Integrated Analysis Plan

Clinical Trial Protocol Identification No.	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
Trial Phase	Phase I
Investigational Medicinal Product(s)	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
Clinical Trial Protocol Version	21 August 2017 / Version 4.0 including Amendment 1 and 2
Integrated Analysis Plan Author	**Coordinating Author** PPD, Merck — PPD **Function** — **Author(s) / Data Analyst(s)** PPD, PPD — PPD PPD, Merck — PPD
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Integrated Analysis Plan Reviewers	**Function** — **Name** PPD, PPD — PPD PPD, Merck — PPD PPD, Merck — PPD PPD, Merck — PPD PPD, Merck — PPD PPD, Merck — PPD PPD, Merck — PPD PPD, Merck — PPD PPD, Merck — PPD PPD, Merck — PPD PPD, Merck — PPD

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Integrated Analysis Plan: MS201926-0001

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

Merck responsible	Date
PPD, PPD	Via ELDORADO approval process
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1 Table of Contents

2 List of Abbreviations and Definition of Terms

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BLRM	Bayesian logistic regression model
BMI	Body Mass Index
BOR	Best Overall Response
BSA	Body Surface Area
CI	Confidence Interval
CRF	Case Report Form
CR	Complete Response
CSR	Clinical Study Report
CT	Computed Tomography
CTC	Common Terminology Criteria
CV	Coefficient of Variation
DCR	Disease Control Rate
DLT	Dose-Limiting Toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FAS	Full Analysis Set
IAP	Integrated Analysis Plan
ICH	International Conference on Harmonization
LVEF	Left Ventricular Ejection Fraction
Max	Maximum
Min	Minimum
Mean	Arithmetic Mean
Median	Median
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerated Dose
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NE	Not Evaluable
ORR	Objective Response Rate

PAS	Pharmacokinetic Analysis Set
PD	Progressive Disease
PLD	Pegylated Liposomal Doxorubicin
PT	Preferred Term
PK	Pharmacokinetic
PR	Partial Response
Q1	25th Percentile
Q3	75th Percentile
QD	Once Daily
QTcF	QT interval with Frederica's correction
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SAF	Safety
SCR	Screening
SD	Stable Disease
SDTM	Study Data Tabulation Model
SOC	System Organ Class
StDev	Standard Deviation
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
UNK	Unknown
WHO-DD	World Health Organization Drug Dictionary

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	26 January 2018	PPD	First version.

4 Purpose of the Integrated Analysis Plan

The purpose of this Integrated Analysis Plan (IAP) is to document technical and detailed specifications for the final analysis of data collected for protocol MS201926-0001. Results of the analyses described in this IAP will be included in the Clinical Study Report (CSR). Additionally, the planned analyses identified in this IAP will be included in regulatory submissions or future manuscripts. Any post-hoc, or unplanned analyses performed to provide results for inclusion in the CSR but not identified in this prospective IAP will be clearly identified in the CSR.

The IAP is based upon section 12 (Statistics) of the trial protocol and protocol amendments and is prepared in compliance with International Conference on Harmonization (ICH) E9.

5 Objectives and Endpoints

	Objective	Endpoint	IAP section
Primary Objective	• 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	• Safety parameters, including adverse events (AEs), dose-limiting toxicities (DLTs), clinical laboratory values (serum chemistry and hematology), vital signs, echocardiogram, and electrocardiogram (ECG) assessments	15
	• To determine the maximum tolerated dose (MTD) of VX-984 in combination with PLD in subjects with advanced solid tumors.	• MTD of VX-984 in combination with PLD.	15.1
Secondary Objective	• To evaluate the pharmacokinetics (PK) of VX-984 when administered alone and in combination with PLD in subjects with advanced solid tumors	• Plasma PK parameter estimates of VX-984, administered alone and in combination with PLD, derived from plasma concentration-time data	16.1
	• To evaluate the PK of PLD when administered in combination with VX-984 in subjects with advanced solid tumors	• Plasma PK parameter estimates of PLD administered in combination with VX-984, derived from plasma concentration-time data	16.1
	• To evaluate preliminary antitumor activity of VX-984 in combination with PLD in subjects with advanced solid tumors.	• Preliminary evidence of anti-tumor activity, including tumor response as evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and tumor markers.	14.1

	Objective	Endpoint	IAP section
Exploratory Objective	• 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.	• 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]	16.2

6 Overview of Planned Analyses

There are no interim analyses planned for this study.

6.1 Final Analysis

All final, planned analyses identified in the Clinical Trial Protocol and in this IAP will be performed only after the last subject has completed the treatment phase of the trial with all trial data in-house, all data queries resolved, and the database locked.

A data review meeting will be held prior to database lock. In addition, no database can be locked until this IAP has been approved.

7 Changes to the Planned Analyses in the Clinical Trial Protocol

The following changes were made in this IAP.

- Due to management decision, Part B from the protocol will not be further pursued. Therefore only Part A from the protocol is covered in this IAP.
- Analysis of exploratory endpoints from the protocol will not be performed.
- Listings will be presented based on the same analysis population as used in corresponding tables, which deviates from the requirement from the protocol: “listings will include all subjects who were enrolled, regardless of whether or not they received study treatment.”
- Analysis of PK will not be performed, concentrations of VX-984 and PLD will only be listed by subject and nominal time.
- The definition of Full Analysis Set (FAS) from the protocol, to be used for efficacy analyses, is not used in this IAP. The updated version of FAS is defined in Section 8.2.

Definition of FAS per protocol: The FAS is defined as all subjects who received at least 1 cycle of study drug and have a baseline scan.

8 Protocol Deviations and Analysis Sets

8.1 Definition of Protocol Deviations

Protocol deviations will be collected by site monitoring and included in clinical trial management system log, no analysis planned.

8.2 Definition of Analysis Sets

Screening Analysis Set (SCR)

The SCR includes all subjects who provided informed consent.

Safety Analysis Set (SAF)

The SAF will include all enrolled subjects who received at least 1 dose of study treatment. Analyses performed on the SAF will consider subjects as treated.

Dose-Limiting Toxicity Evaluable Set (DLT)

The DLT will include all subjects in the SAF 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.

Subjects who do not have a DLT during Cycle 1 will be excluded from the DLT Evaluable Set if the subject does not satisfy either of the following criteria:

- Minimum exposure criterion

  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.

- Completion of Cycle 1

  A subject is considered to have sufficient safety evaluations if the subject has been observed through the end of Cycle 1, which is defined as up to 28 days after the start of study treatment from Cycle 1.

Subjects who have been replaced by Safety Monitoring Committee decision will also be excluded from this analysis set.

Full Analysis Set (FAS)

The FAS will include all enrolled subjects who received at least 1 dose of study treatment.

As the FAS is identical to the SAF, the term FAS/SAF will be used to reflect that those analysis sets contain the same subjects.

Pharmacokinetic Analysis Set (PAS)

The PAS will include of all subjects who receive at least 1 dose of VX-984 or PLD and provide at least one measurable post-dose concentration of VX-984 or one measurable post-dose concentration of PLD. Subjects will be analyzed according to the actual treatment they received. All PK listings will be based on this analysis set.

Use of analysis sets is described in Table 2.

Table 2 Summary of Analysis and Associated Analysis Set

Analyses	SCR	FAS/SAF	DLT	PAS
Dispositions and deaths	✓			
Baseline Assessments		✓		
Past and Concomitant Therapies		✓		
Compliance and Exposure		✓		
Efficacy		✓		
Safety: MTD (Primary endpoint)			✓	
Safety and Tolerability		✓		
PK				✓

9 General Specifications for Data Analyses

Unless otherwise indicated, summary tables will be presented by dose group and overall based on the analysis set of interest; listings will be presented using the same analysis sets as corresponding tables.

Data handling after cut-off date:

Data after cut-off do not undergo the cleaning process. The only exceptions are the date of death and the date last known to be alive, per the source data from the "Long-Term Follow-Up" case report form (CRF) page.

Data other than the date of death and the date last known to be alive obtained after the cut-off will not be displayed in any listings or used for summary statistics, e.g. laboratory values of samples taken after data cut-off, AEs with onset date after data cut-off, etc. will not be included in any analysis or listing.

Pooling of centers:

Because of the high number of participating centers and the anticipated small number of subjects enrolled in each center, data will be pooled across centers.

Presentation of continuous and qualitative variables:

Continuous variables will be summarized using descriptive statistics, i.e.

- Number of subjects, number of subjects with non-missing values (n)
- Arithmetic mean (Mean), standard deviation (StDev)
- Median, 25th Percentile - 75th Percentile (Q1-Q3)
- Minimum (Min), maximum (Max)

If there are missing values, the number of subject counts and percentage should be indicated by a 0 (0.0).

Missing statistics, e.g. when they cannot be calculated, should be presented as "nd". For example, if n=1, the standard deviation cannot be computed and should be presented as "nd".

Qualitative variables will be summarized by counts and percentages.

Unless otherwise stated the calculation of proportions will be based on the number of subjects in the analysis set of interest. Therefore counts of missing observations will be included in the denominator and presented as a separate category.

In case the analysis refers only to certain visits, percentages will be based on the number of subjects still present in the trial at that visit, unless otherwise specified.

Presentation of PK Concentration Data

VX-984 and PLD concentration data will only be listed.

Presentation of PK Data

No PK parameter data will presented.

Definition of treatment day:

Treatment day is defined relative to the start of study treatment (either VX-984 or PLD) from Cycle 1.

Treatment Day 1 is defined as the day of the first administration of study treatment from Cycle 1. The day before is defined as Treatment Day -1 (no Treatment Day 0 is defined). Per protocol, the day of first administration of study treatment in Lead-in Period is Treatment Day -14.

Definition of baseline:

Baseline is defined as the last non-missing measurement prior to the first administration of study treatment (either VX-984 or PLD, whatever is earlier), including the Lead-in Period if available.

Definition of duration:

Duration will be calculated by the difference of start and stop date + 1 (e.g. survival time (days) = date of death – date of randomization + 1) (if not otherwise specified).

The time since an event (e.g. time since first diagnosis) will be calculated as reference date minus date of event.

Unscheduled visits:

Data collected at unscheduled visits will be included and analyzed for both safety and efficacy analyses in the same fashion as the data collected at scheduled visits except where otherwise noted. Assessments from unscheduled visits will be used for the derivation of baseline values and worst on-treatment values. However, descriptive statistics by nominal visit or time point for safety endpoints such as laboratory measurements, ECGs and vital signs will include only data from scheduled visits per protocol**.**

Conversion factors:

The following conversion factors will be used to convert days into months or years: 1 month = 30.4375 days, 1 year = 365.25 days.

Handling of missing data:

Unless otherwise specified, missing data will not be replaced.

In all subject data listings imputed values will be presented. In all listings imputed information will be flagged.

Missing statistics, e.g. when they cannot be calculated, should be presented as “nd”. For example, if n=1, the measure of variability (StdDev) cannot be computed and should be presented as “nd”.

SAS version:

If not stated otherwise, analyses will be performed using SAS® Software version 9.4 or higher.

10 Trial Subjects

The subsections in this section include specifications for reporting subject disposition and treatment/trial discontinuations.

10.1 Disposition of Subjects and Discontinuations

Analysis Set: SCR

A primary table of subject disposition will be provided by dose group and overall:

- Number of screened subjects (overall column only)
- Number of subjects discontinued prior to treatment start (either VX-984 or PLD)

- Number of subjects who continued beyond screening
- Number of subjects who were treated in Lead-in Period
- Number of subjects who were treated in Lead-in Period or Treatment Period
- Number of subjects who completed treatment of VX-984 (discontinuation due to progressive disease or death)
- Number of subjects who completed treatment of PLD (discontinuation due to progressive disease or death)
- Number of subjects discontinued from VX-984 (discontinuation reasons other than progressive disease or death), overall and by reason
- Number of subjects discontinued from PLD (discontinuation reasons other than progressive disease or death), overall and by reason
- Number of subjects who entered the Long-Term Follow-up Period
- Number of subjects alive in the Long-Term Follow-up Period, by subgroups of alive status (subjects alive without progressive disease or new anticancer therapy; subjects progressed; subjects started new anticancer therapy; subjects withdrew consent from the Long-Term Follow-up Period.)
- Number of subjects who completed the trial (including Follow-up Period, per "End of Follow-Up" page from CRF).
- Number of subjects discontinued from trial (including Follow-up Period) overall and by reason (per "End of Follow-Up" CRF page).

A second summary table on analysis sets will be generated by dose group and overall, unless specified otherwise:

- Number of subjects in SCR (overall column only)
- Number of subjects in FAS/SAF
- Number of subjects in DLT
- Number of subjects in PAS

A third summary table will display the number of subjects overall, in each country and in each site (per analysis set).

A listing of subject disposition will include the following information (as applicable): dose group, subject identification number, date of informed consent form, reason for screen failure, date of first and last dose of study treatment (VX-984 and PLD respectively), inclusion or exclusion to the analysis set of: SCR, FAS/SAF and DLT.

A second listing will include the following trial discontinuation information: dose group, subject identification number, end of trial status (completed, ongoing, discontinued), the reason for trial

discontinuation, the date of trial termination, trial duration (with respect to the date of informed consent), and the date of first and last dose of study treatment (VX-984 and PLD respectively).

A third listing will include the following VX-984 discontinuation information: dose group, subject identification number, end of treatment status (completed, ongoing, discontinued), the reason for VX-984 discontinuation, and the date of first and last dose of VX-984.

A fourth listing will include the following PLD discontinuation information: dose group, subject identification number, end of treatment status (completed, ongoing, discontinued), the reason for PLD discontinuation and the date of first and last dose of PLD.

In addition, a listing including long-term follow-up information will be provided with the following information: dose group, subject identification number, date of contact, live status, date of progression, date of a new therapy, date of withdrawal from long-term follow-up and date lost to follow-up.

10.2 Protocol Deviations

As indicated in Section 8.1, protocol deviation data will not be analyzed.

A listing on subjects excluded from the DLT will be produced, indicating the reason for exclusion.

11 Demographics and Other Baseline Characteristics

11.1 Demographics

Analysis Set: FAS/SAF

Demographic characteristics will be summarized using the following information from the "Demography" CRF pages.

- Gender: male, female
- Race: White, Black or African American, Asian, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, not collected and other
- Ethnicity: Hispanic or Latino, not Hispanic or Latino and not collected
- Age (years): summary statistics
- Age categories:
    - < 65 years, ≥ 65 years
    - 65-74 years, 75-84 years, ≥ 85 years

Specifications for computation:

- Age (years) = (date of given informed consent - date of birth + 1) / 365.25

In case of missing day for at least one date, but month and year available for both dates:

- For the derivation of age, the day of informed consent and the day of birth will be set to 1 and the formula above will be used

In case of missing month for at least one date, but year available for both dates:

- For the derivation of age, the day and the month of informed consent and the day and month of birth will be set to 1 and the formula above will be used

All relevant demographic data will be presented in data listings.

11.2 Medical History

Analysis Set: FAS/SAF

The medical history will be summarized from the "Medical History" CRF page, using the latest version of Medical Dictionary for Regulatory Activities (MedDRA), preferred term (PT) as event category and MedDRA system organ class (SOC) body term as Body System category.

Medical history will be displayed in terms of frequency tables: ordered by primary SOC and PT in alphabetical order by dose group and overall.

A supportive listing of medical history data by subject will include all the relevant data fields as collected on the "Medical History" CRF pages.

11.3 Other Baseline Characteristics

Analysis Set: FAS/SAF

Information on other baseline characteristics are collected from "Vital Signs", "ECOG Performance Status" and "Primary Malignancy" pages from CRF. The following characteristics will be summarized at baseline by dose group and overall.

- Height at Baseline (cm): summary statistics
- Weight at Baseline (kg): summary statistics
- Body mass index (BMI) at baseline (kg/m^2): summary statistics
- Eastern Cooperative Oncology Group (ECOG) performance status: 0, 1, 2, 3, 4, 5
- Summary of primary malignancy will include the following variables:
  - Number of subjects with at least one of primary malignancy
  - Primary malignancy: endometrial cancer, non-small cell lung cancer, small cell lung cancer, breast cancer, ovarian cancer, colorectal cancer, lymphoma, prostate cancer, other
  - Histopathological grade of primary malignancy: G1, G2, G3, GX, other
  - TNM staging at diagnosis: T, N, M and associated sub-categories
  - Stage at diagnosis: IA, IB, IIA, IIB, III, IIIA, IIIB, IV, other

- Time elapsed since diagnosis of primary malignancy (months): summary statistics

Specifications for computation:

- BMI (kg/m^2) = weight(kg)/[height(m)]^2

Baseline characteristics with respect to vital signs, physical examinations, and hematology/biochemistry will be part of Section 15 (Safety Evaluation).

All relevant baseline characteristics data will be presented in data listings.

11.4 Disease History

Analysis Set: FAS/SAF

The prior anticancer treatments and procedures are collected under "Prior anti-cancer therapy", "Prior radiotherapy" and "Prior cancer surgery" pages from the CRF.

Summary of prior anticancer therapy/radiotherapy will include the following variables:

- Type of therapy: chemotherapy, hormonal therapy, immunotherapy, investigational therapy, other
- Regimen number of prior anticancer therapy: neoadjuvant, adjuvant, regimen 1,…, regimen 10, unknown
- Best response to regimen from prior anticancer therapy: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), not evaluable (NE), unknown
- Last recorded response to regimen from prior anticancer therapy: CR, PR, SD, PD, NE, unknown
- Time elapsed since most recent anticancer therapy (months): summary statistics
- Duration of most recent anticancer therapy (months): summary statistics
- Location of radiotherapy: brain, breast, lung, pleura, head and neck, esophagus, spinal cord, vertebrae, lymph nodes, bone, other

The listings of prior anticancer therapies will also be provided: a) listing of prior anticancer therapy; b) listing of prior radiotherapy and c) listing of prior cancer surgery. These will include subject identifier and all the relevant collected data-fields on the corresponding CRF pages.

12 Previous or Concomitant Medications/Procedures

Previous or concomitant medications will be summarized from the CRF page of "Previous and Concomitant medications", using the analysis population as indicated below.

Handling of missing data:

For identification of previous or concomitant medications/procedures, no formal imputation will be performed on missing or incomplete dates. Rules presented in Tables 3 and Table 4 will be used

to define if a medication/procedure is considered as a previous, concomitant or both previous and concomitant medication/procedure.

Table 1: Stopping rules for medication/procedure end dates

End date of medication/procedure			Stopping rule
Day	**Month**	**Year**	
UNK	UNK	UNK	After treatment start (ongoing)
UNK	UNK	< Treatment start (year)	Before treatment start
UNK	UNK	≥ Treatment start (year)	After treatment start
UNK	< Treatment start (month and year)		Before treatment start
UNK	≥ Treatment start (month and year)		After treatment start
< Treatment start (complete date)			Before treatment start
≥ Treatment start (complete date)			After treatment start

UNK = unknown.

Table 2: Rules to define previous and/or concomitant medications

Start date of medication/procedure			Stopping rule (see Table 3)	Medication/procedure
Day	**Month**	**Year**		
UNK	UNK	UNK	Before treatment start	Previous
UNK	UNK	UNK	After treatment start	Previous and concomitant
UNK	UNK	≤ Treatment start (year)	Before treatment start	Previous
UNK	UNK	≤ Treatment start (year)	After treatment start	Previous and concomitant
UNK	UNK	> Treatment start (year) and ≤ Treatment end + 30 days (year)	After treatment start	Concomitant
UNK	≤ Treatment start (month and year)		Before treatment start	Previous
UNK	≤ Treatment start (month and year)		After treatment start	Previous and concomitant
UNK	> Treatment start (month and year) and ≤ Treatment end + 30 days (month and year)		After treatment start	Concomitant
≤ Treatment start (date)			Before treatment start	Previous
≤ Treatment start (date)			After treatment start	Previous and concomitant
> Treatment start (date) and ≤ Treatment end + 30 days (date)			After treatment start	Concomitant

UNK = unknown.

12.1 Previous Medications

Analysis Set: FAS/SAF

Previous medications are medications, other than study medications and pre-medications for study treatment, which started before the date of first dose of study treatment (including the Lead-in Period, if any), regardless of when dosing of the medication ended.

To summarize previous medications, Anatomical Therapeutic Chemical (ATC) -2nd level and preferred term will be tabulated as given from the latest version of World Health Organization Drug Dictionary (WHO-DD) dictionary. In case multiple ATCs are assigned to a drug, all ATC-2nd level will be used for reporting.

In case the date values will not allow to unequivocally allocate a medication to previous medication, the medication will be considered as previous medication.

Previous medications will also be listed. The listing will include: subject identification number, dose group and all corresponding collected data-fields on the corresponding CRF page.

12.2 Concomitant Medications

Analysis Set: FAS/SAF

Concomitant treatments are medications, other than study medications, which are taken by subjects any time on-trial (on or after the first day of trial drug treatment for each subject, including the Lead-In Period, if any) or within 30 days after last dose of trial drug.

To summarize concomitant medications, ATC-2nd level and preferred term will be tabulated as given from the latest version of WHO-DD dictionary. In case multiple ATCs are assigned to a drug, all ATC-2nd level will be used for reporting. In case the date values will not allow to unequivocally allocating a medication to concomitant medication the medication will be considered as concomitant medication.

Medications that started before first dose of study treatment from the Lead-in Period, and continued after the first dose of study treatment from the Lead-in Period will be summarized as previous medications and separately as concomitant medications.

All relevant concomitant medication data will be listed, including flags for those medications that started after 30 days of the last dose of study treatment (VX-984 or PLD).

12.3 Concurrent Procedures

Analysis Set: FAS/SAF

Concurrent procedures, which were undertaken any time during the on-treatment period, will be listed according to the CRF page "Non-Pharmacological Treatment or Procedures".

In case the date values will not allow to unequivocally allocating a procedure to concurrent procedure, the procedure will be considered as concurrent procedure.

A listing of concurrent procedures will be created with the relevant information collected on the corresponding CRF page, including flags for procedures that took place prior to, on or after the date of first dose of study treatment (VX-984 or PLD), or after 30 days of the last dose of study treatment (VX-984 or PLD).

13 Treatment Compliance and Exposure

Analysis Set: FAS/SAF

All dosing calculations and summaries will be based on "Study Drug Administration: 984" and "Study Drug Administration: PLD" CRF pages.

- VX-984 is taken by consumption of dosing powder once daily (QD) on Days -14 to -12 as a single agent during a 14-day Lead-in Period, and Days 2 to 4 in a 28-day treatment cycle.
- PLD is administered by infusion to be taken on Day 1 in a 28-day treatment cycle.

Unless specified otherwise, Treatment Period refers to the dosing period that started from Cycle 1 Day 1 (Treatment Day 1); and Lead-in Period refers to the dosing period prior to Treatment Day1, (See the definition of Treatment Day in Section 9).

Total number of infusions of PLD

Total number of infusions is calculated as the sum of the actual number of infusions that a subject received across cycles. The actual number of infusions will be counted directly based on the infusions reported from the CRF, regardless of infusion delays, interruptions, or any other types of deviations from the protocol required schedules. An infusion is regarded to be administered, if either the actual dose received is > 0 mg or the duration of the infusion is > 0 minutes.

- PLD during the Treatment Period: per protocol a subject will receive 1 infusion in a 28-day treatment cycle.

Total number of administrations of VX-984

Total number of administrations is calculated as the sum of the actual number of administrations that a subject received during a period. The actual number of administrations will be counted directly based on the administrations reported from the CRF. A dose is regarded to be administered if the actual dose received is > 0 mg.

- VX-984 during the Lead-in Period: per protocol a subject will receive 3 administrations from the Lead-in Period;
- VX-984 during the Treatment Period: per protocol a subject will receive 3 administrations in a 28-day treatment cycle.

Total number of cycles

Total number of cycles (during the treatment period) is defined as the maximum number of cycles that a subject received across treatment cycles. The number of treatment cycles will be counted based on the data directly from the CRF.

- VX-984 during the Treatment Period: a cycle with at least one administration of VX-984 will be counted per subject.

Total cumulative dose

Total cumulative dose (mg) will be derived separately for Lead-in Period and Treatment Period.

- VX-984 during the Lead-in Period

  It is calculated as the sum of the individual actual dose amount that a subject received during the Lead-in Period, where the individual actual dose amount is taken directly from the "Dose level administered (mg)" on the CRF page of "Study Drug Administration: 984" at each dosing day.

- VX-984 during the Treatment Period

  It is calculated as the sum of the individual actual dose amount that a subject received across treatment cycles, where the individual actual dose amount is taken directly from the "Dose level administered (mg)" on the CRF page of "Study Drug Administration: 984" at each dosing day.

- PLD during the Treatment Period

  PLD is only administered during the treatment cycles. It is calculated as the sum of the individual actual dose amount that a subject received across treatment cycles, where the individual actual dose amount is taken directly from the "Dose level administered (mg)" on the CRF page of "Study Drug Administration: PLD" at each dosing day.

Total planned dose

Total planned dose (mg) will be derived separately for Lead-in Period and Treatment Period.

- VX-984 during the Lead-in Period

  It is the sum of the individual planned dose that a subject will receive from the Lead-in Period, where the individual planned dose is taken directly from the "Planned dose (mg)" on the CRF page of "Study Drug Administration: 984" at each dosing day.

- VX-984 during the Treatment Period

  It is the sum of the individual planned dose that a subject will receive across treatment cycles, where the individual planned dose level is taken directly from the "Planned dose (mg)" on the CRF page of "Study Drug Administration: 984" at each dosing day.

- PLD during the Treatment Period

  It is the sum of the individual planned dose that a subject will receive across treatment cycles, where the individual planned dose level is taken directly from the "Body surface area (BSA) adjusted dose amount (mg)" on the CRF page of "Study Drug Administration: PLD" at each dosing day.

  If any individual planned dosing amount is not collected from the CRF, then the planned dose amount will be derived as follows at each dosing day:

  $$\text{BSA adjusted planned dose (mg)} = \text{planned dose level (mg/m}^2\text{)} \times \text{BSA (m}^2\text{)}$$

  The BSA reported on the CRF will be used. In case BSA is missing at a particular visit, the latest BSA available prior to that visit will be used for calculation.

Duration of therapy – VX-984

The duration of VX-984 will be calculated based on the dosing received from the Lead-in Period (if not omitted) and the Treatment Period. A dose of VX-984 is regarded to be administered, if the actual dose received is > 0 mg.

- During a 14-day Lead-in Period, VX-984 will be administered QD on Days -14 to -12 as a single agent. Hence, the duration for VX-984 during the Lead-in Period will be calculated as:

$$\text{Duration (weeks)} = \left(\frac{\text{date of last dose - date of first dose} + 12}{7}\right)$$

where the dates of first dose and last dose are those implemented during the Lead-in Period.

- During a 28-day cycle, VX-984 will be administered QD on Days 2 to 4 in combination with PLD. Hence, the duration for VX-984 during a treatment cycle will be calculated as:

$$\text{Duration (weeks)} = \left(\frac{\text{date of last dose - date of first dose} + 26}{7}\right)$$

where the dates of first dose and last dose are those implemented during treatment cycles.

Duration of therapy – PLD

- During a 28-day treatment cycle, PLD infusion will be administered on Day 1 only. Hence, the duration for PLD will be calculated as:

$$\text{Duration (weeks)} = \left(\frac{\text{date of last dose - date of first dose} + 28}{7}\right)$$

A dose of PLD is regarded to be administered, if either the actual dose received is > 0 mg, or the duration of the infusion is > 0 minutes.

Dose intensity

- Dose intensity (mg/2 week) of VX-984 from Lead-in Period

  VX-984 administered on Days -14 to -12 during a 2-week Lead-in Period will be calculated as

$$\text{Dose intensity} = \left(\frac{\text{Total Cumulative dose (mg) of VX-984 from Lead-in Period}}{\text{Duration of Lead-in Period (in weeks)/2}}\right)$$

- Dose intensity (mg/4 week) of VX-984 administered on Days 2 to 4 in a 4-week treatment cycle will be calculated as

$$\text{Dose intensity} = \left(\frac{\text{Total Cumulative dose (mg) of VX-984 from Treatment Period}}{\text{Duration of Treatment Period (in weeks)/4}}\right)$$

- Dose intensity (mg/4 week) of PLD administered on Day 1 in a 4-week treatment cycle will be calculated as

$$\text{Dose intensity} = \left(\frac{\text{Total Cumulative dose (mg) of PLD from Treatment Period}}{\text{Duration of Treatment Period (in weeks)/4}}\right)$$

Relative Dose intensity

The relative dose intensity (%) is calculated as the dose intensity (mg/week) divided by the total planned dose intensity (mg/week) of the same dosing period, which is calculated as:

$$\text{Total planned dose intensity (mg/4 week)} = \left(\frac{\text{Total planed dose (mg)}}{\text{Duration of a therapy (in weeks)/4}}\right)$$

Relative dose intensity will be calculated in a similar way as dose intensity based on respective study treatment and dosing period:

- Relative dose intensity (mg/week) of VX-984 from Lead-in Period will be calculated as

$$\left(\frac{\text{Dose Intensity of VX-984 from Lead-in Period (mg/2 week)}}{\text{Total planned dose intensity of VX-984 from Lead-in Period (mg/2 week)}}\right)$$

- Relative dose intensity (%) of VX-984 from Treatment Period will be calculated as

$$\left(\frac{\text{Dose Intensity of VX-984 from Treatment Period (mg/4 week)}}{\text{Total planned dose intensity of VX-984 from Treatment Period (mg/4 week)}}\right)$$

- Relative dose intensity (%) of PLD from Treatment Period will be calculated as

$$\left(\frac{\text{Dose Intensity of PLD from Treatment Period(mg/4 week)}}{\text{Total planned dose intensity of PLD from Treatment Period (mg/4 week)}}\right)$$

The following drug exposure related parameters will be provided by study treatment and dose group:

- Total Number of administrations of VX-984
  - VX-984 from Lead-in Period
  - VX-984 from Treatment Period
- Total number of infusions of PLD from Treatment Period
- Total number of cycles of VX-984 from Treatment Period
- Total cumulative dose (mg) of VX-984
  - VX-984 from Lead-in Period
  - VX-984 from Treatment Period
- Total cumulative dose (mg) of PLD from Treatment Period
- Total planned dose (mg) of VX-984
  - VX-984 from Lead-in Period

- VX-984 from Treatment Period

- Total planned dose (mg) of PLD from Treatment Period
- Duration (weeks) of VX-984 from Treatment Period and by subcategories of: ≤ 4 weeks, > 4 – 8 weeks, > 8 – 12 weeks, > 12 – 16 weeks, > 16 weeks
- Duration (weeks) of PLD from Treatment Period and by subcategories of: ≤ 4 weeks, > 4 – 8 weeks, > 8 – 12 weeks, > 12 – 16 weeks, > 16 weeks
- Dose intensity of VX-984
  - Dose intensity (mg/2 week) VX-984 from Lead-in Period
  - Dose intensity (mg/4 week) VX-984 from Treatment Period
- Dose intensity (mg/4 week) of PLD from Treatment Period
- Relative dose intensity (%) of VX-984 and by subcategories of: < 60%, ≥ 60% - < 80%, ≥ 80% - < 90%, ≥ 90% - ≤ 110%, > 110%
  - VX-984 from Lead-in Period
  - VX-984 from Treatment Period
- Relative dose intensity (%) of PLD from Treatment Period and by subcategories of: < 60%, ≥ 60% - < 80%, ≥ 80% - <90%, ≥ 90% - ≤ 110%, > 110%

14 Efficacy Analyses

14.1 Analysis of Best Overall Response

Analysis Set: FAS/SAF

The best overall response (BOR) will be defined as the best response per RECIST 1.1 across all time points until determination of PD, using the Investigator reported overall response per time point and excluding assessments after further anticancer therapy Clinical deterioration will not be considered as documented disease progression.

Tumor assessments are based on local evaluations by the Investigator according to RECIST 1.1 criteria. Local evaluations of target, non-target and new lesions are used to assess BOR. The date of the overall response assessment is the earliest date for imaging of target, non-target and new lesions of images taken at that response assessment.

BOR will be defined as the best response across all time points (for example, a subject who has SD at the first assessment, PR at the second assessment, and PD at the last assessment has a BOR of PR). The order to obtain the BOR is the following: CR, PR, SD, PD and NE.

When SD is believed to be the best response, it must also meet the protocol-specified minimum 6 weeks from first day of treatment. If the minimum time is not met, the subject's BOR depends on the subsequent assessments. For example, a subject who has SD at the first assessment, PD at

the second assessment and does not meet the minimum duration for SD, will have a BOR of PD. The same subject lost to follow-up after the first SD assessment would be considered NE for BOR.

If a subject has missing baseline tumor assessment and/or no tumor assessment on-treatment, BOR will be NE.

The confirmed BOR will be also analyzed. In this case, CR and PR need to be confirmed at a subsequent assessment, at least 4 weeks after initial overall response assessment of CR/PR. Confirmed BOR will be derived as described in RECIST 1.1 guidance, see Table 5 below.

Both confirmed and unconfirmed BOR will be summarized by tabulating the number and percentage of subjects with CR, PR, SD, PD or NE as BOR. The table will also include the objective response rate (ORR), disease control rate (DCR) and the corresponding 90% Clopper-Pearson confidence intervals (Clopper & Pearson, 1934). The ORR will be defined as the rate of subjects who achieve either a CR or PR. The DCR will be defined as the rate of subjects who achieve either a CR, PR or SD.

The listing of tumor assessments (including e.g. lesion number, description and location, type of lesion, imaging date, assessment method, diameter (mm), sum of diameter of target lesions (mm), BOR (confirmed and unconfirmed) will be provided by subject as recorded from the "Target Lesions", "Sum of Diameters", "Non-Target Lesions", "New Lesions" and "Assessment of disease based on imaging" CRF pages.

Table 3 BOR when confirmation of CR/PR is required

Overall response first time point	Overall response subsequent time point[a]	Confirmed BOR
CR	CR	CR
CR	PR	SD, if minimum criteria for SD duration met at first time point. Otherwise PD
CR	SD	SD, if minimum criteria for SD duration met at first time point. Otherwise PD.
CR	PD	SD, if minimum criteria for SD duration met at first time point. Otherwise PD.
CR	NE	SD, if minimum criteria for SD duration met at first time point. Otherwise NE.
PR	CR	PR
PR	PR	PR
PR	SD	SD, if minimum criteria for SD duration met at subsequent time point. Otherwise NE
PR	PD	SD, if minimum criteria for SD duration met at first time point. Otherwise PD.
PR	NE	SD, if minimum criteria for SD duration met at first time point. Otherwise NE.
NE	NE	NE

[a] Subsequent time point is not necessarily the direct subsequent scan (e.g. PR-SD-PR will have PR as confirmed BOR).

A spider graph will display the percentage change from baseline in sum of longest diameter of target lesion against the date for each subject, overall and per dose level.

A swimmer plot displaying some key radiological milestones will be produced for each dose group separately. For each subject, the time from treatment start until end of follow-up will be represented (from treatment start to last date known to be alive or date of death). In addition, following information will be displayed: time to best overall unconfirmed response (CR, PR or SD), time of confirmation of response, time to progression and status at the end of the follow-up (alive or dead).

In addition, a waterfall plot representing the best percentage change in tumor size from baseline per subject will be provided. The BOR will also be presented as an annotation on each vertical bar.

15 Safety Analyses

The subsections in this section include specifications for summarizing safety endpoints that are common across clinical trials such as adverse events (AEs), laboratory tests and vital signs.

Definition of on-treatment period

On-treatment period is defined as the date from the first dose of study treatment (either VX-984 or PLD, including the Lead-in Period if available), until the minimum (last dose of study treatment + 30 days, date of death).

15.1 MTD (Primary Endpoint)

Analysis Set: DLT

The maximum tolerated dose (MTD) is defined as the highest dose combination for a given schedule that causes DLTs in no more than 33.3% of subjects by the end of Cycle 1. The DLT information will be based on “Adverse Events” CRF page with “Dose limiting toxicity?” = Yes.

The end of Cycle 1 is defined as 28 days after the start of study treatment from Cycle 1 Treatment Day 1.

A summary table of DLTs during the first cycle of study treatment, including the Lead-in Period, will be provided by dose group and overall with:

- Number of subjects with no DLT
- Number of subjects with one or more DLTs

The listing of DLTs will also be provided.

15.2 Adverse Events

Analysis Set: FAS/SAF

AEs will be summarized based on the information collected from the "Adverse Events" CRF page.

- Pretreatment AEs are defined as AEs that were reported or worsened after signing the informed consent form up to the start of study treatment (either VX-984 or PLD), including the Lead-in Period if available.
- Treatment-emergent adverse events (TEAEs) are defined as those events with onset dates occurring within the on-treatment period as defined in Section 15.
- Serious Adverse Events (SAEs): serious adverse events (serious adverse event = yes).
- Adverse Events Leading to permanent treatment discontinuation: (action taken = drug withdrawn).
- Adverse Events Leading to temporary treatment discontinuation: (action taken = drug interrupted).
- Adverse Events Leading to dose reduction: (action taken with study drug = dose reduced).
- Adverse Events Leading to Death: adverse event leading to death (AEs with Grade 5 or outcome "fatal" if Grade 5 not applicable).

All analyses described in Section 15.2 will be based on TEAEs if not otherwise specified.

Incomplete AE-related dates will be handled as follows:

- In case the onset date is missing completely or missing partially but the onset month and year, or the onset year are equal to the start of study drug then the onset date will be replaced by the minimum of start of study drug and AE resolution date.
- In all other cases the missing onset day or missing onset month will be replaced by 1.
- Incomplete stop dates will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of subject's death. In the latter case the date of death will be used to impute the incomplete stop date.
- In all other cases the incomplete stop date will not be imputed. If stop date of AE is after date of cut-off outcome of AE is ongoing at cut-off.
- Further information after cut-off (e.g. fatal outcome) might be taken from Safety database and included separately into the CSR.

15.2.1 All Adverse Events

AEs will be summarized by worst severity (according to National Cancer Institute – Common Terminology Criteria for Adverse Events [NCI-CTCAE] of the latest version) per subject, using the MedDRA preferred term as event category and primary system organ class (SOC) body term as Body System category.

Unless otherwise stated, AEs will be displayed in terms of frequency tables: PT and primary SOC in alphabetical order.

If an AE is reported for a given subject more than once during treatment, the worst severity and the worst relationship to study treatment will be tabulated.

AEs related to study treatment are those events with relationship missing, possibly related or related.

In case a subject had events with missing and non-missing grades, the maximum of the non-missing grades will be displayed.

The following overall frequency tables will be prepared. In addition the tables will be provided by PT and primary SOC in alphabetical order:

- Any TEAE
- Any related TEAEs
    - VX-984 or PLD related TEAEs
    - VX-984 related TEAEs
    - PLD related TEAEs
- Any serious TEAEs
- Any non-serious TEAEs
- Any related serious TEAEs
    - VX-984 or PLD related serious TEAEs
    - VX-984 related serious TEAEs
    - PLD related serious TEAEs
- Any TEAE by NCI-CTCAE severity grade (≥ 3, ≥ 4)
- Any related TEAE by NCI-CTCAE severity grade (≥ 3, ≥ 4)
    - VX-984 or PLD related TEAE by NCI-CTCAE severity grade (≥ 3, ≥ 4)
    - VX-984 related TEAE by NCI-CTCAE severity grade (≥ 3, ≥ 4)
    - PLD related TEAE by NCI-CTCAE severity grade (≥ 3, ≥ 4)
- TEAEs leading to death (AEs with Grade 5 or outcome "fatal" if Grade 5 not applicable)
- Any related TEAEs leading to death (AEs with Grade 5 or outcome "fatal" if Grade 5 not applicable)
    - VX-984 or PLD related TEAEs leading to death
    - VX-984 related TEAEs leading to death
    - PLD related TEAEs leading to death

The listing for all AEs (whether treatment-emergent or not) will include all the data fields as collected on the "Adverse Events" CRF pages.

- Dose group
- Subject identification number
- First and last dose dates of VX-984
- First and last dose date of PLD
- Reported Term with SOC and PT
- Start and end date with their corresponding treatment day
- Treatment Emergent Adverse Events flag (N/Y)
- Related to VX-984 flag (N/Y)
- Related to PLD flag (N/Y)
- Serious Adverse Events flag (N/Y)
- DTL flag (N/Y)
- CTCAE Grade
- Action taken on VX-984
- Action taken on PLD
- Outcome of AE

Clinical trial.gov and EudraCT requirements

Summary tables for non-serious AEs excluding SAEs applying frequency threshold of 5% will be provided by dose group and overall.

15.2.2 Adverse Events Leading to Treatment Discontinuation

The following overall frequency tables will be prepared for the AE actions. In addition, tables by PT and primary SOC in alphabetical order will also be provided:

TEAEs leading to temporary discontinuation

- TEAEs leading to temporary discontinuation of either study treatment (either VX-984 or PLD)
- TEAEs leading to temporary discontinuation of both study treatments (VX-984 and PLD)
- TEAEs leading to temporary discontinuation of VX-984
- TEAEs leading to temporary discontinuation of PLD

TEAEs leading to permanent discontinuation

- TEAEs leading to permanent discontinuation of either study treatment (either VX-984 or PLD)

- TEAEs leading to permanent discontinuation of both study treatments (VX-984 and PLD)
- TEAEs leading to permanent discontinuation of VX-984
- TEAEs leading to permanent discontinuation of PLD

TEAEs leading to dose reduction

- TEAEs leading to dose reduction of either study treatment (either VX-984 or PLD)
- TEAEs leading to dose reduction of both study treatments (VX-984 and PLD)
- TEAEs leading to dose reduction of VX-984
- TEAEs leading to dose reduction of PLD

15.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Analysis Set: FAS/SAF

15.3.1 Deaths

All deaths, deaths within 30 days after last dose, and deaths within 60 days after first dose of study treatment, will be tabulated based on information from the "Long-Term Follow-Up" CRF page.

- Number of deaths
- Number of deaths within 30 days after last dose of study treatment (VX-984 or PLD, whatever is later)
- Number of deaths within 60 days after first dose of study treatment (VX-984 or PLD, whatever is earlier)

In addition, date of death will be provided in individual subject data listing together with selected dosing information (date of first/last administration of study treatment).

- Listing of deaths

Will include columns for:

- AEs with fatal outcome (list preferred terms of AEs with outcome = fatal)
- flag for death within 30 days of last dose of study treatment (VX-984 or PLD, whatever is later)
- flag for death within 60 days of first dose of study treatment (VX-984 or PLD, whatever is earlier)

15.3.2 Serious Adverse Events

SAEs will be summarized for each dose group and overall by SOC and PT in alphabetical order (please refer to Section 15.2.1 for items to be listed).

For these AEs, subject listings of SAEs will be provided in addition.

15.3.3 Other Significant Adverse Event

Not applicable.

15.4 Clinical Laboratory Evaluation

Analysis Set: FAS/SAF

Laboratory values (including corresponding normal ranges) from a local lab will be used for in the analyses. A complete list of laboratory tests is presented in the Appendix 18.1.

Laboratory results will be classified according to the latest version of NCI-CTC as provided by the local laboratory. Additional laboratory results that are not part of NCI-CTC will be presented according to the categories: below normal limits, within normal limits and above normal limits (according to the laboratory normal ranges).

The worst on-treatment grade (i.e. on or after first study treatment administration and within 30 days after last study treatment administration) will be summarized considering only subjects with post baseline laboratory samples: Laboratory tests by NCI-CTC grade (0, 1, 2, 3, 4, any).

NCI-CTC gradable and non-grade lab tests are shown in Table 6 and Table 7.

Tables for NCI-CTC gradable parameters:

- Number and percentage of subjects with any, NCI-CTC grade 0, 1, 2, 3, 4, and grade of 3 or 4 laboratory abnormalities under treatment – (worst case)
- Shifts in toxicity grading baseline to worst on-treatment

The highest NCI-CTC grade during the on-treatment period is considered as the worst grade for the summary.

Table 4 NCI-CTC gradable parameters

Category	Parameter (LBTEST)	Parameter code (LBTESTCD)	Name in NCI-CTC	Direction of abnormality
	Serum chemistry			
Electrolytes	Calcium	CA	Hypocalcemia/Hypercalcemia	Low/High
Electrolytes	Magnesium	MG	Hypomagnesemia/ Hypermagnesemia	Low/High
Electrolytes	Phosphorus (Phosphate)	PHOS	Hypophosphatemia	Low
Electrolytes	Potassium	K	Hypokalemia/Hyperkalemia	Low/High
Electrolytes	Sodium	SODIUM	Hyponatremia/Hypernatremia	Low/High

Category	Parameter (LBTEST)	Parameter code (LBTESTCD)	Name in NCI-CTC	Direction of abnormality
Enzymes/cardial	Creatinine Phosphokinase	CK	CPK increased	High
Enzymes/liver	Alanine Aminotransferase	ALT	Alanine Aminotransferase increased	High
Enzymes/liver	Alkaline Phosphatase	ALP	Alkaline Phosphatase increased	High
Enzymes/liver	Aspartate Aminotransferase	AST	Aspartate Aminotransferase increased	High
Enzymes/liver	Gamma-glutamyltransferase	GGT	GGT increased	High
Enzymes/liver	Total bilirubin	BILI	Blood bilirubin increased	High
Metabolism	Glucose	GLUC	Hypoglycemia/ Hyperglycemia	Low/High
Metabolism	Uric acid (1)	URATE	Hyperuricemia	High
Plasma proteins	Albumin	ALB	Hypoalbuminemia	Low
Renal/kidney	Creatinine	CREAT	Creatinine increased	High
Renal/kidney	Creatinine Clearance	CREATCLR	part of Chronic kidney disease	Low
	Hematology			
Platelets	Platelets Count	PLAT	Platelet count decreased	Low
Red blood cells	Hemoglobin	HGB	Anemia/Hemoglobin increased	Low/High
White blood cells/differential	White Blood Cell Count	WBC	White blood cell decreased/Leukocytosis	Low/High
White blood cells/differential	Absolute Lymphocytes Count	LYM	Lymphocyte count decreased/increased	Low/High
White blood cells/differential	Absolute Neutrophils Count	NEUT	Neutrophil count decreased	Low

(1) According to CTCAE grade, if uric acid value is between ULN and 590 µmol/L it should be graded as follows:
- Grade 1 if there are no physiologic consequences
- Grade 3 if there are physiologic consequences

[a] For a programming perspective, values between ULN and 590 µmol/L will all be graded as Grade 1 (if any physiologic consequences are observed, it should be completed as an adverse event).
[b] Final analysis will be based on the actual data received for the trial, discrepancy with the CTC gradable and non-gradable parameters does not constitute a requirement for IAP amendment.

Tables for non-CTC gradable parameters:

- Number of subjects with shifts from baseline to worst on-treatment post-baseline normal categories.

The normal categories based on the normal range will be produced with the following categories for all hematology and blood chemistry parameters:

- Baseline: Low/Normal/High/Missing/Overall
- Worst On-trial: Low/Normal/High/Missing/Overall

Table 7: NCI-CTC Non-gradable parameters

Category	Parameter (LBTEST)	Parameter code (LBTESTCD)	Direction of abnormality
	Serum chemistry		
Enzymes/cardial	Lactate dehydrogenase	LDH	High
Plasma proteins	Total protein	PROT	Low
Renal/kidney	Blood Urea Nitrogen	BUN	High
	Hematology		
Red blood cells	Hematocrit	HCT	High/Low
Red blood cells	Mean Corpuscular Hemoglobin	MCH	High/Low
Red blood cells	Mean Corpuscular Hemoglobin Concentration	MCHC	High/Low
Red blood cells	Mean Corpuscular Volume	MCV	High/Low
Red blood cells	Red blood cells (Erythrocytes)	RBC	High/Low
Red blood cells	Reticulocytes	RETI	High/Low
White blood cells/differential	Basophils	BASOLE	High
White blood cells/differential	Eosinophils	EOSLE	High
White blood cells/differential	Monocytes	MONOLE	High/Low

Normal category includes low values for high parameters and high values for low parameters.

Subjects without post baseline laboratory samples will be excluded from analyses with respect to values after the baseline.

All CTC gradable and non-CTC gradable parameters will be listed for each measurement. Parameters will be grouped by category.

Listings will include at least the following items:

- Dose group
- Subject identification number
- First/last dosing date of VX-984 and PLD
- Parameters
- Visit
- Date (Treatment day)
- Analysis value
- SI unit
- Change from baseline
- Reference range status (Low, Normal, High)
- CTC grade (with associated CTC name)

- Baseline flag (Yes/No)
- Worst value on-treatment flag (Yes/No)

In addition, a listing displaying parameters with at least one value with grade ≥ 3 will be provided. For each subject, only parameters where at least one value has grade ≥ 3 will be displayed (all visits for the corresponding parameter will be displayed).

Coagulation parameters

All coagulation parameters will be tested only at Screening, and will be presented in a listing only.

Urinalysis

All urinalysis and microscopic analysis will be presented in listings only.

15.5 Vital Signs

Analysis Set: FAS/SAF

All relevant data as collected from "Vital Signs" CRF pages will be presented in listings.

15.6 Other Safety or Tolerability Evaluations

15.6.1 ECOG Performance Status

Analysis Set: FAS/SAF

The listing will include all of the data from the "WHO Performance Status" CRF section.

15.6.2 Electrocardiogram

Analysis Set: FAS/SAF

Electrocardiogram values based on "ECG" CRF section will be used for summary statistics and shift tables by dose group and overall at each scheduled visit.

Descriptive statistics for numeric ECG measures of RR interval, PR interval, QRS interval, QT interval, QTcF interval (QT interval with Frederica's correction) and HR will be summarized by time point. The number of subjects and percentage for categorical ECG parameters will also be summarized by time point.

The QTcF interval is derived as follows:

Frederica's Correction (QTcF) $$QTc_f = \frac{QT}{\sqrt[3]{RR}}$$

where: RR = RR-interval measured in seconds.

The following frequency table will be presented for ECG parameters:

- Shift from normal baseline result to any abnormal on-treatment result
- Summary of observed values and changes from baseline
- Summary of categorical measures by time point
- Summary of maximum on-treatment QTcF values
    - ≤ 450 ms
    - > 450 ms and ≤ 480 ms
    - > 480 ms and ≤ 500 ms
    - > 500 ms
- Summary of maximum on-treatment QTcF changes from baseline
    - ≤ 30 ms
    - > 30 ms and ≤ 60 ms
    - > 60 ms

Two listings will display all ECG results, one on qualitative results and another one on quantitative results. All visits and time points will be included in listings.

15.6.3 Echocardiogram

Analysis Set: FAS/SAF

Echocardiogram values based on "Transthoracic Echocardiogram" CRF section will be used for summary statistics and shift tables by dose group and overall at each scheduled visit.

Descriptive statistics by treatment and time (mean, StDev, median, min and max) relevant for left ventricular ejection fraction (LVEF) will be provided.

- Summary of LVEF values and changes from baseline by visit
- Summary of maximum LVEF on-treatment decrease from baseline value
    - 0 to ≤ 10%
    - > 10% and ≤ 20%
    - > 20%

The number and percentage of subjects by overall interpretation will also be summarized at each scheduled visit.

All relevant data will be presented in listings.

16 Analyses of Other Endpoints

16.1 Pharmacokinetics

Analysis Set: PAS

Concentration listings of VX-984 and PLD will be created using the computer program Phoenix® WinNonlin® version 6.4, or higher (PPD).

The following Listings will be provided.

Listings

- Individual VX-984 plasma concentrations by group
- Individual VX-984 urine concentrations, urine void volume and amount excreted
- Individual PLD concentrations

The Phoenix WinNonlin NCA Core Output will be provided in a separate listing.

17 References

1. Babb J, Rogatko A, Zacks S. Cancer phase I clinical trials: Efficient dose escalation with overdose control. Stat Med 1998;17(10):1103-20.

2. Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to Phase I cancer trials. Stat Med 2008;27(13):2420-39.

3. Clopper, C. J., & Pearson, E. S. (1934). The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. Biometrika, 26, 404–413.

18 Appendices

18.1 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.

CTP MS201926-0001 IAP Phase I Main Text Body Version 1

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
PPD	Business Approval	29-Jan-2018 08:42 GMT+01
PPD	Business Approval	30-Jan-2018 16:27 GMT+01