements.

13.5 Electronic Data Capture

The Sponsor will provide the study sites with secure access to and training on the EDC application sufficient to permit study site personnel to enter or correct information in the CRFs on the subjects for which they are responsible.

A CRF will be completed for each enrolled study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the subject's CRF. Source documentation supporting the CRF data will indicate the subject's participation in the study and will document the dates and details of study procedures, AEs, other observations, and subject status.

The Investigator, or designated representative, will complete the CRF as soon as possible after information is collected.

The audit trail entry will show the user's identification information and the date and time of any correction. The Investigator will provide formal approval of all the information in the CRFs, including any changes made to the CRFs, to endorse the final submitted data for the subjects for whom the Investigator is responsible.

The Sponsor will retain the CRF data and corresponding audit trails. A copy of the final archival CRF in the form of a CD or other electronic media will be placed in the Investigator's study file.

13.6 Publications and Clinical Study Report

13.6.1 Publication of Study Results

Any and all scientific, commercial, and technical information disclosed by the Sponsor in this protocol or elsewhere will be considered the confidential and proprietary property of the Sponsor. The Investigator shall hold such information in confidence and shall not disclose the information to any third party except to such of the Investigator's employees and staff as have been made aware that the information is confidential and who are bound to treat it as such and to whom disclosure is necessary to evaluate that information. The Investigator shall not use such information for any purpose other than determining mutual interest in

performing the study and, if the parties decide to proceed with the study, for the purpose of conducting the study.

The Investigator understands that the information developed from this clinical study will be used by the Sponsor in connection with the development of the study drug and other drugs and diagnostics, and therefore may be disclosed as required to other clinical Investigators, business partners and associates, the FDA, and other government agencies. The Investigator also understands that, to allow for the use of the information derived from the clinical study, the Investigator has the obligation to provide the Sponsor with complete test results and all data developed in the study.

No publication or disclosure of study results will be permitted except under the terms and conditions of a separate written agreement between the Sponsor and the Investigator and/or the Investigator's institution.

13.6.2 Clinical Study Report

A clinical study report, written in accordance with the ICH E3 Guideline, will be submitted in accordance with local regulations.

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15 PROTOCOL SIGNATURE PAGES

15.1 Sponsor Signature Page

Protocol #: VX15-984-001	Version #: 4.0	Version Date: 21 August 2017
Study Title: An Open-Label, Phase I, First-in-Human Study of the Safety, Tolerability, and Pharmacokinetic/Pharmacodynamic Profile of VX-984 in Combination With Chemotherapy in Subjects With Advanced Solid Tumors		

This Clinical Trial Protocol has been reviewed and approved by the sponsor.

PPD

Printed Name

PPD

Signature

PPD

Title

28-Aug-2017

Date

15.2 Investigator Signature Page

Protocol #: VX15-984-001	Version #: 4.0	Version Date: 21 August 2017
Study Title: An Open-Label, Phase I, First-in-Human Study of the Safety, Tolerability, and Pharmacokinetic/Pharmacodynamic Profile of VX-984 in Combination With Chemotherapy in Subjects With Advanced Solid Tumors		

I have read Protocol VX15-984-001, Version 4.0 and agree to conduct the study according to its terms. I understand that all information concerning VX-984 and this protocol supplied to me by EMD Serono Research & Development Institute is confidential.

PPD

Printed Name

PPD

Signature

August 30, 2017

Date