Clinical Study Protocol

Clinical Study Protocol Number	MS201922-0001
Title	An Open-Label Study of the Safety, Tolerability, and Pharmacokinetic/Pharmacodynamic Profile of M4344 (formerly VX-803) as a Single Agent and in Combination with Cytotoxic Chemotherapy in Participants with Advanced Solid Tumors
Phase	I
IND Number	CCI
EudraCT Number	2014-003838-86
Coordinating Investigator	PPD Telephone: PPD
Sponsor	In the UK, Spain, and the Netherlands: Merck KGaA Frankfurter Strasse 250 Darmstadt, Germany In the USA and Canada: EMD Serono Research & Development Institute, Inc., An affiliate of Merck KGaA, Darmstadt, Germany 45A Middlesex Turnpike Billerica, MA, USA Medical Responsible: PPD Merck KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany Telephone: PPD Fax: PPD
Clinical Study Protocol Version	29 January 2020 Version 8.0 including Amendment 7
Replaces Version	28 April 2019 Version 7.0 including Amendment 6

Protocol Amendment Summary of Changes

Protocol History

Version Number	Type	Version Date
1.0	Original Protocol	19-Sep-2014
2.0	Global Amendment 1	14-Nov-2014
3.0	Global Amendment 2	31-Aug-2015
4.0	Global Amendment 3	03-Jun-2016
5.0	Global Amendment 4	16-Aug-2017
6.0	Global Amendment 5	02-Feb-2018
7.0	Global Amendment 6	28-Apr-2019
8.0	Global Amendment 7	29-Jan-2020

Protocol Version [8.0] (29 January 2020)

This amendment is substantial based on the criteria in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

This amendment serves mainly to clarify that evaluation of a drug holiday schedule may be conducted in parallel to other parts of the study. To facilitate that, drug holiday schedules are defined and arranged in a new Part A3.

Furthermore, this amendment incorporates clarifications and changes to allow investigative sites additional ease in enrolling and adhering to the protocol.

Section # and Name	Description of Change	Brief Rationale
Throughout where applicable	Reorganization of drug holiday schedule evaluation in separate Part A3, with methodology, objectives/endpoints, SoAs, etc. specified.	To clarify that the evaluation of a drug holiday schedule may be performed independent from conduct of Parts C
CCI		
Throughout where applicable	Additional Parts C4, C5, C6 added as optional expansion cohorts for Part A3 similar to Part A2 with Parts C1, C2, and C3, these are collectively referred to as "Parts C".	To add that a dose and/or schedule that has been explored in optional expansion Part A3 but is different from that evaluated in Parts C1, C2, and C3 may be evaluated in further Parts C.
Synopsis Planned study and treatment duration per participant	The prescreening and Screening periods merged into 1 Screening period with a duration of 42 days for Parts C.	To clarify and simplify the Screening procedures for Parts C

Section # and Name	Description of Change	Brief Rationale
Table 2 Schedule of Assessments: Screening (Parts C) 5.2.8 Screening 5.3.1 Inclusion Criteria #2 5.4 Criteria for Initiation of study treatment 7.1 Schedule of assessments 7.2 Demographic and other baseline characteristics 7.7.5 Assessment of biomarkers for Parts C: Eligibility Criteria		
CCI		
Synopsis: Planned number of participants	Updated the number of participants for Parts A3 and new C parts	To adjust according to new parts C4-6
Table 7 Treatment and Follow-up Period (M4344 single agent therapy in expansion Parts C1, C2, and C3)	Removed evaluations on Day 2 in Cycle 1 in Parts C1, C2, and C3	The C1D2 assessments serve for PK and additional safety labs. Since the dose used in Parts C1, C2, and C3 has been explored in Part A2 and declared safe, these are not needed
Section 3.1 Scientific Rationale	Added information regarding prevalence of mutations.	To enhance rationale clarity.
Section 3.2 Toxicology and Compound Safety	Updated M6620 exposure information.	For accuracy of data.
Sections 5.1.2 Part A2, 5.1.3 Part A3	Added that "Candidate participants with advanced solid tumors carrying alterations that are suspected to sensitize for treatment with an ATR inhibitor (especially those defined for the Parts C) may be preferentially enrolled."	To increase the potential for benefit of participating patients
Section 5.1.3 Part A3	Added that the purpose of Part A3 is to investigate drug holiday dosing schedules with the goal of improved long-term tolerability relative to continuous regimens in Part A2, clarified the basis for determination of RP2D for Part A3, dosing schedule plan, and outlined enrollment prioritization between Parts A3 and C.	For clarification.
Section 5.1.3 Part A3, 5.2.1 Rationale of study design 8.2 Sample size 8.5.7.2 Safety in Parts A2 and A3	Added Bayesian optimal interval model (BOIN) for dose escalation in Part A3	To increase flexibility and better operating characteristics compared to 3+3 design

Section # and Name	Description of Change	Brief Rationale
Section 5.1.5 All Parts C Section 6.3 Assignment to treatment groups	Added that Parts C1, C2, and C3 may be initiated in parallel or in a staggered manner using a dose and schedule determined to be a RP2D in either Part A or Part A2 at the discretion of the Sponsor and Investigators. Additional Parts C4, C5 or C6 using doses and schedules determined to be RP2D in Part A3 may be initiated at any time.	To clarify details of conduct of Parts C
Section 5.1.5 All Parts C; Figure 5	Added a schematic of eligibility assessments for Parts C.	For clarification.
CCI [redacted]		
Section 5.2.2 Rationale for Study Drug Dose and Duration	Added that if the BID or QD regimen is unfavorable, new dosing schedules, using drug holiday schedules, may be explored in Part A3 at the discretion of the Sponsor and Investigators.	Depending on the RP2D and MTD obtained in Part A2 with a BID or QD regimen, there might be a desire to explore drug holiday schedules.
5.2.8 Screening	Added that Screening Failures for Part C may be considered for participation in Part A3 and indicated assessments that should be repeated.	For clarification.
7.5.2.1 Pregnancy	Added lactation statement.	For clarification and alignment with IB.
7.5.2.2 Contraception	Added that strict contraception use during dosing and for at least 6 months after the last dose of M4344 is required. Also recommended that participants should be informed that fertility might be impaired long-term and may opt to cryopreserve sperm or ova prior to treatment.	For clarification and alignment with IB.
Section 6.6.1 Permitted Medications	Concomitant medications such as leuprolide, goserelin, triptorelin, histrelin, degarelix, abiraterone, enzalutamide, and nilutamide added for participants with prostate cancer	To maintain a castrate level of testosterone in participants with prostate cancer
Section 7.6.1.3 Pharmacokinetic Sampling: Part A3 Table 17 Pharmacokinetic sampling schedule for Part A3 Table 18 Pharmacokinetic sampling schedule for Parts C4, C5, and C6	Added a separate section with PK sampling table for Part A3 and Parts C	To enhance clarity across the separate potential drug holiday schedules

Section # and Name	Description of Change	Brief Rationale
CCI		
Section 7.5.3 Clinical Laboratory Assessments; Table 15 Safety Laboratory Test Panels	Added reticulocytes to hematology assessments	To increase safety information
CCI		
Section 9.3 Participant Identification and Privacy	Added sentence indicating that if a participant is a Screening failure and is re-screened or consents to participate in a different part of the study, that participant will receive a new unique identification number.	For clarity.
Throughout	Minor editorial and document formatting revisions.	Minor, therefore, have not been individually summarized.

Protocol Table of Contents

Table of In-Text Tables

Table of In-Text Figures

List of Abbreviations

AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ATM	Ataxia telangiectasia mutated
ATR	Ataxia telangiectasia mutated and Rad3-related protein
AST	Aspartate aminotransferase
AUC	Area under the concentration versus time curve
β-hCG	β-human chorionic gonadotropin
BID	Twice daily
BIW	Twice weekly
BOIN	Bayesian optimal interval
BRCA-1/2	Breast cancer early onset genes 1 and 2
C_{avg}	Average concentration
CA-125	Cancer antigen 125
CA19-9	Cancer antigen 19-9
CEA	Cancer embryonic antigen
CPAP	Clinical pharmacology analysis plan
CRO	Contract Research Organization
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DEM	Dose Escalation Meeting
DL	Dose level
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DSB	Double-strand DNA breaks
ECG	Electrocardiogram
eCRF	Electronic case report form
FSH	Follicle stimulating hormone
γH2AX	Phosphorylated H2AX

GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Good Laboratory Practice
HED	Human equivalent dose
HNSTD	Highest nonseverely toxic dose
HRT	Hormonal replacement therapy
IAP	Integrated Analysis Plan
IB	Investigators brochure
ICF	Informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IR	Ionizing radiation
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MRSD	Maximum recommended starting dose
MTD	Maximum tolerated dose
MTD_{carbo}	The maximum tolerated dose of M4344 in combination with the highest tolerated dose of carboplatin
$MTD_{SingleBIW}$	The MTD of single agent M4344 administered twice weekly
MUGA	Multiple Gated Acquisition
NCI	National Cancer Institute
OR	Objective tumor response
ORR	Overall response rate
PCWG2	Prostate Cancer Clinical Trials Working Group
PD	Progression of disease
CCI [redacted]	
PFS	Progression-free survival
PK	Pharmacokinetics
pChk1	phosphorylated checkpoint kinase 1
PSA	Prostate-specific antigen
RBC	Red blood cell

RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	Recommended Phase II dose
RS	Replication stress
SAE	Serious adverse event
SE	Standard error
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WBC	White blood cell
WHO	World Health Organization
WHO-DDE	World Health Organization-Drug Dictionary

1 Synopsis

Clinical Study Protocol Number	MS201922-0001
Title	An Open-Label Study of the Safety, Tolerability, and Pharmacokinetic/Pharmacodynamic Profile of M4344 (formerly VX-803) as a Single Agent and in Combination with Cytotoxic Chemotherapy in Participants with Advanced Solid Tumors
Study Phase	I
IND Number	CCI
EudraCT Number	2014-003838-86
Study sites/countries	The study will be conducted at approximately 10 to 15 sites in the UK, the USA, Spain, and the Netherlands
Planned study period (first participant in-last participant out)	January 2015 to December 2021
Trial Registry	ClinicalTrials.gov and EudraCT

Objectives:

Primary objectives:

Part A:

- To evaluate the safety and tolerability of multiple ascending doses of single agent M4344 (henceforth referred to as M4344) administered twice weekly (BIW) in participants with advanced solid tumors
- To determine the maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D) of single agent M4344 administered BIW in participants with advanced solid tumors.

Part A2:

- To evaluate the safety and tolerability of multiple ascending doses of single agent M4344 administered in a twice daily or once daily dose schedule in participants with advanced solid tumors
- To determine the MTD and/or RP2D of single agent M4344 administered in a twice daily or once daily dose schedule in participants with advanced solid tumors.

Part A3:

- To evaluate the safety and tolerability of multiple ascending doses of single agent M4344 when administered in a drug holiday dose schedule (3 days of dosing followed by 4 days of pausing [3d+/4d-] or 5 days of dosing followed by 2 days of pausing

[5d+/2d-] or 7 days of dosing followed by 7 days of pausing [7d+/7d-]) or 14 days of dosing followed by 7 days of pausing [14d+/7d-]) in participants with advanced solid tumors

- To determine the MTD and/or RP2D of single agent M4344 administered in a drug holiday dose schedule in participants with advanced solid tumors.

Part B1:

- To evaluate the safety and tolerability of M4344 when administered in combination with carboplatin in participants with advanced solid tumors
- To determine the MTD and/or RP2D of M4344 administered in combination with carboplatin in participants with advanced solid tumors.

Parts C:

- To evaluate the safety, tolerability, and efficacy in terms of confirmed objective response of M4344 administered at doses and schedules determined as RP2D in Parts A, A2, or A3 in participants with solid tumor harboring loss-of-function mutations in the genes ARID1A (Parts C1, C4), ATRX and/or DAXX (Parts C2, C5), or ataxia telangiectasia mutated (ATM) (Parts C3, C6).

Secondary objectives:

Part A:

- To evaluate pharmacokinetics (PK) of single agent M4344 when administered BIW in participants with advanced solid tumors
- To assess potential antitumor activity of single agent M4344 when administered BIW in participants with advanced solid tumors.

Part A2:

- To evaluate PK of single agent M4344 (and metabolites as appropriate) when administered in a twice daily (BID) or once daily dose schedule in participants with advanced solid tumors.
- To assess potential antitumor activity of single agent M4344 when administered in a BID or once daily dose schedule in participants with advanced solid tumors.

Part A3

- To evaluate the PK of single agent M4344 (and metabolites as appropriate) when administered in a drug holiday dose schedule in participants with advanced solid tumors.
- To assess preliminary antitumor activity of single agent M4344 when administered in a drug holiday dose schedule in participants with advanced solid tumors.

Part B1:

- To evaluate the PK profile of M4344 when administered in combination with carboplatin in participants with advanced solid tumors

- To evaluate potential antitumor activity after administering M4344 in combination with carboplatin in participants with advanced solid tumors.

Parts C:

- To further evaluate efficacy in terms of confirmed best overall response, duration of response, progression-free survival, and overall survival time of M4344 when administered in participants with loss-of-function mutations in the genes ARID1A, ATRX and/or DAXX, or ATM
- To evaluate the PK of M4344 (and metabolites as appropriate) in individual participants with loss-of-function mutations.

CCI

[redacted]

CCI

[redacted]

Methodology: This is a Phase I, first-in-human clinical study using M4344. The study will be conducted in multiple parts (Parts A, A2, A3, B1, C1, C2, C3 and potentially further Parts C4, C5, and C6). Eligible participants in Parts A, A2 and A3 will have advanced solid tumors for which no standard therapy is available which may convey clinical benefit. Eligible participants in Part B1 will have advanced solid tumors for which no standard therapy is available which may convey clinical benefit, and/or participants must have disease progression after at least 1 prior chemotherapy regimen in the metastatic setting, and for which carboplatin would be considered standard of care. Eligible participants in Parts C will have advanced solid tumors for which no recommended standard therapy is available and who carry certain loss-of-function mutations (see below for details).

In Part A, doses of M4344 will be escalated to determine MTD and/or RP2D when administered BIW as a single-agent.

Part A2 will establish the MTD/ RP2D of M4344 as a single agent administered BID or once daily.

Part A3 will establish the MTD/RP2D of M4344 as a single agent administered in a drug holiday schedule (3 days of dosing followed by 4 days of pausing [3d+/4d-] or 5 days of dosing followed by 2 days of pausing [5d+/2d-] or 7 days of dosing followed by 7 days of pausing [7d+/7d-]) or 14 days of dosing followed by 7 days of pausing [14d+/7d-]).

In Part B1, doses of M4344 will be escalated in combination with carboplatin to determine a combination therapy MTD and/or RP2D.

Results of Parts A, A2 and A3 will inform the dose and schedule in Parts C.

In study Parts C the safety, tolerability and efficacy of M4344 administered as a single agent at doses and schedules determined as RP2D in Parts A, A2, or A3 will be evaluated in three different CCI selected populations (loss-of-function mutations in the genes ARID1A in C1 and C4, in ATRX and/or DAXX in C2 and C5, and ATM in C3 and C6). Parts C1, C2, and C3 will use a dose and schedule established in Parts A or A2. Parts C4, C5, and C6 are optional and will use a dose and schedule established in Part A3. Presence of eligible CCI will be assessed during Screening in a mandatory fresh tumor biopsy (a biopsy obtained after the end of the previous treatment regimen is also acceptable) or, if not possible for medical reasons, an archival tumor tissue sample could be used. The CCI for participant selection will be assessed by a central trial assay or by an assay with appropriate regulatory status. Details of this process are provided in supportive documents.

Enrollment is restricted to participants who have exhausted all standard of care options according to NCCN Guidance.

CCI

Planned number of participants: Approximately 300 participants (approximately 25 participants in Part A, 31 participants in Part A2, 40 participants in Part A3, 25 participants in Part B1and 190 in Parts C.

Primary endpoints:

Part A:

- Safety parameters, including AEs, clinical laboratory values (serum chemistry and hematology), vital signs, and electrocardiogram (ECG) assessments
- MTD and/or RP2D of single agent M4344 administered BIW.

Part A2:

- Safety parameters, including AEs, clinical laboratory values (serum chemistry and hematology), vital signs, and ECG assessments
- MTD and/or RP2D of single agent M4344 administered with a twice daily or once daily dose schedule.

Part A3:

- Safety parameters, including AEs, clinical laboratory values (serum chemistry and hematology), vital signs, and ECG assessments
- MTD and/or RP2D of single agent M4344 administered with a drug holiday schedule.

Part B1:

- Safety parameters, including AEs, clinical laboratory values (serum chemistry and hematology), vital signs, and ECG assessments
- MTD and/or RP2D of M4344 administered in combination with carboplatin.

Parts C:

- Occurrence of:
  - Treatment-emergent adverse event (TEAEs) and treatment-related AEs graded according to National Cancer Institute Common Terminology Criteria for Adverse Events Laboratory abnormalities
  - Clinically significant abnormal vital sign
  - Clinically significant abnormal ECG
- Objective response (i.e. confirmed complete response [CR] or partial response [PR]) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 assessed by the Investigator.

Secondary endpoints:

Part A:

- PK parameter estimates of single agent M4344 administered BIW, derived from plasma concentration-time data
- Objective tumor response OR and disease stabilization as evaluated by RECIST 1.1.

Part A2:

- PK parameter estimates of single agent M4344 (and metabolites as appropriate) administered with a twice daily or once daily dose schedule, derived from plasma concentration-time data
- OR and disease stabilization as evaluated by RECIST 1.1.

Part A3:

- PK parameter estimates of single agent M4344 (and metabolites as appropriate) administered with a drug holiday dose schedule, derived from plasma concentration-time data
- OR and disease stabilization as evaluated by RECIST 1.1.

Part B1:

- PK parameter estimates of M4344 administered in combination with carboplatin derived from plasma concentration-time data
- OR as evaluated by RECIST 1.1.

Parts C:

- Confirmed Best Overall Response (response assessment according to RECIST 1.1 as assessed by the Investigator will be used)
- Duration of response assessed from CR or PR until progression of disease, death, or last tumor assessment
- Progression-free survival
- Overall survival
- PK parameter estimates of M4344 (and metabolites as appropriate) in individual participants with loss-of-function mutations.

CCI [redacted]

CCI [redacted]

Pharmacokinetics:

Blood sampling for plasma PK analysis will be conducted in all study parts. Rich sampling is implemented in Parts A, A2, A3 and B1. Sparse sampling is implemented in Parts C. Detailed sampling times are listed in the SoA and Section 7.6.

Efficacy assessments:

Imaging scans (e.g., CT, MRI) will be performed at Screening and at the end of every 2 cycles (i.e. 6 weeks) up to 6 cycles of treatment, and every 3 cycles (i.e., 9 weeks) thereafter until disease progression occurs. In Parts C, participants who discontinue the study treatment for reasons other than disease progression or withdrawal of consent will continue tumor assessments according to the same schedule as participants receiving trial treatment. Bone scan (if positive at Screening) will be performed at the end of Cycle 4 and every 4 to 6 cycles thereafter for those participants continuing beyond 6 cycles or as clinically indicated. For participants with prostate cancer, or other cancers that have bone metastases, bone scans will also be used for evaluation of disease. In addition, for participants with serous ovarian cancer, colon cancer, prostate cancer, or other tumors where appropriate serologic tumor markers are available, these will also be used to monitor antitumor effects.

In Parts C, per RECIST 1.1 objective responses need to be confirmed. Confirmation should be determined at a scan no less than 4 weeks after the original assessment of objective response is made; confirmation of response at the next scheduled tumor assessment is acceptable.

Safety assessments:

Adverse events; clinical laboratory values (serum chemistry, coagulation, and hematology studies); standard 12-lead ECGs; vital signs; and physical examinations.

CCI [redacted]

CCI [redacted]
Diagnosis and key inclusion and exclusion criteria: Male and female participants at least 18 years of age, with tumors measurable by RECIST 1.1. In addition, participants will have the following characteristics: • Parts A, A2, A3, and B1: Advanced solid tumors for which no standard therapy is available and that may convey clinical benefit • All Parts C: Advanced solid tumors for which no recommended standard therapy is available and that harbor loss-of-function mutations in one or more of the following genes ARID1A (C1, C4), ATRX and/or DAXX (C2, C5), ATM (C3, C6). Presence of eligible biomarkers will be assessed during Screening in a mandatory fresh tumor biopsy (a biopsy obtained after the end of the previous treatment regimen is also acceptable) or, if not possible for medical reasons, an archival tumor tissue sample could be used. The biomarkers for participant selection will be assessed by a central trial assay or by an assay with appropriate regulatory status.
Investigational Medicinal Product: dose/mode of administration/ dosing schedule: M4344: An ATR protein kinase inhibitor; 50 mg tablets administered orally. Carboplatin: A DNA-alkylating agent administered up to the AUC = 6 mg min/mL via intravenous infusion. The Sponsor will not supply carboplatin for this study. Sites will use carboplatin as supplied by their pharmacy.
Reference therapy: dose/mode of administration/dosing schedule: Not applicable.

Planned study and treatment duration per participant:

Participants in Parts A, A2, A3, and B1 will have a Screening period of up to 21 days. Participants in Parts C will have a Screening period of up to 42 days.

Following Screening, treatment will last until disease progression. Follow up will include:

- Up to 14 days (± 7 days) for Safety Follow-up (Parts A, A2, A3, and B1) and up to 30 days (± 7 days) for all Parts C;
- Radiologic Follow-up every 6 to 9 weeks following the last cycle of chemotherapy for those participants in Parts B1, and all Parts C without progressive disease;
- Additionally, participants may be followed for overall survival or progression-free survival for up to 1 year or more or until study closure, whichever comes first.

Statistical methods: Analysis of all data will be performed by the Sponsor or designee. Evaluation of efficacy, safety and tolerability of M4344 as a single agent (Parts A, A2, A3 and all Parts C) and in combination with carboplatin (Part B1) will be provided separately. The overall safety profile of M4344 will be assessed in terms of the following safety endpoints:

- Incidence of dose limiting toxicities (DLTs) for Parts A, A2, A3, and B1 only
- Incidence of TEAEs, including AEs leading to dose modifications or discontinuations
- Clinical laboratory values
- ECG outcomes
- Vital signs.

Safety data will be summarized by treatment group and by study part, and overall. In general, safety analyses will be based on the Safety Set, defined as all participants who received at least 1 dose of study drug.

The summary of DLTs will be based on the DLT Evaluable Set.

Efficacy data will be summarized by treatment group and by study part, and overall. Efficacy data may also be summarized by type of cancer, tumor stage at baseline, WHO performance status at baseline, time elapsed since cancer diagnosis, prior chemotherapy and radiation therapy, time elapsed since most recent therapy, duration of most recent cancer therapy, and medical history.

M4344 PK data will be analyzed on an ongoing basis during dose escalation in Parts A, A2, A3, and B1 using standard noncompartmental methods. Pharmacokinetic data for M4344 will be reviewed along with safety data to inform dose escalation. Final PK data for all study parts will be analyzed and reported in accordance with the integrated analysis plan (IAP).

All Parts C:

For each of the Parts C a 3-stage design to evaluate the clinical efficacy of M4344 will be used. After each Stage, of each part, enrollment will only be continued if the prespecified number of participants have shown a best overall response of confirmed CR or PR according RECIST 1.1 and safety has been evaluated.

The analyses of efficacy and safety will be performed separately for each one of the Parts C.

In Stage 1, 9 participants will be evaluated and if no responder is observed, Stage 2 will not open for enrollment and the respective treatment arm will be closed. If at least one responder is observed after 9 evaluable participants are enrolled in Stage 1, then the study will proceed to Stage 2. At completion of Stage 2, the criterion is to observe at least 4 out of 20 participants in Stages 1 and 2 with a best overall response of confirmed CR or PR. If this criterion is not reached, the study part will be stopped. Otherwise the study part will continue to enroll additional 53 participants into Stage 3.

Primary analysis:

The primary analysis will be performed separately for all Parts C after Stage 3 is completed for that part, or when the study part is stopped after Stage 1 or 2, if applicable.

The 95% Clopper-Pearson confidence interval for overall response rate (ORR) will be calculated. When 14 responders are observed out of 73 participants, the corresponding 2-sided 95% Clopper-Pearson confidence intervals for ORR is [11%, 30%] and excludes an ORR of 10%.

Table 1 Schedule of Assessments: Screening (Parts A, A2, A3 and B1)

Assessment	Screening Visits (Day -21 to Day -1)[a]
Informed consent	X
Demographics	X
Medical history	X
Imaging scan disease assessment[b]	X
Bone scan[c]	X
Transthoracic echocardiogram[d]	X
Prior and concomitant medications	X
Height	X
Weight and vital signs	X
Physical examination	X
Clinical disease assessment	X
WHO performance status	X
Standard 12-lead ECG	X
Serum FSH (Postmenopausal female participants < 60 years old only)	X
Serum β-hCG (female participants of childbearing potential only)	X
Hematology	X
Coagulation	X
Serum chemistry	X
Urinalysis	X
Thyroid stimulating hormone[g]	X
Serum total testosterone (male participants only [Part A and Part B1])	X
Archival tumor tissue block[e]	X
Optional fresh tumor biopsy (Parts A2 and A3 only)[f]	X
AEs	Continuous from signing of ICF through Safety Follow-up visit

AE = Adverse event, β-hCG = β-human chorionic gonadotropin, CT = Computerized tomography, ECG = electrocardiogram, FFPE = formalin fixed paraffin embedded tissue, FSH = Follicle stimulating hormone, MRI = Magnetic resonance imaging, WHO = World Health Organization.

a Participants will have a Screening period of up to 21 days (Day -21 to Day -1) before the first dose of the study drug.

b Participants will have a chest and abdominal imaging scan (e.g., CT, MRI) as appropriate and, if clinically indicated, imaging scans of other body areas (e.g., pelvis). Imaging scans performed within 2 weeks of Screening may substitute for assessment of eligibility. For each participant, the same imaging technique should be used to follow the disease (if possible).

c For all participants with prostate cancer or for participants with other malignancies with known or suspected bone metastases or as clinically indicated. If a bone scan has been performed in the 8 weeks before Screening, results from this may be used instead.

d For participants in Parts A and B1 only. If a transthoracic echocardiogram has been performed within 3 months of Screening period of 21 days (Day -21 to Day -1), results from this may be used instead.

e An archival tumor FFPE tissue block will be obtained for all participants before the first dose of study drug (if available). If insufficient tissue is available from an archived specimen, or if the biopsy was obtained more than 12 months before Screening, or at the discretion of the Investigator, participant will be requested to undergo a pretreatment biopsy during Screening.

f Parts A2 and A3 only: an optional fresh FFPE biopsy can be collected for pharmacodynamic analyses during Screening as predose biopsy. The postdose biopsy can be collected on Cycle 1 Day 1, 1 to 3 hours after M4344 administration. If taken, this predose biopsy can replace the archival tumor tissue block to be collected during Screening.

g Not required for Part A3.

Table 2 Schedule of Assessments: Screening (Parts C)

Assessment	Screening Visits (Day -42 to Day -1)[a, b]
Informed consent	X
Demographics	X
Local biomarker data for participant selection[c]	X
Mandatory fresh tumor biopsy[d]	X
Medical history	X
Imaging scan disease assessment[e]	X
Bone scan[f]	X
Prior and concomitant medications	X
Height	X
Weight and vital signs	X
Physical examination	X
Clinical disease assessment	X
WHO performance status	X
Standard 12-lead ECG	X
Serum FSH (Postmenopausal female participants < 60 years old only)	X
Serum β-hCG (female participants of childbearing potential only)	X
Hematology	X
Coagulation	X
Serum chemistry	X
Urinalysis	X
CCI [redacted]	
AEs	Continuous from signing of ICF through Safety Follow-up Visit

AE = Adverse event, β-hCG = β-human chorionic gonadotropin, CT = Computerized tomography, ECG = electrocardiogram, FSH = Follicle stimulating hormone, MRI = Magnetic resonance imaging, WHO = World Health Organization, FFPE = formalin fixed paraffin embedded tissue.

a Participants will have a maximum Screening period of up to 42 days (Day -42 to Day -1) before the first dose of the study drug.

b Participants will undergo confirmation/assessment of selection biomarkers /loss-of-function mutations in the genes ARID1A for Parts C1 and C4, in ATRX and/or DAXX in Parts C2 and C5, and ATM in Parts C3 and C6 (results expected to be available within 21 days). For participants with unknown biomarker status at the time of consent, biopsy biomarker results must be available before completing all other Screening assessments. Participants with known positive biomarkers status can undergo all Screening assessments concurrently.

CCI [redacted]

e Participants will have a chest and abdominal imaging scan (e.g., CT, MRI) as appropriate and, if clinically indicated, imaging scans of other body areas (e.g., pelvis). Imaging scans performed within 2 weeks of Screening may substitute for assessment of eligibility. For each participant, the same imaging technique should be used to follow the disease (if possible).

f For all participants with prostate cancer or for participants with other malignancies with known or suspected bone metastases or as clinically indicated. If a bone scan has been performed in the 8 weeks before Screening, results from this may be used instead.

CCI [redacted]

CCI

Table 3 Treatment and Follow-Up Period (M4344 single Agent Therapy, Part A)

Event/Assessment	Cycle (21 days)								Safety Follow-up 14 days (± 7 days) after the last dose of study drug[a]
	Day 1	Day 2	Day 4	Day 8	Day 9	Day 11	Day 15	Day 18	
Clinical visits	X	X		X[b]	X[b]		X		X
Safety Assessments									
Physical examination[c]	X								X
CT Scan disease assessment[d]	At the end of every 2 cycles until disease progression[e,f]								
Clinical disease assessment[g]									X
Bone scan[h]	At the end of every 4 cycles until disease progression								
WHO performance status	X								X
Ad CA-125 or PSA	Beginning of Cycles 1, 3, and 5[i]								
Weight	X								X
Vital Signs	X[j]			X[b,j]			X[j]		X
Standard 12-lead ECG[k]	X								X
Serum chemistry[l,m]	X[m]	X[b,l]		X[b,l]	X[b,l]		X[l]		X
Hematology[l,m]	X[l]			X[b,l]			X[l]		X
Urine β-hCG[n]	X								X
Serum total testosterone (male participants only)									X
Concomitant medications	Continuous from signing of ICF through Safety Follow-up Visit								
AEs									
Study Drug Administration									
M4344 dosing	X		X	X		X	X	X	
Pharmacokinetic Assessments									
M4344 (Plasma PK collection)[o]	X	X		X	X		X		
CCI [redacted]									

Event/Assessment	Cycle (21 days)								Safety Follow-up 14 days (± 7 days) after the last dose of study drug[a]
	Day 1	Day 2	Day 4	Day 8	Day 9	Day 11	Day 15	Day 18	
CCI									

AE = Adverse event, β-hCG = β-human chorionic gonadotropin, CCI, CA-125 = Cancer antigen 125, CA19-9 = Cancer antigen 19-9, CEA = Cancer embryonic antigen, CT = computerized tomography, ECG = Electrocardiogram, ICF = Informed consent form, PK = Pharmacokinetic, PSA = Prostate specific antigen, WHO = World Health Organization.

a Participants who do not have documented disease progression upon completing the Safety Follow-up Visit should be followed, if possible, for up to 1 year after the Follow-up Visit or until study closure, whichever comes first, on an approximately 3-monthly basis until disease progression, initiation of new therapy, or death.

b Required for Cycle 1 only; however, assessments may be performed at other unscheduled time points at the Investigator's discretion.

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

d CT scan of chest and abdomen should be performed, in addition to CT scan of other body areas (e.g., pelvis), as clinically indicated.

e CT scans will be performed every 2 cycles during the initial 6 cycles of the planned treatment period and every 3 cycles thereafter for those participants continuing beyond 6 cycles.

f If a participant discontinues the study prematurely without evidence of progressive disease on the most recent scan, a follow-up CT scan will be performed within 21 days after the planned last day of the cycle during which the participant discontinued from the study.

g Assessment includes tumor staging (I to IV) and Tumor-Node-Metastasis.

h For all participants with prostate cancer, or for participants with other solid tumors with known or suspected bone metastases.

i CA-125 will be assessed for participants with ovarian cancer and PSA will be assessed in participants with prostate cancer. If treatment is extended beyond 6 cycles, CA-125 or PSA will be measured at the beginning of every 3 cycles or more frequently as clinically indicated. Additional serologic tumor markers may be collected at these time points as deemed appropriate depending on the participant's primary malignancy (e.g., CA19-9 for participants with pancreatic cancer or CEA for participants with colon cancer).

j Vital signs will be measured at 0 hours on Days 1, 8, and 15, and at 4 (± 1) hours after M4344 dosing on Day 1 of Cycle 1. For all subsequent cycles, vital signs will be measured at 0 hours on Days 1 and 15.

k 12-lead ECG will be measured before M4344 dosing (up to 60 minutes before) on Day 1 of every cycle. In addition, 12-lead ECG will be measured 1, 2, and 3 hours after M4344 dosing on Day 1 (± 10 minutes) during Cycle 1 only.

l 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 day of planned study drug administration. See Table 15 for list of analytes and further details regarding laboratory testing schedule.

m Serum chemistry and hematology will be performed on Days 1, 8, and 15 of Cycle 1. For all subsequent cycles, serum chemistry and hematology will be performed on Days 1 and 15 only. In addition, serum chemistry will be performed on Days 2 and 9 of Cycle 1.

n Female participants of childbearing potential only.

o M4344 (and its metabolites as appropriate) plasma PK samples will be collected during Cycle 1 on Days 1 and 8 at 0 (before dosing) and 0.5, 1, 1.5, 2, 3, 4, 8, and 24 hours (Days 2 and 9) after dosing, and on Day 15 at 0 hours (before dosing).

CCI
CCI

r Plasma DNA will be collected from all participants on Day 1 of each cycle and at Safety Follow-up Visit or at disease progression if the participant's disease progresses before the Safety Follow-up Visit.

CCI

Table 4 **Treatment and Follow-Up Period (M4344 Single Agent Therapy, Part A2, and 14d+/7d- schedule of Part A3)**

Event/Assessment	Each Cycle (21 days)							Safety Follow-up 14 days (± 7 days) after the last dose of study drug[b]
	Day 1	Day 2[a]	Days 3-7	Day 8	Days 9-14	Day 15	Days 16-21	
Clinical visits	X	X[c]		X[b]		X		X
Safety Assessments								
Physical examination[d]	X							X
CT Scan disease assessment[e]	At the end of every 2 cycles until disease progression[f,g]							
Clinical disease assessment[h]								X
Bone scan[i]	At the end of every 4 cycles until disease progression							
WHO performance status	X							X
CA-125 or PSA	Beginning of Cycles 1, 3, and 5[j]							
Weight	X							X
Vital Signs	X[l]			X[c,k]		X[k]		X
Standard 12-lead ECG[l]	X							X
Serum chemistry[m, n]	X[n]	X[c,m]		X[c,m]		X[m]		X
Hematology[m, n]	X[m]			X[c,m]		X[m]		X
Urine β-hCG[o]	X							X
Concomitant medications	Continuous from signing of ICF through Safety Follow-up Visit							
AEs								
Study Drug Administration								
M4344 dosing[p]	X	X	X	X	X	X[y]	X[y]	
Pharmacokinetic Assessments								
M4344 (Plasma PK collection)[q]	X	X		X		X		
CCI [redacted]								

Event/Assessment	Each Cycle (21 days)							Safety Follow-up 14 days (± 7 days) after the last dose of study drug[b]
	Day 1	Day 2[a]	Days 3-7	Day 8	Days 9-14	Day 15	Days 16-21	
CCI								

AE = Adverse event, β-hCG = β-human chorionic gonadotropin, CA-125 = Cancer antigen 125, CA19-9 = Cancer antigen 19-9, CEA = Cancer embryonic antigen, CT = computerized tomography, ECG = Electrocardiogram, ICF = Informed consent form, CCI , PK = Pharmacokinetic, PSA = Prostate specific antigen, WHO = World Health Organization.

a Cycle 1 Day 2 assessments applicable only for Part A2.

b Participants who do not have documented disease progression upon completing the Safety Follow-up Visit should be followed, if possible, for up to 1 year after the Follow-up Visit or until study closure, whichever comes first, on an approximately 3-monthly basis until disease progression, initiation of new therapy, or death.

c Required for Cycle 1 only; however, assessments may be performed at other unscheduled time points at the Investigator's discretion.

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

e CT scan of chest and abdomen should be performed, in addition to CT scan of other body areas (e.g., pelvis), as clinically indicated.

f CT scans will be performed every 2 cycles during the initial 6 cycles of the planned treatment period and every 3 cycles thereafter for those participants continuing beyond 6 cycles.

g If a participant discontinues the study prematurely without evidence of progressive disease on the most recent scan, a follow-up CT scan will be performed within 21 days after the planned last day of the cycle during which the participant discontinued from the study.

h Assessment includes tumor staging (I to IV) and Tumor-Node-Metastasis.

i For all participants with prostate cancer, or for participants with other solid tumors with known or suspected bone metastases.

j CA-125 will be assessed for participants with ovarian cancer and PSA will be assessed in participants with prostate cancer. If treatment is extended beyond 6 cycles, CA-125 or PSA will be measured at the beginning of every 3 cycles or more frequently as clinically indicated. Additional serologic tumor markers may be collected at these time points as deemed appropriate depending on the participant's primary malignancy (e.g., CA19-9 for participants with pancreatic cancer or CEA for participants with colon cancer).

k Vital signs will be measured at 0 hours on Days 1, 8, and 15, and at 4 (± 1) hours after M4344 dosing on Day 1 of Cycle 1. For all subsequent cycles, vital signs will be measured at 0 hours on Days 1 and 15.

l 12-lead ECG will be measured before M4344 dosing (up to 60 minutes before) on Day 1 of every cycle. In addition, 12-lead ECG will be measured 1, 2, and 3 hours after M4344 dosing on Day 1 (± 10 minutes) during Cycle 1 only.

m 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 day of planned study drug administration. See Table 15 for list of analytes and further details regarding laboratory testing schedule.

n Serum chemistry and hematology will be performed on Days 1, 8, and 15 of Cycle 1. For all subsequent cycles, serum chemistry and hematology will be performed on Days 1 and 15 only. In addition, serum chemistry will be performed on Days 2 and 9 of Cycle 1.

o Female participants of childbearing potential only.

p Participants in Part A2 and Part A3 will initially be administered M4344 as a single agent under fasting conditions as described in Section 6.2.1.

q M4344 (and metabolites as appropriate) plasma PK samples will be collected during Cycle 1 on Days 1 0 hours (before 1st dose) and 0.5, 1, 1.5, 2, 3, 4, and 8 hours after dosing (before 2nd dose, if applicable) and Day 2 at 0 hours (at time of PBMC sample before 1st Day 2 dose), Day 8 at 0 hours (before 1st dose) and 0.5, 1, 1.5, 2, 3, 4, and 8 hours after dosing (before 2nd dose, if applicable) and on Day 15 at 0 hours (before 1st dose) and 2 hours. Subsequent cycles, Day 1: 0 hours (before 1st dose) and 2 hours. An optional sample may also be collected on Days 1 and 8 at 12 hours after dosing, if the once a day schedule is evaluated. For participants undergoing timed-tumor biopsies, PK samples on Cycle 1 Day 1 at 2 and 3 hours after dosing should be collected only if feasible

CCI [redacted]

CCI [redacted]

t Plasma DNA will be collected from all participants on Day 1 of each cycle and at Safety Follow-up Visit or at disease progression if the participant's disease progresses before the Safety Follow-up Visit.

CCI [redacted]

y Not applicable to participants in Part A3 following the 14d+/7d- drug schedule.

Table 5 **Treatment and Follow-Up Period - M4344 Single Agent Therapy, Part A3 (drug holiday with either 3d+/4d-, 5d+/2d-, or 7d+/7d- schedule)**

NOTE: Part A3 14d+/7d- schedule will use the schedule of assessments from Part A2 (see Table 4).

	Cycle 1 (28 days)				Cycle 2 onward		End of treatment
Event/Assessment	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 15**	**Safety Follow-up 14 days (± 7 days) after the last dose of study drug[a]**
Clinical visits	X	X[b]	X[b]	X[b]	X	X	X
Safety Assessments							
Physical examination[c]	X						X
Weight	X				X		X
Vital Signs	X[b,d]	X[b,d]	X[d]	X[d]	X[d]	X[d]	X
Standard 12-lead ECG[e]	X						X
Serum chemistry[f,g]	X[b,g]	X[b,]	X[f]	X[f]	X[f]	X[f]	X
Hematology[f,g]	X[b,f]	X[b,f]	X[f]	X[f]	X[f]	X[f]	X
Urine β-hCG[h]	X				X		X
Concomitant medications	Continuous from signing of ICF through Safety Follow-up Visit						
AEs							
Clinical disease assessment[i]					X		X
WHO performance status	X				X		X
CA-125 or PSA	Beginning of Cycles 1, 3, and 5[j]						
Imaging Assessments							
CT Scan disease assessment[k]	Every 6 weeks until disease progression[l,m]						
Bone scan[n]	At the end of every 3 cycles until disease progression						
Study Drug Administration							
M4344 dosing[o]	3 days on/4 days off (Day 1-3, 8-10, 15-17, 22-24) 5 days on/2 days off (Day 1-5, 8-12, 15-19, 22-26) 7days on/7 days off (Days 1-7, 15-21)						

	Cycle 1 (28 days)				Cycle 2 onward		End of treatment
Event/Assessment	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 15**	**Safety Follow-up 14 days (± 7 days) after the last dose of study drug[a]**
Pharmacokinetic Assessment							
M4344 (Plasma PK collection)[p]	X	X (3d+/4d- and 5d+/2d- only)	X		X		
CCI [redacted]							

AE = Adverse event, β-hCG = β-human chorionic gonadotropin, CA-125 = Cancer antigen 125, CA19-9 = Cancer antigen 19-9, CEA = Cancer embryonic antigen, CT = computerized tomography, ECG = Electrocardiogram, ICF = Informed consent form, CCI [redacted], PK = Pharmacokinetic, PSA = Prostate specific antigen, WHO = World Health Organization.

a Participants who do not have documented disease progression upon completing the Safety Follow-up Visit should be followed, if possible, for up to 1 year after the Follow-up Visit or until study closure, whichever comes first, on an approximately 3-monthly basis until disease progression, initiation of new therapy, or death.

b Required for Cycle 1 only; however, assessments may be performed at other unscheduled time points at the Investigator's discretion.

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

d Vital signs will be measured at 0 hours on Days 1, 8, and 15, and at 4 (± 1) hours after M4344 dosing on Day 1 of Cycle 1. For all subsequent cycles, vital signs will be measured at 0 hours on Days 1 and 15

e 12-lead ECG will be measured before M4344 dosing (up to 60 minutes before) on Day 1 of every cycle. In addition, 12-lead ECG will be measured 1, 2, and 3 hours after M4344 dosing on Day 1 (± 10 minutes) during Cycle 1 only.

f 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 day of planned study drug administration. See Table 15 for list of analytes and further details regarding laboratory testing schedule.

g Serum chemistry and hematology will be performed on Days 1, 8, and 15 of Cycle 1. For all subsequent cycles, serum chemistry and hematology will be performed on Days 1 and 15 only. In addition, serum chemistry will be performed on Day 2 of Cycle 1.

h Female participants of childbearing potential only.

i Assessment includes tumor staging (I to IV) and Tumor-Node-Metastasis.

j CA-125 will be assessed for participants with ovarian cancer and PSA will be assessed in participants with prostate cancer. If treatment is extended beyond 6 cycles, CA-125 or PSA will be measured at the beginning of every 3 cycles or more frequently as clinically indicated. Additional serologic tumor markers may be collected at these time points as deemed appropriate depending on the participant's primary malignancy (e.g., CA19-9 for participants with pancreatic cancer or CEA for participants with colon cancer).

k CT scan of chest and abdomen should be performed, in addition to CT scan of other body areas (e.g., pelvis), as clinically indicated.

l CT scans will be performed every 6 weeks until disease progression.

m If a participant discontinues the study prematurely without evidence of progressive disease on the most recent scan, a follow-up CT scan will be performed within 28 days after the planned last day of the cycle during which the participant discontinued from the study.

n For all participants with prostate cancer, or for participants with other solid tumors with known or suspected bone metastases.

o Participants in Part A3 will initially be administered M4344 as a single agent under fasting conditions as described in Section 6.2.1. The drug holiday schedules selected for Part A3 (e.g. "3 days on followed by 4 days off" or "7 days on followed by 7 days off" will be selected based on the RP2D after Part A2).

p M4344 (and metabolites as appropriate) plasma PK samples will be collected as described in Section 7.6.1.3, Table 17.

q Genomic DNA samples will be collected during Cycle 1 only.

CCI [redacted]

Table 6 Treatment and Follow-Up Period (M4344 and Carboplatin Combination Therapy, Part B1)

Event/Assessment[b]	Each Cycle (21 days)								Follow-up[a]	
	Day 1	Day 2	Day 3	Day 5	Day 8	Day 9	Day 12	Day 15	*All participants:* Safety Follow-up 14 days (± 7 days)	*Participants without PD only:* Radiologic Follow-up: every 6-9 weeks[c]
Clinical visits	X	X[d]	X[e]	X[f]	X	X[e]	X	X	X	
Safety Assessments										
Physical examination[g]	X[h]							X	X[h]	
Imaging scan disease assessment[i]	At the end of every 2 cycles for the first 6 cycles, then every 3 cycles until disease progression[j]									
Clinical disease assessment[k]									X	
Bone scan[l]	At the end of Cycle 4, then every 4 to 6 cycles until disease progression									X
WHO performance status	X								X	
CA-125 or PSA	Beginning of Cycles 1, 3, 5[m]									
Weight	X								X	
Vital Signs	X[n]	X[o]				X[e,o]			X	
Standard 12-lead ECG		X[p]							X	
Serum chemistry	X[q]	X[e,q]				X[e,q]		X[q]	X	
Hematology	X[q]	X[e,q]				X[e,q]		X[q]	X	
Urine β-hCG[r]	X								X	
Serum total testosterone (male participants only)									X	
Concomitant medications	Continuous from signing of ICF through Safety Follow-up Visit									
AEs										
Study Drug Administration										
M4344 dosing		X		X[s]		X				
Carboplatin dosing	X									
Pharmacokinetic Assessment										
M4344 (Plasma PK collection)		X[t]	X[t]			X[u]				

Event/Assessment[b]	Each Cycle (21 days)								Follow-up[a]	
	Day 1	Day 2	Day 3	Day 5	Day 8	Day 9	Day 12	Day 15	*All participants:* Safety Follow-up 14 days (± 7 days)	*Participants without PD only:* Radiologic Follow-up: every 6-9 weeks[c]
CCI										

AE = Adverse event, β-hCG = β-human chorionic gonadotropin, BRCA = Breast cancer early onset genes 1 and 2, CA-125 = Cancer antigen 125, CA 19-9 = Cancer antigen 19-9, CEA = Cancer embryonic antigen, CT = Computerized tomography, CCI, ECG = electrocardiogram, MRI = Magnetic resonance imaging, MTD = Maximum tolerated dose, PD = Pharmacodynamic, PK = Pharmacokinetics, PSA = Prostate specific antigen, RP2D = Recommended Phase II Dose, WHO = World Health Organization.

a Follow-up will include a Safety Follow-up Visit 14 (± 7) days following the last dose of study drug and Radiologic Follow-up every 6 to 9 weeks following the last cycle of chemotherapy. Radiologic Follow-up Visits are not required for those participants with progressive disease on prior imaging scan. Participants who do not have documented disease progression upon completing the Safety Follow-up Visit should be followed up for survival, if possible, for up to 1 year after the Follow-up Visit or until study closure, whichever comes first, on an approximately 3-monthly basis until disease progression, initiation of new therapy, or death (see Section 5.2.11).

b Please see Section 6.2.4 for guidance on missed assessments.

c Radiologic Follow-up Visits are not required for those participants with progressive disease on prior imaging scan. Participants should attend Radiologic Follow-up Visits until disease progression is observed, new anticancer treatment is started, death, or the end of the study, whichever comes first. For the first 6 months after the start of study treatment, Radiologic Follow-up Visits should occur every 6 weeks, subsequently they should occur every 9 weeks.

d Required for Cycles 1 and 2 only.

e Required for Cycle 1 only; however, assessments may be performed at other unscheduled time points at the Investigator's discretion.

f Required for Cycle 1 at MTD/RP2D if additional dosing days for M4344 are added.

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

h A hearing assessment will be performed on Day 1 of each cycle and at the Safety Follow-up Visit as part of the physical examination.

i Imaging scan (e.g., CT, MRI) of chest and abdomen should be performed, in addition to imaging scan of other body areas (e.g., pelvis), as clinically indicated. Imaging scans may be performed ± 5 days before the end of indicated cycles; however, the imaging scan must be performed before Day 1 dosing of the subsequent cycle. For each participant, the same imaging technique should be used to follow the disease (if possible).

j If a participant discontinues the study prematurely without evidence of progressive disease on the most recent scan, a follow-up imaging scan will be performed within 21 days after the planned last day of the cycle during which the participant discontinued from the study.

k Assessment includes tumor staging (I to IV) and Tumor-Node-Metastasis.

l For all participants with prostate cancer, or for participants with other solid tumors with known or suspected bone metastases.

m CA-125 will be assessed in participants with ovarian cancer and PSA assessed in participants with prostate cancer. If treatment is extended beyond 6 cycles, CA-125 or PSA will be measured at the beginning of every 3 cycles or more frequently as clinically indicated. Additional serologic tumor markers may be collected at these time points as deemed appropriate depending on the participant's primary malignancy (e.g., CA19-9 for participants with pancreatic cancer or CEA for participants with colon cancer).

n Vital signs will be measured on Day 1 at 0 hours (before carboplatin dosing).

o Vital signs will be measured on Day 2 of Cycles 1 and 2 at 0 hours (before M4344 dosing), on Day 2 of Cycle 1 only at 4 (± 1) hours after M4344 dosing, and on Day 9 of Cycle 1 at 0 hours (before M4344 dosing).

p 12-lead ECG will be measured before M4344 dosing (up to 60 minutes before) on Day 2 of Cycles 1 and 2 only. In addition, on Day 2 of Cycle 1 only, 12-lead ECG will be measured 1, 2, and 3 hours after M4344 dosing (± 10 minutes).

q To facilitate timely administration of study drug, safety labs on Day 1 may be obtained up to 3 days before study drug dosing. If labs are drawn before the day of dosing, they should be recorded as corresponding to day of planned study drug administration. See Section 7.5.3 for list of analytes and further details regarding laboratory testing schedule. See Section 6.2.2 for criteria for administration of chemotherapy or M4344.

r Female participants of childbearing potential only.

s Required only at MTD/RP2D in Part B1 if additional dosing days for M4344 are added.

t M4344 plasma PK samples will be collected during Cycle 1 on Day 2 at 0 (before dosing) and at 0.5, 1, 1.5, 2, 3, 4, 8, and 24 hours (Day 3) after dosing. For participants undergoing the timed-tumor biopsies, PK sample collection at 2 and 3 hours after dosing will be optional and will be collected only if feasible.

u M4344 plasma PK samples will be collected during Cycle 1 on Day 9 at 0 hours (before dosing).

v M4344 urine PK samples will be collected during Cycle 1 on Day 2 at 0 hour (before dosing) and at 0 to 4, 4 to 8, 8 to 12, and 12 to 24 hours (Day 3) after dosing.

CCI [redacted]

CCI [redacted]

y For participants with breast cancer or ovarian cancer during Cycle 1 only. This is not required if assessment has been performed previously and results are available for use in this study.

CCI [redacted]

Table 7 **Treatment and Follow-up Period (M4344 single agent therapy in Parts C1, C2, and C3 and the 14d+/7d- schedule described in Parts C4, C5, and C6)**

Event/Assessment[a]	Cycle 1 (21 Days)			Cycle 2 (21 Days)			Subsequent cycles (21 days)	Follow-up[b]	
	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	*All participants:* Safety Follow-up 30 days (± 7 days)	*Participants without PD only:* Radiologic Follow-up[c] every 6-9 weeks
Clinical visits	X	X	X	X	X	X	X	X	X
Safety Assessments									
Physical examination[d]	X							X	
Weight	X			X			X		
Vital Signs[e]	X	X	X	X	X	X	X	X	
Standard 12-lead ECG[f]	X[f]							X	
Triplicate 12-lead ECG (Stage 1 and 2 only)[g]	X[g]								
Serum chemistry	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X	
Hematology	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X	
Urine β-hCG[l]	X[l]			X			X	X	

Event/Assessment[a]	Cycle 1 (21 Days)			Cycle 2 (21 Days)			Subsequent cycles (21 days)	Follow-up[b]	
	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	*All participants:* Safety Follow-up 30 days (± 7 days)	*Participants without PD only:* Radiologic Follow-up[c] every 6-9 weeks
Concomitant medications	Continuous from signing of ICF through Safety Follow-up Visit								
AEs									
Clinical disease assessment[k]	X			X			X	X	
WHO performance status	X			X			X	X	
CCI [redacted]									
Imaging Assessments									
CT scan disease assessment[n]	Every 6 weeks, at the end of every 2 cycles for the first 6 cycles, then every 3 cycles until disease progression[o]								X
Bone scan[p]	Every 4 to 6 cycles until disease progression								X
Study drug administration									
M4344 dosing[q]	Continuous dosing[q]								
Pharmacokinetic Assessments									
M4344 (Plasma PK collection)	X[r]	X	X[r]	X[r]			X[r]		

AE = Adverse event, β-hCG: beta-human chorionic gonadotropin, CCI [redacted], CEA = Cancer embryonic antigen, CT = Computerized tomography, DNA = Deoxyribonucleic acid, ECG = Electrocardiogram, ICF = Informed consent form, MRI = Magnetic resonance imaging, CCI [redacted], PD = progression of disease, PK = Pharmacokinetics, RECIST = Response Evaluation Criteria In Solid Tumors, RP2D = Recommended Phase II dose, WHO = World Health Organization.

a Please see Section 6.2.4 Missed Doses and Study Visits for guidance on missed assessments.

b Follow-up Visit will include a Safety Follow-up Visit 30 (± 7) days following the last dose of study drug and Radiologic Follow-up every 6 to 9 weeks following the last cycle of chemotherapy. Radiologic Follow-up Visits are not required for those participants with progressive disease on prior imaging scan. Participants should be followed up for survival every 3 months until the end of study (see Section 5.2.11).

c Radiologic Follow-up Visits are not required for those participants with progressive disease on prior imaging scan. Participants should attend Radiologic Follow-up Visits until disease progression is observed, new anticancer treatment is started, death, or the end of the study, whichever comes first. For the first 6 months after the start of study treatment, Radiologic Follow-up Visits should occur every 6 weeks, subsequently they should occur every 9 weeks.

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

e Vital signs will be measured predose.

f **In Stage 3 of Parts C1, C2, and C3**: 12-lead ECG will be measured before M4344 dosing (up to 60 minutes before) on Day 1.

g **In Stages 1 and 2 of Parts C1, C2, and C3 only**: triplicate 12-lead ECG with digital upload for centralized analysis will be measured at the times of M4344 PK sampling on Day 1 of Cycle 1 only. Day 1 predose ECG may be measured up to 60 min before dosing. ECG assessment should be performed within 10 minutes prior to PK blood sample collection, such that the blood sample is collected at the nominal time.

h 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 day of planned study drug administration. See Table 15 for list of analytes and further details regarding laboratory testing schedule. See Section 6.2.2 for criteria for administration of M4344.

i Female participants of childbearing potential only.

j If β-hCG is measured on Day -7, assessment will not be repeated on Day 1.

k Assessment includes tumor staging (I to IV) and Tumor-Node-Metastasis.

CCI [redacted]

CCI [redacted]

n Imaging scan (e.g., CT, MRI) of chest and abdomen should be performed every 6 weeks, in addition to imaging scan of other body areas (e.g., pelvis), as clinically indicated. Imaging scans may be performed ± 5 days before the end of indicated cycles; however, the imaging scan must be performed before Day 1 dosing of the subsequent cycle. For each participant, the same imaging technique should be used to follow the disease (if possible). Per RECIST 1.1, objective responses need to be confirmed. Confirmation should be determined at a scan no less than 4 weeks after the original assessment of objective response is made; confirmation of response at the next scheduled tumor assessment is acceptable.

o If a participant discontinues the study prematurely without evidence of progressive disease on the most recent scan, a follow-up imaging scan will be performed within 21 days after the planned last day of the cycle during which the participant discontinued from the study.

p For participants with positive bone scans at Screening.

q M4344 will be administered at a dose and schedule that has been determined as RP2D in either study Part A or A2, or if using the 14d+/7d- schedule, determined in study Part A3.

r M4344 (and metabolites as appropriate) plasma PK samples will be collected during Cycle 1 on Day 1 at 0 (before dosing), between 0.5 to 2 hours after dosing, and at the end of visit at least 1 hours after the previous sample, on Cycle 1 Day 8 and Day 15 (at the start and end of the visit, at least 1 hours apart-2 samples), continuing on Day 1 of every second cycle during Cycles 2-8 and every fourth cycle from Cycle 12 onwards. In case of the 14d+/7d- drug holiday schedule, PK sampling timepoints listed above that fall on days without dosing will be omitted.

Table 8 **Exploratory Assessments (M4344 single agent therapy in Parts C1, C2 and C3 and the 14d+/7d- schedule described in Parts C4, C5, and C6)**

Event/Assessment[a]	Cycle 1		Cycle 2		Subsequent Cycles	Disease Progression or Safety Follow-up[b]
	Day 1	Day 15	Day 1	Day 15	Day 1	
CCI [redacted]						

CCI [redacted]

a Please see Section 6.2.4 Missed Doses and Study Visits for guidance on missed assessments.

b Follow-up Visit will include a Safety Follow-up Visit 30 (± 7) days following the last dose of study drug.

CCI [redacted]

f Stage 1 only. The samples must be taken on Day 1 predose, 3 and 5 hours after M4344 administration in Cycle 1, and on Day 1 predose and 3 hours after M4344 administration in Cycle 2.

Table 9 **Treatment and Follow-up Period (M4344 single agent therapy in Parts C4, C5 and C6, except for the 14d+/7d- schedule)**

Event/Assessment[a]	Cycle 1 (28 Days)				Cycle 2 (28 Days)				Subsequent cycles (28 days)	Follow-up[b]	
	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	*All participants:* Safety Follow-up 30 days (± 7 days)	*Participants without PD only:* Radiologic Follow-up[c] every 6-9 weeks
Clinical visits	X	X	X	X	X		X		X	X	X
Safety Assessment											
Physical examination[d]	X									X	
Weight	X				X				X		
Vital Signs[e]	X	X	X	X	X	X	X	X	X	X	
Standard 12-lead ECG[f]	X[f]									X	
Triplicate 12-lead ECG (Stage 1 and 2 only)[g]	X										
Serum chemistry	X[i]	X[h]	X[h]	X	X[h]	X[h]	X[h]		X[h]	X	
Hematology	X[h]	X[h]	X[h]	X	X[h]	X[h]	X[h]		X[h]	X	
Urine β-hCG[j]	X[j]				X				X	X	
Concomitant medications	Continuous from signing of ICF through Safety Follow-up Visit										
AEs											
Clinical disease assessment[k]	X				X				X	X	

Event/Assessment[a]	Cycle 1 (28 Days)				Cycle 2 (28 Days)				Subsequent cycles (28 days)	Follow-up[b]	
	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	*All participants:* Safety Follow-up 30 days (± 7 days)	*Participants without PD only:* Radiologic Follow-up[c] every 6-9 weeks
WHO performance status	X				X				X	X	
CCI [redacted]											
Imaging Assessments											
CT scan disease assessment[n]	Every 6-weeks until disease progression[o]										X
Bone scan[p]	Every 3 to 4 cycles until disease progression										X
Study Drug Administration											
M4344 dosing[q]	3 days on/4 days off (Day 1-3, 8-10, 15-17, 22-24) 7 days on/7 days off (Days 1-7, 15-21) 5 days on/2 days off (Day 1-5, 8-12, 15-19, 22-26)[q]										
Pharmacokinetic Assessments											
M4344 (Plasma PK collection)[r]	X[r]	X[r]	X[r]		X[r]				X[r]		

AE = Adverse event, β-hCG: beta-human chorionic gonadotropin, CCI [redacted], CEA = Cancer embryonic antigen, CT = Computerized tomography, CCI [redacted], ECG = Electrocardiogram, ICF = Informed consent form, MRI = Magnetic resonance imaging, CCI [redacted], PD = progression of disease, PK = Pharmacokinetics, RECIST = Response Evaluation Criteria In Solid Tumors, RP2D = Recommended Phase II dose, WHO = World Health Organization

a Please see Section 6.2.4 Missed Doses and Study Visits for guidance on missed assessments.

b Follow-up Visit will include a Safety Follow-up Visit 30 (± 7) days following the last dose of study drug and Radiologic Follow-up every 6 to 9 weeks following the last cycle of chemotherapy. Radiologic Follow-up Visits are not required for those participants with progressive disease on prior imaging scan. Participants should be followed up for survival every 3 months until the end of study (see Section 6.2.4).

c Radiologic Follow-up Visits are not required for those participants with progressive disease on prior imaging scan. Participants should attend Radiologic Follow-up Visits until disease progression is observed, new anticancer treatment is started, death, or the end of the study, whichever comes first. For the first 6 months after the start of study treatment, Radiologic Follow-up Visits should occur every 6 weeks, subsequently they should occur every 9 weeks.

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

e Vital signs will be measured predose.

f **In Stage 3 of Parts C4, C5, and C6**: 12-lead ECG will be measured before M4344 dosing (up to 60 minutes before) on Day 1.

g **In Stages 1 and 2 of Parts C4, C5, and C6 only**: triplicate 12-lead ECG with digital upload for centralized analysis will be measured at the times of M4344 PK sampling on Day 1 of Cycle 1 only. Day 1 predose ECG may be measured up to 60 min before dosing. ECG assessment should be performed within 10 minutes prior to PK blood sample collection, such that the blood sample is collected at the nominal time.

h 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 day of planned study drug administration. See Table 15 for list of analytes and further details regarding laboratory testing schedule. See Section 6.2.2 for criteria for administration of M4344.

i Female participants of childbearing potential only.

j If β-hCG is measured on Day -7, assessment will not be repeated on Day 1.

k Assessment includes tumor staging (I to IV) and Tumor-Node-Metastasis.

CCI [redacted]

n Imaging scan (e.g., CT, MRI) of chest and abdomen should be performed every 6 weeks, in addition to imaging scan of other body areas (e.g., pelvis), as clinically indicated. Imaging scans may be performed ± 5 days before the end of indicated cycles; however, the imaging scan must be performed before Day 1 dosing of the subsequent cycle. For each participant, the same imaging technique should be used to follow the disease (if possible). Per RECIST 1.1, objective responses need to be confirmed. Confirmation should be determined at a scan no less than 4 weeks after the original assessment of objective response is made; confirmation of response at the next scheduled tumor assessment is acceptable.

o If a participant discontinues the study prematurely without evidence of progressive disease on the most recent scan, a follow-up imaging scan will be performed within 21 days after the planned last day of the cycle during which the participant discontinued from the study.

p For participants with positive bone scans at Screening.

q M4344 will be administered at a dose and schedule that has been determined as RP2D in either study Part A3.

r M4344 (and metabolites as appropriate) plasma PK samples will be collected as described in Section 7.6.1.4, Table 18.

Table 10 **Exploratory Assessments (M4344 single agent therapy in Parts C4, C5 and C6, except for the 14d+/7d- schedule)**

Event/Assessment[a]	Cycle 1		Cycle 2		Subsequent Cycles	Disease Progression or Safety Follow-up[b]
	Day 1	Day 15	Day 1	Day 15	Day 1	
CCI						

DNA = Deoxyribonucleic acid, PBMC = Peripheral blood mononuclear cells.

a Please see Section 6.2.4 Missed Doses and Study Visits for guidance on missed assessments.

b Follow-up Visit will include a Safety Follow-up Visit 30 (± 7) days following the last dose of study drug.

CCI e

CCI

2 Sponsor, Investigators and Study Administrative Structure

This clinical study is sponsored by: Merck KGaA, Darmstadt, Germany and EMD Serono Research & Development Institute, Inc., Billerica, MA, USA in North America.

The study will be conducted at approximately 10 to 15 sites. Countries participating in this study will include the UK, the USA, the Netherlands and Spain.

The Coordinating Investigator (PPD), represents all Investigators for decisions and discussions regarding this study, consistent with the International Council for Harmonisation (ICH) Topic E6 Good Clinical Practice (GCP; hereafter referred to as ICH GCP). The Coordinating Investigator will provide expert medical input and advice relating to study design and execution and is responsible for the review and signoff of the clinical study report on behalf of all Investigators.

Signature pages for the Protocol Lead and the Coordinating Investigator as well as a list of Sponsor responsible persons are in Appendix I.

The study will appear in the following clinical trial registries: ClinicalTrials.gov and EudraCT.

Details of structures and associated procedures will be defined in a separate Manual of Operations, which will be prepared under the supervision of the Clinical Study Leader.

3 Background Information

Cancer is a group of diseases characterized by dysregulation of cell differentiation, proliferation, and survival. In advanced stages, tumor cells can spread to other areas of the body including vital organs and bone, which can be fatal if not brought under control (American Cancer Society 2011). Through advancements in detection, surgery, and therapy, patients' prognoses are generally improving, and 5-year survival rates for a number of cancers are rising. However, the need for better treatment options remains. The International Agency for Research on Cancer estimates that total cancer-related deaths worldwide in 2008 were 7.6 million, which is expected to rise to 13.2 million cancer deaths by 2030 (American Cancer Society 2011, Ferlay 2010).

Deoxyribonucleic acid (DNA)-damaging agents and ionizing radiation (IR) are widely used as standard of care for the treatment of many solid tumors. However, for most patients, they provide only modest benefit due to highly proficient cellular processes that are able to detect and repair the damaged DNA (Olaussen 2006, Hegi 2005, Norquist 2011).

3.1 Scientific Rationale

The protein kinase ataxia telangiectasia mutated (ATM) and Rad3-related (ATR) are the primary mediator of an important DNA damage surveillance and repair pathway that responds to replication stress (RS) (Cimprich 2008). Replication stress arises when the cell's DNA replication machinery attempts to copy through an unresolved damage lesion. Such events are common after cells are treated with DNA-damaging agents. Left unresolved, RS can lead to double-strand DNA

breaks (DSB) and cell death. The RS pathway is closely associated with a DSB repair pathway mediated by the ATR-related kinase, ATM (Kastan 2004). Inhibition of ATR in noncancer cells has been shown to lead to activation of a compensatory ATM mediated response that protects cells from the lethal consequences of unrepaired RS (Reaper 2011). In contrast, many cancer cells depend on ATR for survival from DNA damage as a result of defects in the ATM signaling pathway and/or as a result of high background levels of RS that can arise from a number of mechanisms, including expression of certain oncogenes (Cancer Genome Atlas N 2012, Ding 2008, Greenman 2007, Jiang 2009). Such defects in ATM signaling can cause a dependence on ATR for survival from RS caused by treatment with DNA-damaging agents (Reaper 2011, Toledo 2011, Murga 2009, Nghiem 2002, Sangster-Guity 2011, Nghiem 2001). Accordingly, while noncancer cells have been shown to tolerate combinations of ATR inhibitors and DNA-damaging drugs, it is expected that an ATR inhibitor will sensitize many cancer cells to various DNA-damaging agents (Reaper 2011). High levels of RS are evident in some cancer cells even in the absence of DNA-damaging agents. This can result from expression of oncogenes that drive dysregulated replication, a hypoxic environment, or from defects in other DNA repair pathways. This high RS in cancer cells can drive a reliance on ATR for survival and thus, ATR inhibitors may have benefit as single agents (Gilad 2010, Schoppy 2012, Murga 2011, Pires 2012, Hammond 2004).

M4344 (initially developed by Vertex Pharmaceuticals Incorporated under the code VX-803) is a potent and selective inhibitor of ATR (inhibition constant < 150 pM) with a concentration resulting in 50% maximal inhibition of 8 nM for the treatment of advanced malignancies. M4344 sensitizes many human cancer cell lines to the cytotoxic effects of various DNA-damaging agents. In contrast, extensive studies with other ATR inhibitors have shown that noncancer cells tolerate ATR inhibition with only a reversible increase in growth arrest attributable to activation of compensatory, ATM-mediated, DNA repair signaling (Reaper 2011).

CCI

Mutations in specific DNA damage response related genes (including ARID1A, ATRX/DAXX and ATM) have been shown to increase reliance on ATR signaling for tumor cell survival and growth (Flynn 2015, Williamson 2016, Min 2017). Published data suggest that loss-of-function mutations in specific tumor genes involved in the DNA damage repair process as candidates to predict sensitivity to ATR inhibitors as monotherapy. Williamson and co-authors showed in an ribonucleic acid interference Screening in cell lines that ARID1A was the top hit gene that was synthetically lethal with the ATR inhibitor VX-821, and that there was a noticeable statistically significant difference in sensitivity to M6620 (VX-970) between the ARID1A wild type and mutated xenografts (Williamson 2016). Flynn and coauthors demonstrated in vitro and in vivo that tumor cells preserving chromosome integrity throughout the alternative lengthening of telomere

process, a mechanism associated with loss-of-function mutations in either the genes ATRX or DAXX which involves DNA homologous recombination, are sensitive to ATR inhibition (Flynn 2015). Antitumor activity of M4344 as monotherapy has been shown in preclinical xenograft harboring such mutations (Vertex Report E0453-U1607-G292&SK-N-F1_VX-803). The co-inactivation of ATM and ATR functions results in synthetic lethality, which has been shown in a gastric cancer xenograft model carrying a mutation in ATM with the ATR inhibitor AZD6738 (Min 2017). Together, these data support the rationale that patients with solid tumors harboring loss-of-function mutations in ARID1A, ATRX or DAXX, and ATM may benefit from treatment with M4344 monotherapy, independent of anatomic tumor localization.

The prevalence of these loss of function mutations is variable and generally low across tumor types. According to a study Sponsor analysis conducted in September 2018 on data of The Cancer Genome Atlas (TCGA) in the National Cancer Institute Genomic Data Commons (NCI GDC), the frequency of loss of function mutations in ARID1A, ATRX, DAXX, ATM is expected to be 6.7%, 3.3%, 0.2%, 2.1%, respectively, in the oncologic patient population (definition of "loss of function" is reported in Section 7.7.5). The indications with the highest prevalence of mutations are in endometrial carcinoma, stomach adenocarcinoma, urothelial carcinoma, and cholangiocarcinoma for ARID1A (30%, 20%, 14%, 11% of cases, respectively), in lower grade glioma and sarcoma for ATRX (31% and 11%, respectively), and colon adenocarcinoma for ATM (11%).

3.2 Toxicology and Compound Safety

M4344 has been evaluated in non-Good Laboratory Practice (GLP) dose-range finding and GLP toxicology studies. Following BIW administration of M4344 at doses of 10, 30, and 45 mg/kg for 14 days in a non-GLP dose-range finding study, a maximum tolerated dose (MTD) of 45 mg/kg was established for rats (ITR Laboratories Report for 72171 2013). In a GLP study, when M4344 was administered BIW to rats at doses of 3, 10, and 30 mg/kg for 28 days (MPI Research for 863-165 2014), the identified target organs of toxicity were consistent with both the pharmacology of ATR inhibition (Ruzankina 2007) and the non-GLP findings and included: bone marrow (regeneration) with corresponding changes to the hematopoietic system (reductions in white blood cell [WBC] and red blood cell [RBC] mass); thymus (lymphoid depletion); spleen (decreased lymphocytes/extramedullary hematopoiesis); liver (extramedullary hematopoiesis); and testes (spermatocyte/spermatid degeneration with concomitant oligospermia/germ cell debris in epididymides) (MPI Research for 863-165 2014). All findings, with the exception of those in the testes, had resolved by the end of the 14-day recovery period (MPI Research for 863-165 2014) however, a duration of 14 days is insufficient for sperm production to completely recover (Creasy 2002). A severely toxic dose to 10% of the population could not be determined in rats.

In a non-GLP 14-day dose-range finding study conducted in dogs at doses of 3, 10, and 30 mg/kg BIW, a single dose of 30 mg/kg resulted in moribundity due to severe gastrointestinal (GI) toxicity; body weight loss and continued deteriorating health led to the early termination of the high-dose (30 mg/kg) group on Study Day 3 (ITR Laboratories Report for 61388 2013). M4344 was also poorly tolerated at 10 mg/kg resulting in emesis, inappetence, liquid stool, brown/green material in the cage tray, and body weight loss (up to 23%); however, effects noted at 3 mg/kg were

minimal. Based on these findings, it was concluded that the MTD was exceeded at 10 mg/kg (ITR Laboratories Report for 61388 2013).

In a GLP 28-day study conducted in dogs assessing BIW administration at doses of 1, 2, and 4 mg/kg, M4344 was poorly tolerated (soft/watery/mucoid feces, red material in the feces and/or in the cage tray, and body weight loss) at the highest dose (4 mg/kg) (MPI Research Report for 863-166 2014). Moribundity, due to GI toxicity and extreme weight loss (14%), observed in 1 high-dose (4 mg/kg) male led to the early sacrifice of that animal on Study Day 24 (MPI Research Report for 863-166 2014). Consistent with the non-GLP findings and the pharmacology of ATR inhibition (Ruzankina 2007), target organs of toxicity identified in this GLP study in dogs at doses of ≥ 2 mg/kg were: bone marrow (regeneration) with corresponding changes in the hematopoietic system (decrease in RBC mass); spleen (extramedullary hematopoiesis); liver (extramedullary hematopoiesis); thymus (lymphoid depletion); GI (inflammation of lamina propria and gut associated lymphoid tissue); and testes (spermatocyte/spermatid degradation and secondary effect on epididymides; germ cell debris) (MPI Research Report for 863-166 2014). Following a 14-day recovery period, all hematology findings had resolved, and an ongoing regenerative response was evident in the bone marrow, thymus, spleen, and liver. Additionally, the findings noted in the GI had resolved at the 2 mg/kg dose; however, as expected, the testicular findings had not resolved at the end of the recovery period (MPI Research Report for 863-166 2014) since duration of 14 days is not sufficient for sperm production to completely recover (Creasy 2002). Based on these data, the highest nonseverely toxic dose (HNSTD) in dogs is considered to be 2 mg/kg BIW. The animal-to-human exposure multiple calculated on an area under the concentration versus time curve (AUC) basis at the HNSTD is expected to be 2-fold the projected human exposure at the efficacious dose.

In addition to toxicology data for M4344, Vertex Pharmaceuticals Incorporated and Merck KGaA also have obtained initial clinical safety data on VX-970/M6620, the first-in-class intravenously administered ATR inhibitor currently in two Phase I clinical studies, MS201923-0001 and VX13-970-002, in the USA and UK. M6620 has been administered in Merck-/Vertex-sponsored studies to over 300 participants with advanced solid tumors, either as a single agent or in combination with either gemcitabine or cisplatin.

Furthermore, initial clinical safety data are available from 40 participants receiving M4344 at doses ranging from 10 mg to 1200 mg) obtained in the ongoing Part A of this study and 13 participants in Study 0001 Part B1 who received M4344 at doses of 350 to 500 mg in combination with carboplatin at the dose AUC 5. Refer to the current version of the Investigator's Brochure (M4344 IB) for further details.

Based on the evaluation of safety data from Study 0001, elevations in hepatic transaminases (ALT and AST) have been established as a new important potential risk associated with the administration of M4344.

M4344 causes hyperbilirubinemia (predominantly indirect or unconjugated bilirubin) via inhibition of bilirubin glucuronidation by UGT1A1. Initially, serious adverse events (SAEs) of increased blood bilirubin and hyperbilirubinemia were reported as dose-limiting toxicities (DLTs) in 3 participants and resulted in study drug withdrawal. After the mechanism of hyperbilirubinemia was determined based on a review of clinical and nonclinical data and outside expert assessment,

the definition of a DLT was revised in a 2016 protocol amendment to exclude increases in bilirubin that are assessed as arising from inhibition of bilirubin glucuronidation, as long as the bilirubin level remains below 15 mg/dL (257 µmol/L) (see Section 5.2.6).

In Part A, bilirubin elevations were dose-dependent, observed at doses ≥ 300 mg. The onset of increased blood bilirubin was within 1 day of administration of the drug and was severe (i.e. Grade ≥ 3) and was not typically associated with other adverse consequences. The incidence of increased blood bilirubin as an SAE was also dose-dependent, and was reported at doses ≥ 700 mg. At 1,200 mg, the highest M4344 dose administered in Study 0001 Part A, 4 participants of 7 participants (57.1%) had SAEs of blood bilirubin increased. In Part B1, 3 participants (23.1%) reported AEs of blood bilirubin increased (1 participant at each of the 3 M4344 doses of 350, 400, and 500 mg); 1 participant (7.7%) reported an SAE of hyperbilirubinemia while receiving 400 mg M4344.

In Part A, DLTs confirmed in dose escalation meetings (DEMs) occurred in 3 of 40 participants in the safety set. One participant in the 1,050 mg group had DLTs of ALT and AST increased, blood bilirubin increased, and neutropenia. Two participants in the 1,200 mg group had a DLT of blood bilirubin increased. No DLTs occurred at M4344 doses from 10 to 700 mg twice weekly.

In Part B1, DLTs confirmed in DEMs occurred in 4 of 13 participants in the safety set. All DLTs were reported in participants receiving M4344 500 mg + AUC5 carboplatin. Three participants had a DLT of neutropenia; DLTs of febrile neutropenia, gastrointestinal inflammation, thrombocytopenia, and vomiting were reported in 1 participant each.

Nausea and vomiting are considered adverse drug reactions (ADRs) for M4344 due to a possible causal association between M4344 treatment and these events. In Study 0001 Part A, nausea occurred in 67.5% of participants and vomiting in 47.5%. These events were usually nonserious, of Grade 1 or Grade 2 intensity, and many occurred on the same day as M4344 administration; the majority did not result in interruption or permanent discontinuation of M4344 treatment.

CCI

4 Study Objectives

4.1 Primary Objectives

4.1.1 Part A

- To evaluate the safety and tolerability of multiple ascending doses of single agent M4344 administered BIW in participants with advanced solid tumors
- To determine the MTD and/or recommended Phase II dose (RP2D) of single agent M4344 administered BIW ($MTD_{SingleBIW}$) in participants with advanced solid tumors.

4.1.2 Part A2

- To evaluate the safety and tolerability of multiple ascending doses of single agent M4344 when administered in a twice daily or once daily dose schedule in participants with advanced solid tumors
- To determine the MTD and/or RP2D of single agent M4344 administered in a twice daily or once daily dose schedule in participants with advanced solid tumors.

4.1.3 Part A3

- To evaluate the safety and tolerability of multiple ascending doses of single agent M4344 when administered in a drug holiday dose schedule in participants with advanced solid tumors
- To determine the MTD and/or RP2D of single agent M4344 administered in a drug holiday dose schedule in participants with advanced solid tumors.

4.1.4 Part B1

- To evaluate the safety and tolerability of M4344 when administered in combination with carboplatin in participants with advanced solid tumors
- To determine the MTD and/or RP2D of M4344 administered in combination with carboplatin in participants with advanced solid tumors.

4.1.5 All Parts C

- To evaluate the safety, tolerability, and efficacy in terms of confirmed objective response of M4344 when administered in participants with solid tumor harboring loss-of-function mutations in the genes ARID1A (Parts C1, C4), ATRX and/or DAXX (Parts C2, C5), or ATM (Parts C3, C6).

4.2 Secondary Objectives

4.2.1 Part A

- To evaluate the pharmacokinetics (PK) of single agent M4344 when administered BIW in participants with advanced solid tumors
- To assess potential antitumor activity of single agent M4344 when administered BIW in participants with advanced solid tumors.

4.2.2 Part A2

- To evaluate the pharmacokinetics (PK) of single agent M4344 (and metabolites as appropriate) when administered in a twice daily or once daily dose schedule in participants with advanced solid tumors
- To assess antitumor activity of single agent M4344 when administered in a twice daily or once daily dose schedule in participants with advanced solid tumors.

4.2.3 Part A3

- To evaluate the pharmacokinetics (PK) of single agent M4344 (and metabolites as appropriate) when administered in a drug holiday dose schedule in participants with advanced solid tumors
- To assess preliminary antitumor activity of single agent M4344 when administered in a drug holiday dose schedule in participants with advanced solid tumors.

4.2.4 Part B1

- To evaluate the PK profile of M4344 when administered in combination with carboplatin in participants with advanced solid tumors
- To evaluate potential antitumor activity after administering M4344 in combination with carboplatin in participants with advanced solid tumors.

4.2.5 All Parts C

- To further evaluate efficacy in terms of confirmed best overall response, duration of response, progression free survival and overall survival time of M4344 when administered in participants with loss-of-function mutations in the genes ARID1A (Parts C1, C4), ATRX and/or DAXX (Parts C2, C5), or ATM (Parts C3, C6)
- To evaluate the PK of M4344 (and metabolites as appropriate) in individual participants with loss-of-function mutations.

CCI

[redacted]

CCI [redacted]

5 Investigational Plan

5.1 Overall Study Design and Plan

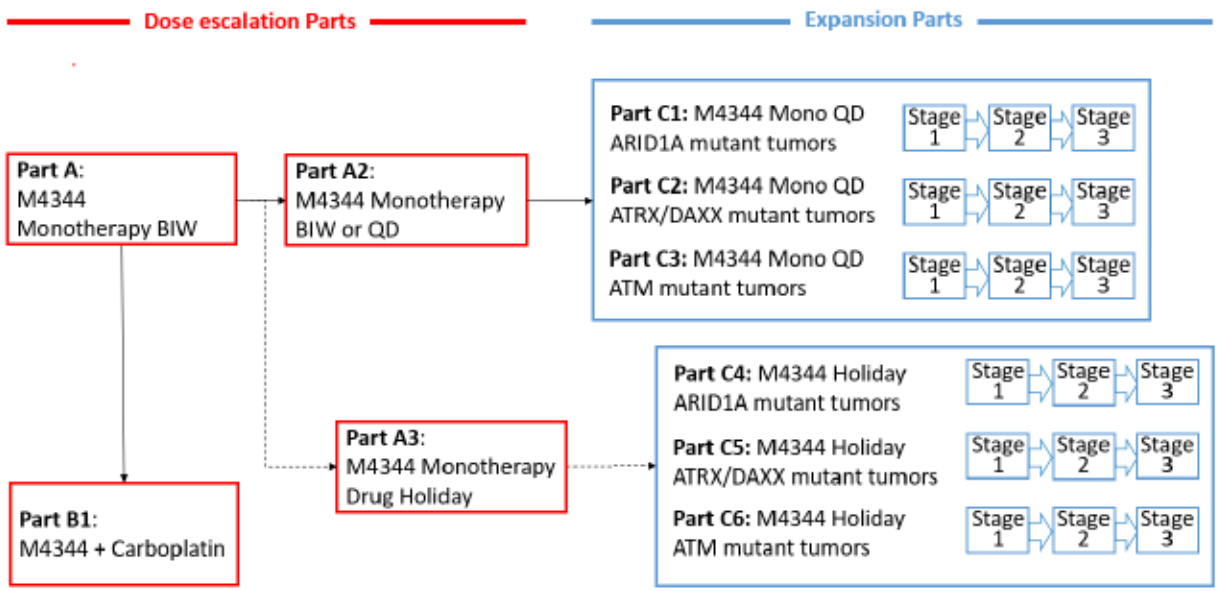
This is an open-label Phase I, first-in-human clinical study conducted in multiple Parts (Parts A, A2, A3, B1, C1, C2, C3, C4, C5, and C6). Part A will establish the MTD/RP2D of M4344 as a single agent administered BIW. Part A2 will establish the MTD/RP2D of M4344 as a single agent administered BID (twice daily) or once daily. Part A3 is optional and will establish the MTD/RP2D of M4344 as a single agent administered in a drug holiday schedule applying a 3-days-on/4-days-off, 5-days-on/2-days-off, 7-days-on/7-days-off and/or 14-days-on/7-days-off schedule. Part B1 will establish the MTD/RP2D of M4344 administered in combination with carboplatin. Parts C1, C2, and C3 will be expansion cohorts to evaluate the tolerability and antitumor activity of single agent continuous M4344 administration in participants with solid tumors with loss-of-function mutations and will use a dose and schedule established in Part A or A2. Parts C4, C5, and C6 are optional expansion cohorts to evaluate the tolerability and antitumor activity of single agent M4344 administered in a drug holiday schedule in participants with solid tumors with loss-of-function mutations and will use a drug holiday dose and schedule established in Part A3.

Results of Part A will inform the starting dose of M4344 in Part B1. Results of Parts A and A2 will inform the dose and schedule in Parts C1, C2, and C3. Results of Part A3 will inform the dose and schedule in Parts C4, C5, and C6. If safety and tolerability preclude escalation of M4344 dose in Part A or A2 to a dose that corresponds to efficacy in preclinical models, then the Sponsor may decide not to initiate the expansion cohorts in Parts C.

The study was designed in accordance with the European Medicine Agency's guidance document, "Guideline on Strategies to Identify and Mitigate Risks for First In Human Clinical Studies With Investigational Medicinal Products."

A schematic of the study design is included in Figure 1.

Figure 1 Schematic of Study Design



ATM = Ataxia telangiectasia mutated, BID = Twice daily, BIW = Twice weekly, QD = Once daily

5.1.1 Part A

Part A will be a dose escalation study, to evaluate the safety, tolerability, and PK, as well as establish the MTD/RP2D of M4344 when administered as a single agent in participants with advanced solid tumors. Approximately 25 participants will be included in Part A. These participants will be administered M4344 as a single agent, on Days 1, 4, 8, 11, 15, and 18 of a 21-day cycle under fasting conditions as described in Section 6.2.1.

The maximum recommended starting dose (MRSD) of single agent M4344 for BIW administration will be 10 mg based on the HNSTD identified in dogs following BIW administration for 28 days. The initial dose escalation of M4344 will utilize a single participant per cohort Phase I study design. One participant will be enrolled at the MRSD. If the starting dose of M4344 is tolerated in this participant through 1 cycle (21 days) without any Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 or greater toxicity that is possibly, probably, or definitely related to study drug, the dose of M4344 may be increased by up to 100% in a subsequent participant, depending on toxicities and tolerabilities observed. In this way, the dose of M4344 may be escalated in subsequent cohorts of single participants until a CTCAE toxicity of Grade 2 or greater that is possibly, probably, or definitely drug-related is observed. In addition, at the discretion of the Sponsor and Investigators up to 2 additional participants (3 per cohort) may be enrolled in the single participant cohort at any dose level, irrespective of the toxicity, to further explore safety and/or PK.

If any of the following CTCAE Grade 2 toxicities that are possibly, probably, or definitely drug-related are observed in a single participant cohort, the dose of M4344 will be increased by up to 50% in a subsequent cohort of 3 participants:

- Nausea
- Vomiting
- Diarrhea
- Fatigue

If no DLTs are observed through 1 cycle in this expanded cohort of 3 participants, the dose will be increased by up to 50% and evaluated in a new cohort of 3 participants, following a standard 3 + 3 design. In this manner, the dose will be increased by up to 50% in subsequent cohorts of 3 participants, until a DLT is observed (Figure 2).

For any other CTCAE Grade 2 or greater toxicity that is possibly, probably, or definitely drug-related, which does not qualify as a DLT observed in a single participant cohort, the tolerability of that dose of M4344 will be evaluated in an expanded cohort of at least 3 participants (2 additional participants) before further dose escalation. If this dose of M4344 is tolerated in the additional 2 participants without a DLT, the dose of M4344 will be increased by up to 50% and evaluated in a new cohort of 3 participants. If no DLTs are observed through 1 cycle in this cohort of 3 participants, the dose will be increased by up to 50% and evaluated in a new cohort of 3 participants, following a standard 3 + 3 design. In this manner, the dose will be increased by up to 50% in subsequent cohorts of 3 participants, until a DLT is observed (Figure 2).

If a single DLT occurs during the single participant cohort dose escalation, then 2 additional participants will be enrolled and evaluated at that same dose level of M4344 to expand the cohort size to 3 participants. If no DLTs are observed in the 2 additional participants, then 3 additional participants will be evaluated at the same dose level of M4344, for a total cohort size of 6 participants. If a single DLT occurs during the 3 + 3 dose escalation in a 3-participant cohort, then 3 additional participants will be enrolled and evaluated at that same dose level of M4344 in order to expand the cohort size to 6 participants. If there are no further DLTs in the additional participants, then up to a 50% dose escalation may proceed in a subsequent cohort of 3 participants.

If there are ≥ 2 DLTs in the initial cohort of 3 participants, dose escalation will cease, and the dose level below will be expanded to 6 participants, or an intermediate dose level will be enrolled with 3 new participants to further explore the safety and tolerability of this dose. Similarly, if a cohort of 3 participants needs to be expanded to 6 participants due to ≥ 1 DLTs and an additional DLT occurs in the 3 subsequent participants, dose escalation will cease, and the dose level below will be expanded to 6 participants, or an intermediate dose level will be enrolled with 3 new participants to further explore the safety and tolerability of this intermediate dose (Figure 2).

The $MTD_{SingleBIW}$ will be the highest dose level at which there is no more than 1 DLT in 6 participants (Figure 2). If, at the discretion of the Sponsor and Investigators, the toxicity and tolerability profile of M4344 remains ambiguous after dosing of 6 participants at any dose level, including the MTD or if additional PK data is felt necessary at any dose level before MTD, up to 6 additional participants may be studied at that dose level to better define the toxicity, tolerability,

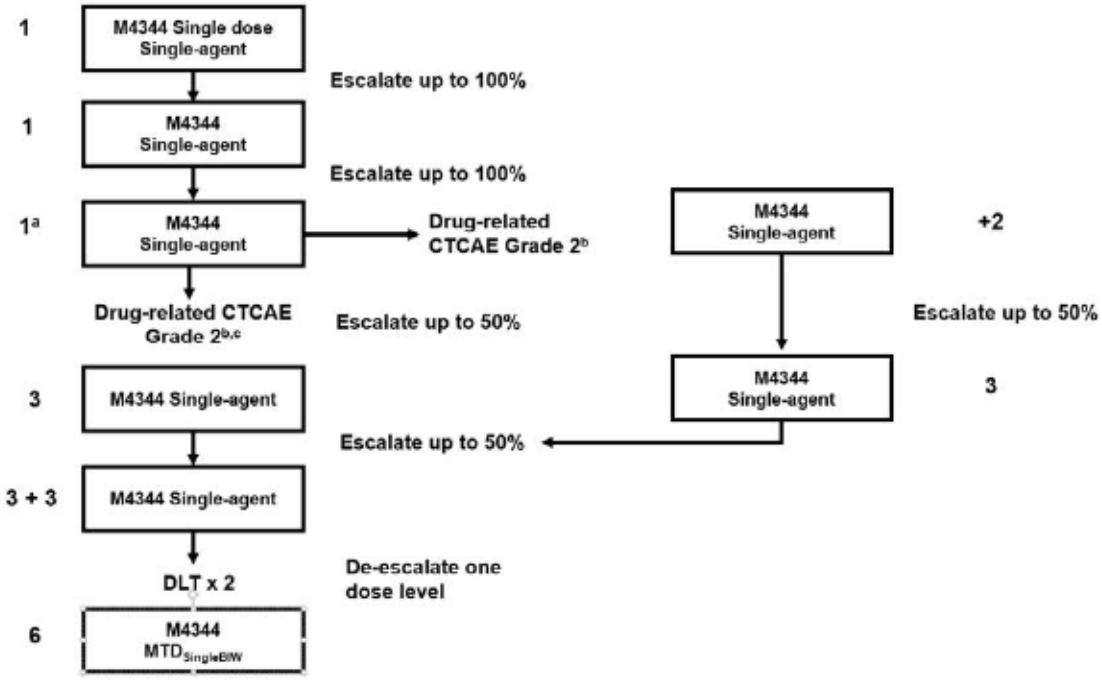
and PK of M4344. Additionally, if evidence of antitumor activity is observed in the dose escalation of M4344 as a single agent, up to 6 additional participants may be studied at the $MTD_{SingleBIW}$ at the discretion of the Sponsor and Investigators. If at a given dose level before MTD, observed exposure exceeds target exposure of AUC = 700 ng hr/mL, this dose level may be considered as the RP2D and Part B1 may be initiated.

During single agent M4344 treatment, computerized tomography (CT) scans will be performed every 2 cycles during the initial 6 cycles of the planned treatment period and every 3 cycles thereafter for those participants continuing beyond 6 cycles or as clinically indicated. Participants will continue on treatment until there is evidence of disease progression (as determined using Response Evaluation Criteria in Solid Tumors [RECIST 1.1] [Scher 2008]) or treatment is no longer tolerated. If a participant discontinues the study prematurely without evidence of progressive disease on the most recent scan, a follow-up CT scan will be performed within 21 days after completion of the final 21-day cycle of therapy. For all participants with prostate cancer, or for participants with other solid tumors with known or suspected bone metastases, bone scans will be performed as described in Table 3 at the end of every 4 cycles until disease progression. In addition, at the beginning of Cycles 1, 3, and 5, participants with ovarian cancer will have serum cancer antigen 125 (CA-125) (Rustin 2004) assessed and participants with prostate cancer will have serum PSA assessed. If treatment is extended beyond 6 cycles, CA-125 or PSA will be measured at the beginning of every 3 cycles or more frequently as clinically indicated. Additional serologic tumor markers may be collected as deemed appropriate depending on the participant's primary malignancy (e.g., cancer antigen 19-9 (CA19-9) for participants with pancreatic cancer or cancer embryonic antigen (CEA) for participants with colon cancer). Disease response in prostate cancer participants may be determined using the Recommendations of the Prostate Cancer Clinical Trials Working Group (PCWG2) and RECIST 1.1 (Scher 2008).

Intraparticipant dose escalation:

Intraparticipant dose escalation is not permitted, except in the case where the M4344 study drug at that dose level is no longer available for the participant who is continuing dosing, responding to treatment and has no significant toxicity. In this case, the participant may be escalated to the next available M4344 dose after prior consultation with the Sponsor. No further dose escalation will be permitted.

Figure 2 Part A: Dose Escalation Schematic for M4344 as a Single Agent



CTCAE = Common Terminology Criteria for Adverse Events, DLT = dose limiting toxicity, $MTD_{SingleBIW}$ = The maximum tolerated dose of single agent M4344 administered twice weekly, PK = Pharmacokinetic

Provisional dose escalation scheme is for illustrative purposes. Number of dose escalation groups, number of participants per group, and amount of dose escalations may differ, as described in Section 5.1.1.

a At the discretion of the Sponsor and Investigators up to 2 additional participants (3 per cohort) may be enrolled in the single participant cohort at any dose level, irrespective of the toxicity, to further explore safety and/or PK.

b Includes CTCAE Grade 2 toxicities or greater that are possibly, probably, or definitely drug-related.

c Limited to include only Grade 2 toxicities of nausea, vomiting, diarrhea, and/or fatigue that are possibly, probably, or definitely drug-related.

5.1.2 Part A2

Part A2 will be a dose escalation study, to evaluate the safety, tolerability, and PK, as well as establish the MTD/RP2D of M4344 when administered as a single agent in participants with advanced solid tumors in a denser schedule than evaluated in Part A. Candidate participants with advanced solid tumors carrying alterations that are suspected to sensitize for treatment with an ATR inhibitor (especially those defined for the Parts C) may be preferentially enrolled.

Approximately 31 participants will be included in Part A2. Participants in Part A2 will initially be administered M4344 as a single agent BID on a daily regimen and under fasting conditions as described in Section 6.2.1.

The M4344 starting dose in Part A2 will be 100 mg (single dose) administered BID (200 mg daily).

The dose escalation of M4344 will follow a 3+3 design. Dose escalations will occur in steps of 50 mg or 100 mg per dose (Figure 3). Subsequent dose levels will be determined in agreement between Investigators and Sponsor.

With no Grade 3 or greater toxicity that is possibly, probably, or definitely related to study drug, the single dose of M4344 may be increased by up to 100 mg in subsequent dose levels, depending on toxicities and tolerabilities observed, and in agreement between the Investigator and Sponsor. If no DLTs are observed throughout the first cycle in a dose cohort of 3 participants, the dose will be escalated to the next dose level. If a single DLT occurs during the 3 + 3 dose escalation in a 3-participant cohort, then 3 additional participants will be enrolled and evaluated at that same dose level of M4344 in order to expand the cohort size to 6 participants. If there are no further DLTs in the additional participants, then the dose escalation may proceed in a subsequent cohort of 3 participants.

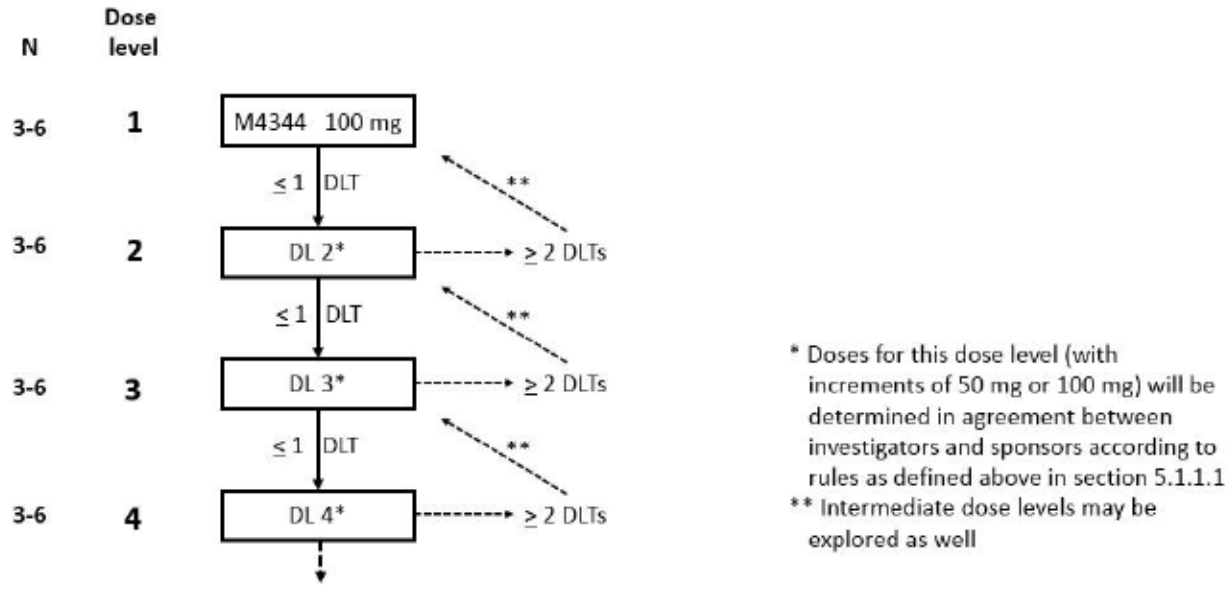
If there are ≥ 2 DLTs in a cohort, the dose escalation will cease, and the dose level below will be expanded to 6 participants, or an intermediate dose level will be enrolled with 3 new participants to further explore the safety and tolerability of this dose. Similarly, if a cohort of 3 participants needs to be expanded to 6 participants due to 1 DLTs and an additional DLT occurs in the 3 subsequent participants, dose escalation will cease, and the dose level below will be expanded to 6 participants, or an intermediate dose level will be enrolled with 3 new participants to further explore the safety and tolerability of this intermediate dose (Figure 3).

The MTD will be the highest dose level at which there is no more than 1 DLT in 6 participants (Figure 3). If, at the discretion of the Sponsor and Investigators, the toxicity and tolerability profile of M4344 remains ambiguous after dosing of 6 participants at any dose level, including the MTD or if additional PK data is felt necessary at any dose level below the MTD, up to 6 additional participants may be studied at that dose level to better define the toxicity, tolerability, and PK of M4344.

Additionally, if evidence of antitumor activity is observed in the dose escalation of M4344 as a single agent, up to 12 additional participants may be studied at the RP2D at the discretion of the Sponsor and Investigators.

Once an MTD is reached with the BID daily regimen or if the safety profile of the BID daily regimen is considered unfavorable, a new schedule with once daily dosing may be explored at the discretion of the Sponsor and Investigators. The single daily starting dose may not exceed the total daily dose of the MTD of the BID schedule. The starting dose of any new schedule will be determined based on available safety and/or PK data in agreement between the Sponsor and Investigators. Dose escalation would follow the same principles as described above.

Figure 3 **Part A2: Dose Escalation Schematic for M4344 with Dense Monotherapy Schedule**



Note: This schematic applies for any dosing schedule in Part A2
Abbreviations: DL = dose level; DLT = dose-limiting toxicity.

5.1.3 Part A3

Part A3 will be an optional dose escalation study, to evaluate the safety, tolerability, and PK, as well as establish the MTD/RP2D of M4344 when administered as a single agent in participants with advanced solid tumors in a drug holiday schedule. The purpose of Part A3 is to investigate drug holiday dosing schedules with the goal of improved long-term tolerability relative to continuous regimens in Part A2. Part A3 will be conducted at selected sites.

M4344 will be administered to participants in Part A3 as a single agent on a drug holiday schedule. Different schedules with either 3 days QD or BID dosing followed by 4 days of pausing (3d+/4d-), 5 days of QD or BID dosing followed by 2 days of pausing (5d+/2d-), 7 days of QD or BID dosing followed by 7 days of pausing (7d+/7d-) or 14 days of QD or BID dosing followed by 7 days of pausing (14d+/7d-) may be explored under fasting conditions as described in Section 6.2.1. One cycle will consist of 4 weeks for a total of 28 days except for the 14d+/7d- schedule, for which a cycle will be 21 days. The first schedules to be explored in Part A3 may be 3 days of BID dosing followed by 4 days of pausing (3d+/4d-) and 7 days of QD dosing followed by 7 days of pausing (7d+/7d-). Other dosing holiday schedules may be explored if agreed by the Sponsor and Investigators. Different schedules may be open concurrently, and concurrent schedules may enroll in a staggered manner, e.g. enrollment in 3d+/4d- dose level (DL) 1 would be completed before starting enrollment in 7d+/7d- DL 1 and this would apply to all subsequent cohorts.

The starting dose for all drug holiday schedules will be determined in agreement between Sponsor and Investigators. For QD schedules, the daily dose will be no more than 100 mg higher than the

RP2D or MTD determined in Part A2. For BID schedules, the cumulative weekly starting dose will not exceed the weekly cumulative dose of the MTD assessed in any previously explored BID schedule.

A RP2D (dose and schedule) will be determined from Part A3 by agreement between Investigators and the Sponsor and may be different from the MTD. Determination of RP2D will be based on clinical safety data, total weekly dose, dose per administration, available PK data and any available efficacy data in agreement between Investigators and the Sponsor.

CCI

[redacted]

Part A3 and Parts C may enroll in parallel but enrollment in Parts C will be prioritized versus Part A3:

- Candidate participants with advanced solid tumors carrying the qualifying mutations for Parts C (see Section 7.7.5 for full details) should be considered for enrollment in Parts C1, C2 or C3 before being considered for participation in Part A3.
- If a participant is not eligible for Parts C, the participant may be considered for participation in Part A3 (see Figure 5, Schematic of Eligibility Assessments in Parts C) provided that the inclusion / exclusion criteria for Part A3 are met.
- Candidate participants may solely be considered for participation in Part A3 at the discretion of the Investigator.

5.1.4 Part B1

Part B1 will be a standard Phase I study design 3 + 3 dose escalation to evaluate the safety, tolerability, and PK, as well as to establish the MTD/RP2D of M4344 when administered in combination with carboplatin in participants with advanced solid tumors.

For each M4344 dose level tested, participants will receive carboplatin on Day 1 and M4344 on Days 2 and 9 of a 21-day cycle. M4344 will be administered under fasting conditions as described in Section 6.2.1.

The starting dose of M4344 will not exceed 50% of the M4344 $MTD_{SingleBIW}$ or RP2D obtained in Part A. The starting dose of carboplatin for Part B1 will be AUC 5 mg·min/mL. The starting doses of M4344 and carboplatin will be evaluated in a cohort of 3 participants.

Safety data, including adverse events (AEs), laboratory values, and electrocardiogram (ECG) results, obtained through the end of Cycle 1, as well as available PK data (as needed), will be assessed to determine the next dose level of M4344. Each dose level will be evaluated in a new cohort of participants.

If the initial dose of M4344 in combination with carboplatin at AUC = 5 mg·min/mL is tolerated in a cohort of 3 participants without a single DLT through the end of Cycle 1, then in subsequent cohorts of 3 participants each, the M4344 dose may be escalated by up to 50%, until a M4344 combination MTD or RP2D with carboplatin AUC = 5 mg·min/mL is reached (Figure 4). The MTD is defined as the highest tolerated dose at which there is no more than 1 DLT in 6 participants treated with both M4344 and carboplatin. In subsequent cohorts, the carboplatin dose may be increased to yield a target AUC of 6 mg·min/mL, while either keeping the dose of M4344 at the MTD/RP2D established with carboplatin AUC = 5 mg·min/mL constant, or de-escalating to lower M4344 dose levels, in order to establish the MTD/RP2D of M4344 with carboplatin AUC = 6 mg·min/mL (Figure 4).

If the initial dose of M4344 with carboplatin AUC = 5 mg·min/mL is not tolerated, then either the carboplatin dose may be reduced to yield an AUC of 4 mg·min/mL or the M4344 dose may be reduced by ≥ 25%. These doses will be explored in subsequent cohorts, at the discretion of the Sponsor and Investigators, until the MTD or RP2D of M4344 with carboplatin AUC = 4 or 5 mg·min/mL (Figure 4) is obtained.

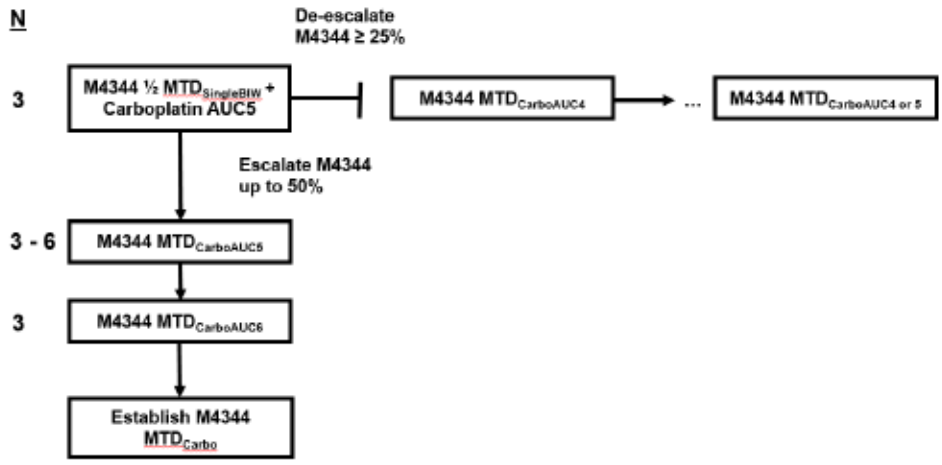
Once the MTD of the combination or the RP2D dose is obtained, an additional cohort of participants may be enrolled to evaluate the safety of 1 additional dose of M4344 on Day 5 during the 21-day cycle. These participants will receive carboplatin on Day 1, and M4344 on Days 2, 5, and 9 of a 21-day cycle. If the established MTD of the combination is not tolerated with the additional day of dosing, the dosing schedule will revert back to dosing carboplatin on Day 1 and M4344 on Days 2 and 9 of a 21-day cycle.

If, at the discretion of the Sponsor and Investigators, the toxicity and tolerability profile of M4344 and carboplatin remains ambiguous after dosing of 6 participants at any dose level, including the MTD, or if additional PK data is felt necessary at any dose level before MTD, up to 6 additional

participants may be studied at that dose level to better define the toxicity, tolerability, and PK of M4344 and carboplatin.

At all dose levels of M4344, participants will continue treatment until there is evidence of disease progression (as determined using RECIST 1.1) or treatment is no longer tolerated. Imaging scans (e.g., CT and magnetic resonance imaging [MRI]) will be performed every 2 cycles for the first 6 cycles of treatment and every 3 cycles thereafter for those participants continuing beyond 6 cycles, or as clinically indicated. For each participant, the same imaging technique should be used to follow the disease (if possible). Bone scan will be performed as described in Table 6 at the end of Cycle 4 and every 4 to 6 cycles thereafter for participants continuing beyond 6 cycles or as clinically indicated. If there is evidence of progressive disease as determined using RECIST 1.1, the participant's treatment will be discontinued. In addition, at the beginning of Cycles 1, 3, and 5, participants with ovarian cancer will have serum CA-125 assessed, and participants with prostate cancer will have serum PSA assessed. If treatment is extended beyond 6 cycles, CA-125 or PSA will be measured at the beginning of every 3 cycles or more frequently as clinically indicated. Additional serologic tumor markers may be collected as deemed appropriate depending on the participant's primary malignancy (e.g., CA19-9 for participants with pancreatic cancer or CEA for participants with colon cancer). Disease response in prostate cancer participants may be determined using the Recommendations of the PCWG2 and RECIST 1.1 (Scher 2008).

Figure 4 **Dose Escalation Schematic for M4344 in Combination With Carboplatin (Part B1)**



BIW = Twice Weekly, MTD = Maximum tolerated dose, $MTD_{SingleBIW}$ = Maximum tolerated dose of M4344 administered BIW from Part A, MTD_{carbo} = Maximum tolerated dose of M4344 in combination with the highest tolerated dose of carboplatin

Provisional dose escalation scheme is for illustrative purposes. Number of dose escalation groups, number of participants per group, and amount of drug escalation may differ, as described in Section 5.1.3.

5.1.5 All Parts C

Study Parts C will be expansion cohorts to explore potential antitumor efficacy and to confirm the safety and tolerability of single agent M4344 administered at a dose and schedule that has been determined as RP2D in study Part A, A2 or A3.

Parts C1, C2, and C3 may be initiated in parallel or in a staggered manner using a dose and schedule determined to be a RP2D in either Part A or Part A2 at the discretion of the Sponsor and Investigators. Additional Parts C4, C5, and/or C6 using a RP2D determined in Part A3 may be initiated at any time. The decision on the RP2D from Part A3 to be used in Parts C4, C5 and C6 will be made based on clinical safety data, total weekly dose, dose per administration, available PK data and any available efficacy data in agreement between Investigators and the Sponsor. The decision on whether to proceed to Parts C4, C5 and C6 will also consider whether a RP2D from Part A3 is considered more favorable than that of Part A or A2.

The target population will consist of participants whose tumors have certain CCI that have been identified to sensitize to ATR inhibition in preclinical models and for whom no standard treatment options are available.

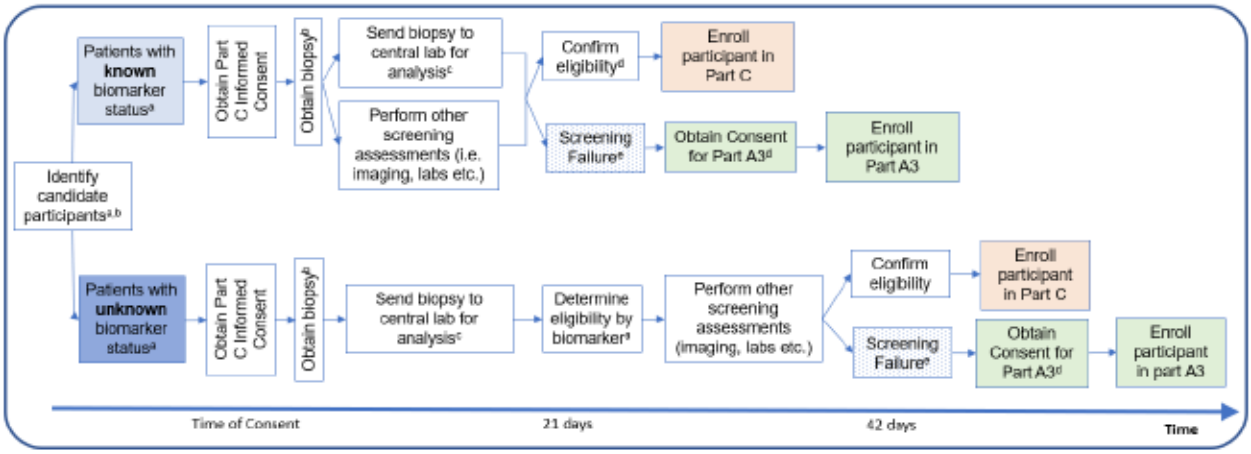
Parts C1 and C4 will enroll participants whose tumor carry a loss-of-function mutation in the gene for ARID1A.

Parts C2 and C5 will enroll participants whose tumor carry a loss-of-function mutation in the genes for ATRX and/or DAXX (leading to an alternative lengthening of telomeres-positive phenotype).

Parts C3 and C6 will enroll participants whose tumor carry a loss-of-function mutation in the gene for ATM.

Figure 5 provides a schematic of eligibility assessments in Parts C.

Figure 5 Schematic of Eligibility Assessments in Parts C



a Loss-of-function mutation(s) in ARID1A, ATRX, DAXX, or ATM. See Section 7.7.5 for full details.

b If information on biomarker status is not available at time of Informed Consent, candidate participants must confirm the CCI eligibility (presence of mutations) prior to performing any of the additional Screening assessments (lower part of the figure). If information on biomarker mutations is available at time of Informed Consent, the patient is allowed to perform the biopsy analysis and the remainder of Screening procedures in parallel (upper part of the figure).

c A biopsy obtained after the end of the previous treatment regimen is also acceptable. If collection of a fresh tumor biopsy is not possible for medical reason(s) and a biopsy obtained after the end of the previous treatment regimen is not available, available archival tumor material may be used (historical data should not be used to confirm biomarker status).

d Only after confirmation from the central lab of the presence of tumor mutations (and all other inclusion/exclusion criteria are met) can participants start the treatment period.

e If analysis of biopsy does not reveal a qualifying mutation, but all other Inclusion / Exclusion criteria are met, then the candidate participant may be considered for participation in Part A3.

Participants may be selected for Screening based on locally available data showing presence of ≥ 1 selection biomarkers (e.g. from archival tumor material). Participants with known positive biomarker status at the time of consent, according to locally available data, can undergo the Screening Biopsy analysis and the rest of Screening assessments concurrently (Table 2). Participants with unknown biomarker status at the time of consent can only undergo the Screening assessments once the presence of ≥ 1 selection biomarkers (defined in Section 7.7.5) is confirmed.

The biopsy analysis will consist of an assessment of the presence of such mutations by a central trial assay or by an assay with appropriate regulatory status. This assessment should be conducted

on a fresh tumor biopsy (or a biopsy that was obtained after the end of the previous treatment regimen). If this is not possible for medical reason(s), available archival tumor material may be used for this assessment (historical data should not be used to confirm biomarker status). Participants will consent to Screening procedures prior to any Screening activities.

Treatment will continue until disease progression, unacceptable toxicity, participant's withdrawal or any other reason to end study treatment. After disease progression, participants will be followed-up for survival until the End of Study. Tumor assessment according to RECIST 1.1 will be performed at baseline and at the end of every 6 weeks for the first 6 cycles, then every 9 weeks thereafter until disease progression or start of new anti-cancer treatment line.

Each of the selected CCI populations (any Part C) will follow a single arm 3-stage design. The initial stage will consist of 9 participants in each part. If 1 or more responses (partial response [PR] or complete response [CR], as per RECIST 1.1) are observed in a part, this part will proceed to the Stage 2, adding 11 participants to a total of n = 20. If at least 4 responders out of 20 evaluable participants are observed a third stage may be started, which will consist of 53 participants.

Efficacy readout will be based on the response rate, determined according to RECIST 1.1.

5.2 Discussion of Study Design

5.2.1 Rationale for the Study Design

M4344 is a potent, selective inhibitor of ATR, an enzyme that is critical for DNA damage surveillance and repair. Many anticancer treatments act by damaging DNA; however, resistance to these agents is common. This resistance can be attributed to effective DNA damage repair processes that include the pathway mediated by ATR. In nonclinical experiments, ATR inhibition by M4344 has been shown to markedly enhance the anticancer effects of DNA-damaging agents such as carboplatin in a range of human cancer cell lines and participant-derived explants. In addition, M4344 exhibits monotherapy efficacy in a mouse xenograft model of colorectal cancer characterized by defective ATM signaling (Vertex Report K235 2014) and models characterized as utilizing an alternative lengthening of telomeres mechanism (Flynn 2015).

Parts A, A2, and B1 of the study use conventional Phase I dose escalation study 3+3 designs to establish RP2Ds of either single agent M4344 treatment or of the combination of M4344 with carboplatin. Part A3 uses a BOIN design for dose escalation. In view of the nonclinical toxicities observed, safety assessments will be carried out at each investigational center. The decision to decrease the magnitude of dose escalation of M4344 between cohorts to less than 100% will be based on review of drug-related or possibly drug-related DLTs and non-DLT AEs of Grade 2 or higher, other safety trends, and/or results from PK data as specified in Section 5.1. Parts C aim at establishing safety and demonstrating antitumor activity of single agent M4344 administered at the RP2D in participants whose tumors carry certain molecular defects that are expected to confer sensitivity towards ATR inhibition.

5.2.2 Rationale for Study Drug Dose and Duration

The starting dose of M4344 is based on the HNSTD determined in the GLP 28-day repeat dose toxicity study in dogs (MPI Research Report for 863-166 2014). The MRSD of 10 mg is 1/6th the human equivalent dose (HED) of the HNSTD determined in dogs, which was the most sensitive species.

After an initial participant receives M4344 at the MRSD, dose escalation will continue in successive cohorts with a 100% increase (i.e. doubling of dose), unless a trend in non-DLT Grade 2 or higher CTCAE grade toxicity is observed. At that point, depending on review of all safety and available PK data, dose escalation will be conducted as described in Section 5.2.10 until the M4344 MTD is identified. Doses may increase by less than 100% or less than 50% at any point, if indicated based on review of safety and PK data. In addition, following reports of a DLT, an intermediate lower dose may be evaluated in a new cohort of participants.

The MRSD of 10 mg is approximately 1/9th the predicted optimally efficacious dose based on mouse xenograft models of 90 mg (Vertex Report K084 2014). With single-participant cohorts and 100% dose escalation between cohorts, approximately 4 participants will receive doses of M4344 that fall below the predicted optimally efficacious dose. The single-participant cohort escalation thus minimizes the number of participants exposed to potentially subtherapeutic doses of M4344.

In Part A of clinical study MS201922-0001 (formerly VX14-803-001), the maximum administered dose was 1200 mg, twice weekly. At this dose, the observed plasma exposure, average concentration (C_{avg}), was below the target efficacious exposure determined in preclinical models testing M4344 as monotherapy. Though the criteria for maximum tolerated dose were not yet fulfilled, one DLT of Grade 3, fever, was observed. There was also an unacceptable pill burden with the current 50 mg strength tablet. Together this indicates that the 1200 mg twice weekly regimen may not be appropriate to support its use as monotherapy.

Part A2 of study MS201922-0001 is designed to evaluate whether sufficient C_{avg} can be achieved and is tolerated to support M4344 use as monotherapy. The BID daily regimen that will be evaluated in Part A2 is based on (i) preclinical xenograft studies, and (ii) clinical PK data obtained from Part A, described below. If the BID regimen is considered unfavorable, a new schedule with once daily dosing may be explored at the discretion of the Sponsor and Investigators.

Furthermore, in Part A3, drug holiday schedule(s) may be explored (see Section 5.1.3 for details).

Generally, ATR signaling is required to enable cancer cells to progress through to S/G2-phase, and inhibition of ATR lethally compromises this process. Repeated or prolonged ATR inhibition is expected to result in increased antitumor efficacy (M6620 Investigator Brochure). For M4344 monotherapy, preclinical murine xenograft studies of M4344 in ALT+ models demonstrate that increased frequency of dosing is associated with, and possibly required for optimal antitumor activity in the monotherapy setting (Vertex Report E0453-U1607 2016) while maintaining tolerability based on body weight and mortality. These data suggest that prolonged or repeated inhibition of ATR not only potentiates the cytotoxic effects of DNA damage, but it may also be efficacious as monotherapy in cancers which are reliant on ATR signaling (Flynn 2015). Of note, similar antitumor activity was observed for the same total weekly dose when administered once daily or twice daily in the preclinical study (Vertex Report E0453-U1607 2016). Daily dosing of M4344 monotherapy of 20 mg/kg per day (10 mg/kg BID and 20 mg/kg once daily) demonstrated increased antitumor activity compared to every other or every 3rd day dosing in the SKNF1 (neuroblastoma utilizing the alternative lengthening of telomeres pathway) xenograft model. Similar results were also obtained in the G292 (ALT positive) osteosarcoma model. These preclinical data suggest that sustained ATR inhibition in the monotherapy setting and high antitumor activity may be achieved with more frequent BID dosing compared with twice weekly dosing.

Tumor growth inhibition modeling of the SKNF1 and G292 xenograft data was performed and identified the plasma concentration (C_{avg}) that must be maintained to achieve tumor stasis. This value was used as a target to achieve in human.

In light of the relatively short half-life of M4344 (1-4 h, estimated in Part A VX-803 (M4344) Investigator's Brochure), more frequent divided dosing is expected to sustain ATR inhibition throughout the dose interval with reduced fluctuation, and a lower maximum concentration (C_{max}) required to achieve an increased plasma C_{avg}. Furthermore, the associated reduction in C_{max} may improve safety and tolerability. Finally, more frequent, smaller doses would also provide more manageable doses per administration (i.e. reduce pill burden) to the participant.

Therefore, BID daily dosing was selected as the initial schedule for Part A2.

A 100-mg single dose administered BID (200 mg daily) was selected as starting dose for Part A2.

This starting dose is based on the available clinical experience in 36 participants treated with up to the 1200 mg twice weekly dosing schedule in Part A. As of December 2017, in total 7 participants have completed the DLT period at the 1200 mg dose level. One DLT of Grade 3 fever was observed and the criteria for MTD were not yet fulfilled. The 1200 mg twice weekly schedule results in a total weekly dose of 2400 mg. A 100-mg dose administered twice daily results in a total weekly dose of 1400 mg and is therefore expected to be a tolerable starting dose.

When M4344 is administered twice daily, the second daily dose is hypothesized to be optimally administered at 12-hour intervals to provide sustained ATR inhibition. However, a 4-hour window (8 to 16 hours) is permitted for participant convenience. Since the terminal half-life of M4344 is approximately 2 hours, minimal drug accumulation is expected with the twice daily or once daily schedules.

Preclinical modeling of the PK-efficacy relationship for M4344 monotherapy in the MV4.11 xenograft model has been used to predict human efficacious dose and schedules. The human PK profile was incorporated into a tumor growth inhibition model and used to identify doses and schedules to achieve at least a 60% tumor growth inhibition. With continuous dosing a human efficacious dose of approximately 275 mg once daily is predicted.

Further preclinical data suggest that efficacy can be achieved with different doses and schedules, including various drug holiday schedules. In general, treatment interruptions improved tolerability but with potential reduction in efficacy. This implies that drug holiday schedule(s) may only be preferred if they enable escalation to higher doses per administration and, ideally, are able to meet or exceed the total weekly dose. Therefore, Part A3 of this study is designed to explore one or more drug holiday schedules.

The dosing schedule for M4344 in combination with carboplatin in Part B1 is based on the optimal timing of ATR inhibition after drug exposure to DNA damaging agents. In vitro cell culture experiments and animal models suggest that delaying dosing of M4344 for approximately 24 hours after the dosing of DNA-damaging agents will promote cell death in tumor cells (M6620 IB). Furthermore, cell studies, animal studies, and PK data support infrequent dosing of M4344 to provide optimal efficacy, tolerability, and exposure in combination with chemotherapy. The standard dose of carboplatin used for treatment of ovarian cancer per National Comprehensive Cancer Network (NCCN) guidelines (NCCN Guidelines 2013) is approximately AUC = 5 mg·min/mL. Carboplatin dosing at AUC = 4 mg·min/mL, or at AUC = 6 mg·min/mL, is used in certain clinical situations or for certain indications. The 21-day dosing cycle and the dosing frequency of carboplatin used in this study are based on standard of care regimens.

The dose and schedule of single agent M4344 to be used in all Parts C will be a RP2D, determined in Parts A, A2, or A3 of this study.

5.2.3 Rationale for Participant Selection

Eligible participants in Parts A, A2, and A3 will have advanced solid tumors for which no standard therapy is available which may convey clinical benefit. Eligible participants in Part B1 will have

advanced solid tumors for which no standard therapy is available which may convey clinical benefit, and/or participants must have disease progression after at least 1 prior chemotherapy regimen in the metastatic setting, and for which carboplatin (Part B1), would be considered standard of care. 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 chemotherapy sensitizing agent.
Participants enrolled in Parts C will have advanced solid tumors for which no recommended standard therapy is available, i.e. participants who have exhausted all standard of care options according to NCCN Guidance and for whom M4344 may convey clinical benefit. Furthermore, they will be selected based on the following biomarkers:

- Parts C1 or C4: will enroll participants whose tumors carry a loss-of-function mutation in the gene ARID1A
- Parts C2 or C5: will enroll participants whose tumor carry a loss-of-function mutation in ATRX and/or DAXX
- Parts C3 or C6: will enroll participants whose tumor carry a loss-of-function mutation in the gene ATM.

These biomarkers for participants selection will be assessed by a central trial assay or by an assay with appropriate regulatory status (see Section 5.1.4).

5.2.4 Rationale for Study Assessments

Participants will be monitored frequently for AEs that are predicted to be potential consequences of therapy with M4344, based on nonclinical toxicology, and of concurrent chemotherapy, based on prior experience in participants.

Based on non-GLP dose-range finding studies and GLP 28-day toxicity studies in rat and dog, the following target organs for M4344 toxicity have been identified: hematopoietic system (decrease in RBC and or WBC); spleen (extramedullary hematopoiesis); liver (extramedullary hematopoiesis); thymus (lymphoid depletion); and testes (spermatocyte/spermatid degradation and secondary effect on epididymides; germ cell debris) (ITR Laboratories Report for 72171 2013, MPI Research Report for 863-165 2014, ITR Laboratories Report for 61388 2013, MPI Research Report for 863-166 2014). Additionally, in dogs, GI was also noted as a target (inflammation of lamina propria and gut associated lymphoid tissue) (MPI Research Report for 863-166 2014).

Based on these findings, participants will be monitored weekly during Cycle 1, and at least twice per cycle thereafter for adverse effects to the bone marrow or liver. Male participants in Parts A and B1 will have testosterone measurements at baseline and at Safety Follow-up to assess for chronic effects on gonadal function. Participants will be managed symptomatically for GI adverse effects.

Imaging scans will be used periodically to monitor for tumor response to treatment, and response will be judged using RECIST 1.1. Participants who have disease progression, or for whom the

treating physician considers that it is not in their best interest to continue, will discontinue treatment.

5.2.5 Inclusion of Special Populations

For definition of participants for Parts C, please see Section 5.2.3.

5.2.6 Definition of Dose Limiting Toxicity

Participants will be monitored for DLTs throughout dosing cycles. DLTs will be defined using the National Cancer Institute (NCI) CTCAE (Part A and B1: Version 4.0; Parts A2, A3: Version 5.0).

A DLT is defined as related or possibly drug-related:

- Neutropenia Grade 4 for > 7 days duration or requiring hemopoietic growth factors
  - In the event of Grade 4 neutropenia, a full blood count must be performed no more than 7 days after the onset of the event to determine if a DLT has occurred. The participant will be closely monitored until resolution to Grade 3 or less.
- Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection in the setting of Grades 3 or 4 neutropenia)
- Infection (documented clinically or microbiologically) with Grades 3 or 4 neutropenia (absolute neutrophil count < 1.0×10^9/L)
- Thrombocytopenia Grade 3:
  - associated with clinically significant bleeding
  - requiring platelet transfusion or hemopoietic growth factors
- Thrombocytopenia Grade 4 for > 7 days duration or requiring hemopoietic growth factors
  - In the event of Grade 4 thrombocytopenia, a full blood count must be performed no more than 7 days after the onset of the event to determine if a DLT has occurred. The participant will be closely monitored until resolution to Grade 3 or less.
- Grades 3 or 4 toxicity to organs other than the bone marrow including Grades 3 and 4 biochemical AEs and DLTs, excluding the following:
  - Grade 3 nausea or vomiting in participants who have not received optimal treatment with anti-emetics
  - Grade 3 diarrhea in participants who have not received optimal treatment with anti-diarrheal
  - Grade 3 fatigue
  - Any Grade 3 elevation of aspartate aminotransferase (AST) "and" "or" alanine aminotransferase (ALT) lasting ≤ 7 days (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 less).

- Any Grade 3 or 4 increase in bilirubin unless the increase is assessed as arising from inhibition of bilirubin glucuronidation. If the increase in bilirubin is assessed as arising from inhibition of bilirubin glucuronidation, then only bilirubin levels above 15 mg/dL (257 µmol/L) will be considered DLTs
- Death due to drug-related complications
- 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 atrioventricular block), severe sustained/symptomatic sinus bradycardia less than 45 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 < 40% (by 2D-echocardiogram or Multiple Gated Acquisition [MUGA] scan) or a relative decrease > 20% from historical assessment of ejection fraction performed within 12 months
  - Troponin-T: level which is consistent with myocardial infarction
- Any drug-related toxicity that causes interruption of treatment for > 2 weeks (14 successive days). If a participant is deemed fit to restart treatment on Day 15 then this is not a DLT.

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 as this may affect dose escalation decisions.

5.2.7 Participant Evaluability

5.2.7.1 Parts A, A2, A3, and B1

All participants who meet the eligibility criteria and receive at least 1 dose of M4344 will be evaluable for safety.

Participants must meet 1 of the 2 criteria below to be considered evaluable for dose escalation decisions:

1. Participant must have received the following minimum required doses of study drug(s) in Cycle 1 (i.e. the DLT period). See Section 6.2.4 for guidance on acceptable time windows for drug administration:
   - Part A: at least 80% (5 out of 6) of scheduled M4344 doses.

- Part A2: at least 80% of scheduled M4344 doses. One cycle is defined as 21 calendar days of daily dosing.
- Part A3: at least 80% of scheduled M4344 doses. Refer to section 5.1.3 for definition of cycle length.
- Part B1: carboplatin dose on Day 1 and M4344 dose on Day 2. If the additional dosing day (Day 5) is explored, M4344 dose on Day 5 will be required in addition to the other doses.
- Parts A/A2/A3/B1: Compliance with prohibited medicine and dietary restrictions during Cycle 1.

Or

2. The participant must have had a DLT before the end of Cycle 1.

Participants who do not meet 1 of the 2 criteria above will not be evaluable for dose escalation decisions and will be replaced. Also, if an additional participant is enrolled during dose-escalation in Parts A2/A3, and B1 in order to obtain a timed-tumor biopsy, the safety or PK data from this additional participant may not be required for making dose-escalation decisions. If the dose escalation decision had been made; this additional participant will be considered non-evaluable for dose escalation decision-making.

5.2.7.2 All Parts C

Eligible participants are required to have measurable disease according to RECIST 1.1. All participants who meet the eligibility criteria and are administered at least 1 dose of M4344 will be evaluable for safety. All participants who receive at least 1 cycle of treatment, have a baseline assessment during Screening, will be evaluable for response and for disease progression or survival.

5.2.8 Screening

Screening Visit assessments are listed in Table 1 for Parts A, A2, A3, and B1. Screening Visit assessments are listed in Table 2 for Parts C.

Participants will consent to Screening procedures prior to any Screening activities.

In Parts C, participants will undergo a Screening Biopsy (Table 2) to confirm/assess the selection biomarkers (loss-of-function mutations in the genes ARID1A for Parts C1 and C4, in ATRX and/or DAXX in Parts C2 and C5, and ATM in Parts C3 and C6):

- Participants with known positive biomarker status at the time of consent, according to locally available data, can undergo the Screening Biopsy analysis and the rest of Screening assessments concurrently (Table 2).
- Participants with unknown biomarker status at the time of consent can only undergo the Screening assessments once the presence of ≥ 1 selection biomarkers is confirmed

central trial assay or by an assay with appropriate regulatory status (biopsy results expected within 21 days).

Screening assessments to confirm that participants meet the selection criteria will be complete within 21 days from time of consent in Parts A, A2, A3, and B1 and within 42 days in Parts C (allowing for Biopsy results to become available before the rest of the Screening assessments can be conducted) before the first dose of study drug for all participants.

If a participant is a Screen Failure for Part C, the participant may be considered for participation in Part A3. Screening results from Part C may be used to determine eligibility for Part A3 with no necessity to repeat the assessments (at the Sponsor's discretion). However, if start of treatment in Part A3 is planned outside of the 21-day window (see previous paragraph), the following assessments must be repeated:

- Prior and concomitant medications:
- Weight and vital signs
- Physical examination
- Clinical disease assessment
- Hematology
- Coagulation
- Serum chemistry
- Urinalysis
- AEs

The Investigator (or an appropriate authorized designee at the Investigator site) will obtain informed consent from each participant. If the time between Screening and dosing exceeds the specified Screening Window as a result of operational delays (e.g., delayed drug shipment, delay in central trial assay results, clinic closures or short-term, reversible medical conditions [e.g., intervening upper respiratory illness, correctible anemia]), then participants do not require rescreening if laboratory results within 7 days of the first dose of study drug meet the eligibility criteria. Participants who are unable to dose within the Screening Window because of substantial complications of disease progression will be replaced.

To prepare for study participation, participants will be instructed on the Lifestyle Guidelines (Section 6.6.3) and use of concomitant medications (Section 6.6). A participant who qualified, but did not enroll for an earlier cohort, may be used in a subsequent cohort with no required rescreening if the Day 1 laboratory results and World Health Organization (WHO) Performance Status meet the eligibility criteria. A chest and abdominal imaging scan and, if clinically indicated, a pelvic imaging scan must be repeated if more than 28 days have transpired since most recent imaging scan.

Participants who fail Screening once may be rescreened if, 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 from prior chemotherapy).

5.2.9 Treatment Period

Treatment Period assessments are presented in Table 3, Table 4, Table 5, Table 6, Table 7, and Table 9. For details on dosing, see Section 6.

5.2.10 Dose Escalation Decision Making

A Medical Monitoring Plan will be provided which details a plan for routine and urgent communication between the Sponsor, the Investigators, and the contract research organization (CRO) involved in assisting sites and the Sponsor with monitoring participant safety. The Medical Monitoring Plan will describe the anticipated frequency and means of communication between Sponsor, sites, and CROs to review participant data to inform decisions on dose escalation between cohorts.

Decisions regarding dose escalation between cohorts in Parts A, A2, A3, and B1 will be made by the DEM consisting of Sponsor, representatives from the study sites, and medical representatives from the CROs (if appropriate) after a review of safety information. AEs occurring up to and including the end of Cycle 1 will be reviewed as soon as they are available for a given cohort. DLTs that may have occurred through the end of Cycle 1 of the current cohort, as well as DLTs that have occurred in prior cohorts in later cycles, will be identified.

The M4344 MTD will primarily be determined by DLTs that occur up to and including the end of the DLT period. The M4344 MTD is defined using the NCI-CTCAE (Parts A and B1: Version 4.0; Parts A2 and A3: Version 5.0). If ≥ 2 out of up to 6 participants at the same dose level have a DLT, as defined in Section 5.2.6, the M4344 MTD will be determined as the dose level below or an intermediate dose. The exact dose will be determined following discussion between the Sponsor and the Investigators of all the relevant toxicity, including DLTs that occur in prior cohorts beyond the end of the DLT period.

A RP2D should be determined for each applicable part of the study in agreement between Sponsor and Investigators. It may not be higher than the MTD.

5.2.11 Follow-up

Participants in Parts A, A2, A3, and B1, regardless of reason for discontinuation, will have a Safety Follow-up Visit 14 days (± 7 days) following the last dose of study drug, during which the procedures listed in Table 3, Table 4, Table 5, and Table 6 will be completed. Participants in Parts C will have a Safety Follow-up Visit 30 days (± 7 days) following the last dose of study drug, procedures listed in Table 7, Table 8, Table 9, and Table 10 will be completed.

Participants in Parts B1 and C without progressive disease on a prior imaging scan should attend Radiologic Follow-up Visits until disease progression is observed, new anticancer treatment is started, death, or the end of the study, whichever comes first. For the first 6 months after the start

of study treatment, Radiologic Follow-up Visits should occur every 6 weeks, subsequently they should occur every 9 weeks. During these visits, the procedures listed in Table 5, Table 6, Table 7, and Table 9 will be completed.

Participants in Parts A, A2, A3, and B1 who do not have documented disease progression upon completing the Safety Follow-up Visit should be followed for overall survival, if possible, for up to 1 year after the Follow-up Visit, or until study closure, whichever comes first.

Participants in Parts C should be followed for overall survival, if possible, until study closure.

Data may be obtained either per routine site participant follow-up (if the site continues to follow the participant) or via telephone, electronic, or mail communication. The following information should be obtained, if possible, on a 3-monthly basis:

- If the participant is deceased, and if so, date of death and whether death is related to primary malignancy
- If the participant is alive, if the disease progressed, and if so, what is the date of progression
- If the participant started on a subsequent line of therapy for the primary malignancy, and if so, date of starting new therapy
- If the participant is deceased, has progressive disease, or has started on new therapy then further follow-up information does not need to be collected.

Lost-to-Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wants to or should continue in the study.
- Before a participant is deemed "lost to follow-up", the Investigator or designee must make every effort to regain contact with the participant: 1) where possible, make 3 telephone calls; 2) if necessary, send a certified letter (or an equivalent local method) to the participant's last known mailing address, and 3) if a participant has given the appropriate consent, contact the participant's general practitioner for information. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

5.3 Selection of Study Population

Only persons meeting all inclusion criteria and none of the exclusion criteria may be enrolled into the study as participants. Prior to performing any study assessments not part of the participant's routine medical care, the Investigator will ensure that the participant or the participant's legal representative has provided written informed consent following the procedure described in Section 9.2.

5.3.1 Inclusion Criteria

1. Men and women ≥ 18 years of age
2. Disease status:
   - Parts A, A2, and A3: Participants with 1 histologically or cytologically confirmed malignant advanced solid tumors for which no standard therapy is available which may convey clinical benefit
   - Part B1: Participants with 1 histologically or cytologically confirmed malignant advanced solid tumors for which no standard therapy is available which may convey clinical benefit, and/or participants must have progressed after at least 1 prior chemotherapy regimen in the metastatic setting, and for which carboplatin would be considered standard of care
   - Parts C: Participants with 1 histologically or cytologically confirmed malignant advanced solid tumors for which no recommended standard therapy is available (i.e. participants who have exhausted all standard of care options according to NCCN Guidance) which may convey clinical benefit, and whose tumor has at least 1 of the following biomarkers as determined by a central trial assay or by an assay with appropriate regulatory status (see Section 7.7.5 for further details):
     - C1 or C4: loss-of-function mutations in the gene ARID1A
     - C2 or C5: loss-of-function mutations in the genes ATRX and/or DAXX
     - C3 or C6: loss-of-function mutation in the gene ATM

     This mandatory biomarker assessment must be conducted during Screening on a fresh tumor biopsy (or a biopsy obtained after the end of the previous treatment regimen). If this is not possible for medical reason(s), available archival tumor material can be used (historical data should not be used to confirm biomarker status).
3. Measurable disease either according to RECIST criteria (Version 1.1)
4. WHO performance status of 0 or 1
5. Life expectancy of ≥ 12 weeks
6. Hematological and biochemical indices within the ranges shown below at Screening. These values must be confirmed at the first day of dosing, before study drug administration:

- Hemoglobin: ≥ 9.0 g/dL for Parts A and B; ≥ 8.0 g/dL and no blood transfusions in the preceding 28 days for Parts C
- Absolute neutrophil count: ≥ 2.0 x 10^9/L
- Platelet count: ≥ 125 x 10^9/L
- Serum bilirubin: ≤ 1.5 x upper limit of normal (ULN), except in the case of known or suspected Gilbert's syndrome
- ALT, AST, and alkaline phosphatase (liver origin): ≤ 2.5 x ULN or ≤ 5 x ULN in presence of liver metastases
- Serum albumin: ≥ 2.5 g/dL
- Estimated glomerular filtration rate: ≥ 50 mL/min for Parts A and B; ≥ 40 mL/min for Parts C
- Prothrombin time: < 1.25 x ULN
- In addition, there should not be other clinically significant metabolic or hematologic abnormalities that are uncorrectable or that require ongoing, recurrent pharmacologic management.

7. Sign and date an informed consent document

8. Willing and able to comply with scheduled visits, treatment plan, lifestyle, laboratory tests, contraceptive guidelines, and other study procedures.

5.3.2 Exclusion Criteria

1. Radiotherapy, unless brief course for palliative therapy, endocrine therapy, target-specific therapy, immunotherapy, or chemotherapy during the 4 weeks (6 weeks for nitrosoureas and Mitomycin-C, and 4 weeks for investigational medicinal products) or 4 drug half-lives before first dose of study drug, whichever is greater

2. Part B1: More than 6 cycles of prior therapy with carboplatin, unless discussed with and approved by the Medical Monitor.

3. Ongoing toxic manifestations of previous treatments. Exceptions to this are alopecia or certain Grade 1 toxicities, which in the opinion of the Investigator should not exclude the participant
   - Part B1: Any known history of Grade 4 thrombocytopenia with any prior chemotherapy regimen (not applicable for Parts C)

4. Brain metastases unless asymptomatic, treated, stable, and not requiring steroids for at least 4 weeks before first dose of study drug

5. Female participants who are already pregnant or lactating, or plan to become pregnant within 6 months of the last dose of study drug are excluded. Female participants of childbearing potential must adhere to contraception guidelines as outlined in Section 7.5.2. Female

participants will be considered to be of nonchildbearing potential if they have undergone surgical hysterectomy or bilateral oophorectomy or have been amenorrheic for over 2 years with a Screening serum follicle-stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal females

6. Male participants with partners of childbearing potential must agree to adhere to contraception guidelines in Section 7.5.2.2. Men with pregnant or lactating partners or partners who plan to become pregnant during the study or within 6 months of the last dose of study drug are excluded

7. Major surgery ≤ 4 weeks before first dose of study drug or incomplete recovery from a prior major surgical procedure

8. Cardiac conditions as follows:
   - Clinically significant cardiovascular event within 6 months before study entry:
     - congestive heart failure requiring therapy
     - unstable angina pectoris
     - myocardial infarction
     - Class II/III/IV cardiac disease (New York Heart Association)
     - presence of severe valvular heart disease
     - presence of a ventricular arrhythmia requiring treatment
   - History of arrhythmia that is symptomatic or requires treatment (CTCAE Grade 2), symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia. Participants 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 > 470 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)
   - Clinically-significant abnormality, including ejection fraction below normal institutional limits, present on transthoracic echocardiogram performed at Screening, for Parts A and B

9. Prior bone marrow transplant or extensive radiotherapy to greater than 15% of bone marrow

10. Participation, or plan of participation, in another interventional clinical study while taking part in this Phase I study of M4344. Participation in an observational study would be acceptable

11. Any other condition which in the Investigator's opinion would not make the participant a good candidate for the clinical study, including:
    - History of HIV-1, HIV-2, or unresolved Hepatitis B or unresolved Hepatitis C infection
    - High medical risk because of nonmalignant systemic disease including active uncontrolled infection
    - Participants who have been diagnosed with Li-Fraumeni Syndrome or with ataxia telangiectasia
12. Current 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 that has been in remission for at least 3 years would not be excluded
13. Current therapy:
    - Participants receiving treatment with medications that are known to be strong inhibitors or inducers of cytochrome P450 (CYP) 3A4 that cannot be discontinued at least 1 week before first dose of study drug and for the duration of the study. Examples of strong CYP3A4 inhibitors or inducers are provided in Table 13
    - Participants receiving treatment with proton-pump inhibitors that cannot be discontinued at least 1 week before first dose of study drug and for the duration of the study. Examples of proton-pump inhibitors are provided in Table 13
    - For Part B1: participants receiving treatment with ototoxic or nephrotoxic medications that cannot be discontinued at least 7 days before first dose of study drug and for the duration of the study. Short-term use on study will not cause a participant to be ineligible. If a short course of therapy with nephrotoxic or ototoxic medication is anticipated and required, carboplatin or cisplatin should be discontinued until 7 days after this course is completed
    - Participants receiving prior treatment with any ATR inhibitor
14. Participants who cannot comply with restrictions for medications or food as specified in Table 13.

5.4 Criteria for Initiation of Study Treatment

Eligibility for participation in this study will be checked at Screening for Parts A, A2, A3, and B1 (see Table 1) and Parts C (see Table 2).

5.5 Criteria for Participant Withdrawal

5.5.1 Withdrawal from Study Therapy

A participant must be withdrawn from M4344 if any of the following occur:

- Participant withdrew consent
- Participant lost to follow up

- Participation in another clinical study or start of new anti-cancer treatment
- Noncompliance of study drug dosing or study procedure
- Any events that unacceptably endanger the safety of the participant.

If participants drop out for any reason other than disease progression, every effort should be made to continue to follow the participant in the trial for tumor assessment.

5.5.2 Withdrawal from the Study

Participants may withdraw from the study at any time without giving a reason, or at the discretion of the Investigator for administrative reasons. Withdrawal of consent will be considered withdrawal from the study. Participants who prematurely discontinue study drug dosing will be asked to return to the clinical site for Safety Follow-up Visit 14 days (±7 days) after their last dose of study drug (30 days [± 7 days] for Parts C). Safety Follow-up Visit assessments are presented in Table 3, Table 4, Table 5, Table 6, Table 7, and Table 9.

If a participant does not return for a scheduled visit, reasonable effort will be made to contact the participant. In any circumstance, reasonable effort will be made to document participant outcome. The Investigator will inquire about the reason for withdrawal, request that the participant return for a Safety Follow-up Visit (see Section 5.2.11), if applicable, and follow up with the participant regarding any unresolved AEs.

It may be appropriate for the participant to return to the clinic for final safety assessments and to be questioned regarding their reason for withdrawal. Assessments may include:

- Physical examination
- Blood pressure and pulse rate measurements
- ECG
- Blood and urine specimen's collection (for safety laboratory tests and pregnancy test, if applicable)
- Blood sample for PK analysis.

If the participant withdraws consent, 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.

Participants may be discontinued from study drug for toxicity or lack of efficacy, as specified in Section 6.4.

For participants in Parts C who have not progressed, see Section 5.2.11 for more details.

5.5.3 Replacement of Participants

In Parts A, A2, A3, or B1, participants who withdraw or are withdrawn from treatment for reasons other than DLT before the assessment on Day 1 of Cycle 2, and who have not had the minimum exposure to study drugs described in Section 5.2.7, will be replaced to maintain the dose escalation scheme. Participants in Parts A, A2, A3, and B1 beyond the assessment on Day 1 of Cycle 2, and all participants in Parts C, who withdraw or are withdrawn for non-safety reasons may be replaced at the Sponsor's discretion.

5.6 Premature Termination of the Study

The clinical study may be terminated prematurely or suspended at the request of Health Authorities or if new safety or efficacy information leads to an unfavorable risk benefit judgment for any study drug. The Sponsor may discontinue the study if it becomes unjustifiable for medical or ethical reasons, for poor enrollment, or because of discontinuation of clinical development of a study drug or withdrawal of a study drug or comparator from the market for safety reasons.

Health Authorities and Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) will be informed about the discontinuation of the study in accordance with applicable regulations.

5.7 Definition of End of Study

The study will end when:

- All participants in Parts A, A2, and A3 have completed the Safety Follow-up Visit 14 days (± 7 days) after the last dose of the study drug, AND
- All participants in Parts B1 and C have completed treatment and been followed up for a minimum of 1 year from the start of study treatment.

At the end of the current study, participants who continue to benefit from treatment with M4344 after more than 12 months of treatment may be switched to another study protocol, if available, which serves to monitor the long-term safety of treatment with M4344 and where the participants can continue on the same schedule and dose of M4344 as in the current study.

6 Investigational Medicinal Product and Other Drugs Used in the Study

The term "Investigational Medicinal Product" refers to an active substance or a placebo being tested or used as a reference therapy in a clinical study, including products that have a marketing authorization but are formulated, packaged, or administered differently from the authorized form, used for an unauthorized indication, or used to gain further information about the authorized form.

6.1 Description of the Investigational Medicinal Product

M4344 will be supplied as 50 mg tablets in CCI [redacted], each containing 20 tablets.

The Sponsor will not supply carboplatin for this study. Sites will use carboplatin as supplied by their pharmacy.

6.2 Dosage and Administration

6.2.1 Administration

M4344, 50 mg tablets, will be administered orally with 240 mL (8 fluid ounces) of ambient temperature water. Carboplatin will be administered via intravenous infusion.

M4344 will be administered under fasting conditions throughout the study; all participants will abstain from all food for at least 3 hours before oral administration of M4344 and for 1 hour after administration of M4344. Water can be consumed as desired.

Time and date of administration of the last dose prior to each PK sample is to be recorded on the electronic case report form (eCRF).

All participants will follow the dietary and meal restrictions outlined in Section 6.6.3.1. Participants will swallow the study drug whole and will not chew the drug before swallowing. Participants will be instructed not to lie down (sitting in an upright or reclining position is acceptable) for 2 hours after taking the study drug, except when required for study procedures. When M4344 is administered twice daily, the second daily dose should be administered within 8 to 16 hours after the first dose.

Anti-emetics and other supportive therapies will be administered or dispensed to participants for use in combination with carboplatin according to individual site standard of care. Anti-emetics, anti-diarrheals, and hematopoietic growth factors will not be administered prophylactically during Part A during Cycle 1. Anti-emetics, anti-diarrheals, and growth factors can be used per institutional guidelines for management of symptoms.

6.2.2 Criteria for Study Drug Administration

When clinical chemistry and/or hematology laboratory testing is required before administration of chemotherapy or M4344 as presented in the Schedule of Assessments (Table 3, Table 4, Table 5, Table 6, Table 7, and Table 9), the laboratory criteria specified in Table 12 must be met before dosing. To facilitate timely administration of study drug, this laboratory testing may be performed up to 3 days before dosing.

After Cycle 1, Day 1, if a participant does not meet 1 or more criteria, dosing may be paused and resumed once the laboratory abnormality(ies) has resolved with or without medical intervention, at the discretion of the Investigator and Medical Monitor.

Table 12 Laboratory Values Required for Administration of Chemotherapy or M4344

Laboratory Parameter	Cycle 1 Day 1	Day 1 of Subsequent Cycles	Other Days M4344 is Administered[a]
Hemoglobin	≥ 9.0 g/dL (Parts A and B) ≥8 .0 g/dL (Parts C)	≥ 7.0 g/dL (if asymptomatic)	≥ 7.0 g/dL (if asymptomatic)
Absolute neutrophil value	≥ 2.0 x 10^9/L	≥ 1.5 x 10^9/L	≥ 1.5 x 10^9/L
Platelet count	≥ 125 x 10^9/L	≥ 100 x 10^9/L	≥ 100 x 10^9/L
AST, ALT, and ALP (liver origin)	≤ 2.5 x ULN or ≤ 5 x ULN in presence of liver metastases	≤ 2.5 x baseline value or ≤ 5 x baseline value in presence of liver metastases	≤ 2.5 x baseline value or ≤ 5 x baseline value in presence of liver metastases
Estimated glomerular filtration rate	≥ 50 mL/min (Parts A and B) ≥ 40 mL/min (Parts C)	Does not meet DLT criteria	Does not meet DLT criteria
Total bilirubin (serum)[b]	≤ 1.5 x ULN	≤ 15 mg/dL	≤ 15 mg/dL
Serum albumin	≥ 2.5 g/dL	≥ 2.5 g/dL	≥ 2.5 g/dL

ALP = Alkaline phosphatase, ALT = Alanine aminotransferase, AST = aspartate aminotransferase;
DLT = Dose-limiting toxicity, ULN = Upper limit of normal

a Based on most current laboratory values available. Laboratory testing will be conducted as described in Table 3, Table 4, Table 5, Table 6, Table 7, and Table 9; additional testing will not be required to confirm these values prior to every dose.

b Participants with known or suspected Gilbert's syndrome are exempt from serum bilirubin exclusion.

6.2.3 Dose Modification for Toxicity

No dose modifications of M4344 may be made during Cycle 1 of Parts A, A2, A3, or B1, except as specified in Sections 5.1.1 and 5.1.3.

Parts A, A2, and A3:

Doses of M4344 may be reduced other than in Cycle 1 of Parts A, A2, and A3 for toxicity using the following guidelines:

- For Grade 4 hematologic toxicity: the dose of M4344 will be reduced by 25%
- For Grade 3 non-hematologic toxicity: the dose of M4344 will be reduced by 25%
- For Grade 4 non-hematologic toxicity: the dose of M4344 will be reduced by 50%

Parts A2, A3:

Participants in Parts A2 and A3, who experience an ADR meeting DLT criteria after completion of the DLT assessment period need to interrupt study treatment but may continue on study treatment at a reduced dose provided the reaction has resolved to baseline value or Grade ≤ 1 within 2 weeks and there is no progressive disease. The dose of M4344 will be reduced to 1 dose level below the current dose. If indicated, a further dose reduction is possible on agreement between the Sponsor and Investigator. Once the dose of M4344 has been reduced in an individual

participant, it must not be escalated again. If more than 2 dose reductions are indicated, the participant will be permanently discontinued from study treatment.

See Section 5.2.6 for additional details of toxicity modifications.

Part B1:

Doses of M4344 and/or carboplatin may be reduced or delayed beyond Cycle 1 of Part B1 for toxicity using the following guidelines. The final dose reduction or delay for each participant may be determined by the Sponsor and Investigators. However, these guidelines provide the minimum dose reduction or delay criteria. Additionally, if a participant who is responding to treatment experiences toxicity even after 2 dose reductions, the participant may continue to receive treatment if in the judgment of the Investigator it is in the best interest of the participant. In this case the dose of either the chemotherapeutic agent and/or M4344 will further be reduced by at least 25%.

- In case of 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 or lower, at the discretion of the Investigator. Dose modifications may be applied according to the recommendations given for Parts A, A2, and A3 (see above).
- For the following hematologic toxicities, once the toxicity has returned to Grade 2 or lower, dosing can be resumed at a lower dose of chemotherapy (carboplatin = AUC 4 mg·min/mL or 25% reduction in dose of chemotherapy) and/or lower dose of M4344 (25% reduction):

- 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 or lower, dosing can be resumed at a lower dose of chemotherapy (carboplatin = AUC 4 mg·min/mL or 25% reduction in dose of chemotherapy) and/or lower dose of M4344 (25% reduction):
- Grade 3 non-hematologic toxicity (except for fatigue or nausea, vomiting, or diarrhea adequately controlled by medication)
- Any Grade 2 or lower 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 of chemotherapy (carboplatin = AUC 4 mg·min/mL or 25% reduction dose of chemotherapy) and at a lower dose of M4344 (25% reduction) when toxicity has returned to Grade 2 or lower.

If any toxicity not described above results in delay in dosing in any part of the study and the participant may be benefitting from therapy, then at the discretion of the Investigator, the doses of M4344 or chemotherapy may be further reduced.

Parts C:

Doses of M4344 may be reduced for toxicity using the following guidelines:

- For Grade 4 hematologic toxicity: the dose of M4344 will be reduced by 25%
- For Grade 3 non-hematologic toxicity: the dose of M4344 will be reduced by 25%
- For Grade 4 non-hematologic toxicity: the dose of M4344 will be reduced by 50%

In agreement between Investigator and Sponsor, any dose reduction for toxicity deviating from the above guidelines may be applied.

6.2.4 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 when all toxicities have returned to Grade 2 or less.

Study visits that are missed because of clinic or participant 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 Parts A2 and A3, and all Parts C, any missed doses will be skipped. For Parts A and B1, any missed dose of study drug (with the exception of M4344 doses scheduled to occur 24 hours after carboplatin, dosing in Cycle 1 of Part B1) should be taken within 2 days (48 hours) of the scheduled dose. If more than 48 hours have transpired since the scheduled dose, then the dose should be skipped and will be considered a missed dose for the purpose of evaluability in Cycle 1 of Parts A or B1. For doses of M4344 that are scheduled to occur 24 hours after carboplatin dosing in Cycle 1 of Part B1, if more than 36 hours have transpired since the dose of chemotherapy (i.e., more than 12 hours from the scheduled dose of M4344), the M4344 dose will be considered a missed dose for the purpose of evaluability. 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 participant 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 Medical Monitor.

6.3 Assignment to Treatment Groups

This is an open-label study. Participants will be enrolled into dose level cohorts according to the dose escalation scheme described above in Section 5.

Participants may be screened in parallel or staggered manner for Parts A2, A3, and C and will be enrolled into Parts C according to the molecular lesion of their tumor (see Section 5.1.4 for details). If a participant's tumor has more than one qualifying molecular lesion, the participant will be assigned to all respective study parts.

6.4 Stopping Rules

Participants may be discontinued from study drug for toxicity or lack of efficacy, as follows:

- Participants experiencing nonreversible or life-threatening toxicity may be discontinued from study drug at the Investigator's discretion. Participants who experience reversible and nonlife-threatening toxicity and, in the judgment of the Investigator, who may be exhibiting clinical benefit, may resume therapy after the toxicity has decreased to Grade 2 or below
- Participants who experience a DLT during Cycle 1 will be discontinued from study drug
- Participants with progressive disease beyond Cycle 1 will be discontinued from study drug. Participants with progressive disease before the end of Cycle 1 may be discontinued at the discretion of the Investigator.

Participants who are discontinued from study drug will continue to complete the appropriate follow-up assessments. Follow-up procedures are discussed Section 5.2.11. For stopping criteria of enrollment for Parts C, see Section 8.1 for details

6.5 Non-investigational Medicinal Products to be Used

Not applicable.

6.6 Concomitant Medications and Therapies

All concomitant medications taken by the participant during the study, from the date of signature of informed consent are to be recorded in the appropriate section of the eCRF, noting the name, dose, duration and indication of each drug. Nondrug interventions and any changes to a concomitant medication or other intervention should also be recorded in the eCRF.

6.6.1 Permitted Medicines

Any medications that are considered necessary to protect participant welfare and will not interfere with the study medication may be given at the Investigator's discretion.

Rescue medications may be administered to address ineffective treatment, anticipated adverse reactions or anticipated emergency situations.

Concomitant treatment with the following compounds to maintain a castrate level of testosterone in participants with prostate cancer is permitted: leuprolide, goserelin, triptorelin, histrelin, degarelix, abiraterone, enzalutamide, and nilutamide. For these compounds, no risk for drug-drug-

interaction with M4344 is anticipated, however, no drug-drug-interaction studies have been conducted.

6.6.2 Prohibited Medicines

In vitro drug metabolism studies suggest that M4344 is a substrate of Cytochrome P450 (CYP) 3A4 (Vertex Report K220 2014, Vertex Report K064 2014) and systemic exposure may be affected by concomitant medications that are strong CYP3A4 inhibitors or inducers. Restrictions for prior and concomitant medications that are strong inhibitors or inducers of CYP3A4 are provided in Table 13 and in the supplemental Study Prohibited and Cautioned List. Based upon in vitro data, M4344 is not a potent inhibitor or inducer of human CYP enzymes in isolated enzyme systems and therefore the probability of M4344 interaction with other medications that are substrates of CYP metabolism is expected to be low. However, Investigators should use standard precautions when prescribing medications, as with any novel therapeutic for which there is limited clinical experience.

- Participants will abstain from concomitant medications as described in Table 13. If a prohibited medication is considered medically necessary for a participant, the participant will be withdrawn from the study.
- Participants should not receive prophylactic treatment with hematopoietic growth factors, anti-emetic, and anti-diarrheal medications during Cycle 1 of Part A of the study. These treatments may be used to specifically address participant symptoms, per institutional practice, as long they adhere to restrictions listed in Table 13. Neutrophil growth factors (e.g., granulocyte-colony stimulating factor) should not be used in Part B1 during Cycle 1. Otherwise, anti-emetics, anti-diarrheals, and growth factors can be used for participants in Part B1 of the study, per institutional practice for administration of carboplatin and to treat symptoms.
- The Investigator should refer to the package inserts for carboplatin for guidance on prohibited mediations during treatment with this agent (Carboplatin SmPC). Participants enrolled in Part B1 should not use nephrotoxic or ototoxic medications from 7 days before the first dose of study drug through the Safety Follow-up Visit. Short-term use on study will not cause a participant to be ineligible. If a short course of therapy with nephrotoxic or ototoxic medication is anticipated and required, carboplatin or cisplatin should be discontinued until 7 days after this course is completed.
- 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 name and dose, indication, route of administration, and start and stop dates of administration. All participants will be questioned about concomitant medication at each clinic visit.

In vitro data indicates that absorption of M4344 may be affected by acid-modifying agents. Restrictions for acid-modifying agents such as proton-pump inhibitors, H_2-receptor antagonists, and antacids which may reduce the absorption and effects of M4344 are provided in Table 13.

Table 13 Study Restrictions

Restricted Medication/Food/Activity	Study Period	
	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
Strong CYP3A4 inhibitors or inducers • Examples of strong CYP3A4 inhibitors include clarithromycin, itraconazole, Hepatitis C virus and HIV protease inhibitors, ketoconazole, nefazodone, posaconazole, telithomycin, and voriconazole. • Examples of potent CYP3A4 inducers include avasimibe, carbamazepine, rifampin, phenytoin, and St. John's wort[a]	None allowed within 7 days before the first dose of study drug	None allowed through the Safety Follow-up Visit
Anti-emetics or anti-diarrheals	Allowed for symptom management	Prophylactic use not allowed during Cycle 1 of Part A. Allowed if given per institutional practice (Parts B and C), or for symptom management
Hematopoietic growth factors	Not allowed for Parts A or B	Prophylactic use not allowed. Therapeutic use allowed per institutional practice
Nephrotoxic medications	Part B1 only: None allowed within 7 days before the first dose of study drug	None allowed through the Safety Follow-up Visit (except as specified in Section 6.6)
Proton-Pump Inhibitors Examples of proton-pump inhibitors include omeprazole (Prilosec®, Omesec Zegerid®), lansoprazole (Prevacid®), esomeprazole (Esomeprazole Strontium, Nexium®), pantoprazole (Protonix®), and rabeprazole (AcipHex®)	None allowed within 7 days before the first dose of study drug	None allowed until permanent discontinuation of M4344, unless discussed with and approved by the Medical Monitor
H_2-Receptor Antagonists and Antacids • Examples of H_2-receptor antagonists include ranitidine (Zantac®), famotidine (Pepcid®), cimetidine (Tagamet®), and nizatidine (Axid®). • Examples of antacids include Alka-Seltzer®, Gelusil, Maalox®, Mylanta®, Pepto-Bismol®, Rolaids®, and Tums®	• H_2-receptor antagonists and antacids can be taken without restriction on all days when M4344 is not administered. • On all days when M4344 is administered[b] once daily, H_2-receptor antagonists and antacids will not be permitted within 12 hours before dosing of M4344 and until 4 hours after dosing of M4344. On all days when M4344 is administered[b] twice daily, none are allowed until permanent discontinuation of the medication M4344, unless discussed with and approved by the Medical Monitor.	

CYP = Cytochrome P450

a Refer to the study reference manual for a more complete list of prohibited or cautioned medications in this study.
b M4344 will be administered as described in Table 3 for Part A, Table 4 for Part A2 and the 14d+/7d- schedule of Part A3, Table 5 for A3, Table 6 for Part B1, Table 7 for Parts C1, C2, and C3, Table 9 for Parts C4, C5, and C6.

6.6.3 Other Interventions

6.6.3.1 Meals and Dietary Restrictions

M4344 will be administered under fasting conditions throughout the study.

The study drug will be administered with 240 mL (8 fluid ounces) of ambient temperature water. Participants will abstain from all food for at least 3 hours before study drug administration and for 1 hour after study drug administration. Water can be consumed as desired.

Restrictions for consumption of specific foods and non-alcoholic beverages are provided in Table 13.

6.6.3.2 Activity

Participants 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.

Participants should avoid prolonged or intense sun exposure, sunlamps, and tanning beds. Use of sunscreen, clothing, and eyewear that decrease sun exposure is recommended.

6.6.4 Special Precautions

Not applicable.

6.6.5 Management of Specific Adverse Events or Adverse Drug Reactions

Not applicable.

6.7 Packaging and Labeling of the Investigational Medicinal Product

The Sponsor will supply 50 mg M4344 tablets. Study drug labeling will be in compliance with applicable local and national regulations. Additional details regarding packaging, labeling, and dispensing for M4344 will be included in the Pharmacy Manual.

All study drugs will be packaged and labeled in accordance with all applicable regulatory requirements and Good Manufacturing Practice Guidelines.

6.8 Preparation, Handling, and Storage of the Investigational Medicinal Product

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

Tablets will be dispensed into individual dosing containers at the clinical site by 2 operators, 1 of whom is a qualified pharmacist, and following national and local laws and regulations.

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, and in accordance with applicable regulatory requirements (See Table 14). To ensure adequate records, all study drugs will be accounted for as detailed in Section 6.9 or via the drug accountability forms as instructed by the Sponsor.

Table 14 Study Drug

Drug Name	Formulation/ Route	Dosage	Packaging	Storage Condition
M4344	Tablet/Oral	50 mg M4344	CCI [redacted]	CCI [redacted]

HDPE = High density polyethylene.

6.9 Investigational Medicinal Product Accountability

The pharmacist or designated study site staff is responsible for ensuring study drug accountability, including reconciliation of drugs and maintenance of records.

- Upon receipt of study drug, the responsible person will check for accurate delivery and acknowledge receipt by signing or initialing and dating the appropriate documentation and returning it to the location specified. A copy will be archived for the Investigator Site File
- Study drug dispensing will be recorded on the appropriate drug accountability forms so that accurate records will be available for verification at each monitoring visit
- Study site study drug accountability records will include the following:
  - Confirmation of study drug receipt, in good condition and in the defined temperature range
  - The inventory of study drug provided for the clinical study and prepared at the site
  - The use of each dose by each participant
  - The disposition (including return, if applicable) of any unused study drug
  - Dates, quantities, batch numbers, kit number, expiry dates, formulation (for study drug prepared at the site), and the individual participant study numbers

The Investigator site should maintain records, which adequately document that participants were provided the doses specified in this protocol, and all study drugs provided were fully reconciled.

Participants will be instructed to return all used and unused materials associated with the study drug to the site. These materials associated with the study drug will be retained at the site according to instructions provided by the Sponsor or its designee until inventoried by the Study Monitor.

The study site staff or pharmacy personnel will retain all materials returned by the participants 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. After study monitor authorization study drug should be destructed 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.

The Study Monitor will review study drug records and inventory throughout the study, and will periodically collect the study drug accountability forms.

6.10 Assessment of Investigational Medicinal Product Compliance

For study drug doses administered during the inpatient periods of the study, doses will be administered under the direct supervision of the Investigator or designee.

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 participant and recorded in the source documents. If participants demonstrate continued noncompliance of study drug dosing despite educational efforts, the Investigator will contact the medical monitor to discuss discontinuing the participant from the study.

For all doses of study drug, the number of units administered and missed doses will be recorded. All modifications in study drug dose or interval between dosing will be recorded, as well as the reason for modifications.

Individual participant compliance will be monitored by the Sponsor and clinical site designee every 2 weeks and participants will be notified when they are being noncompliant with dosing schedule. Continued noncompliance to dosing schedule will result in the participant being removed from the study.

6.11 Blinding

Blinding not applicable as this is an open-label study.

6.12 Emergency Unblinding

Not applicable.

6.13 Treatment of Overdose

An overdose is defined as any dose greater than the highest daily dose included in a clinical study protocol or planned for an individual participant enrolled in the study. Even if it does not meet

other criteria for a SAE, any overdose must be recorded in the study medication section of the eCRF and reported to Drug Safety in an expedited manner using the SAE Report Form, and following the procedure in Section 7.5.

6.14 Medical Care of Participants after End of Study

The Sponsor will not provide any additional care to participants after they leave the study because such care should not differ from what is normally expected for participants with advanced solid tumors.

7 Study Procedures and Assessments

7.1 Schedule of Assessments

Prior to performing any study assessments that are not part of routine medical care for the participant, the Investigator will obtain written informed consent as described in Section 9.2. The timing of assessments are presented in Table 1 for Screening, Table 3 for Part A, Table 4 for Part A2 and the 14d+/7d- schedule of Part A3, Table 5 for A3, and Table 6 for Part B1. For Parts C, the timing of assessments are presented in Table 2 for Screening and Table 7 and Table 8 for Parts C1, C2, and C3 and the 14d+/7d- holiday schedule described in Parts C4. C5, and C6, and Table 9 and Table 10 for Parts C4, C5, and C6 (except the 14d+/7d- schedule).

Participants in any of the Parts C can only start treatment once eligibility has been confirmed based on the presence of these loss-of-function mutations, which are defined in Section 7.7.5, and the rest of Screening assessments. Figure 5 provides a schematic of eligibility assessments in Parts C.

7.2 Demographic and Other Baseline Characteristics

At Screening, the following demographic data will be collected: date of birth, sex (gender), race, ethnicity.

7.3 Participant and Disease Characteristics

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

7.4 Efficacy Assessments

Parts A, A2, A3, and B1

Although efficacy response is not the Primary Endpoint of Parts A, A2, A3, and B1 of this study, tumor response, clinical disease assessment, and WHO performance status will be assessed in these parts.

Participants with measurable disease will be assessed by standard criteria (RECIST 1.1) or by PCWG2 criteria (prostate cancer). 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 (Eisenhauer 2009).

Participants must have an imaging scan (e.g., CT, MRI) at Screening to document the extent of initial disease. Participants will have a chest and abdominal imaging scan (e.g., CT, MRI) as appropriate and, if clinically indicated, imaging scans of other body areas (e.g., pelvis). For all Parts, participants should have a repeat imaging scan as described in Table 3, Table 4, Table 5, and Table 6. All imaging scans to assess disease progression should be performed using similar CT platforms and imaging techniques, including the use or absence of contrast, and should be of consistent anatomic locations with prior imaging scans, whenever possible.

Imaging scans will be locally read for all parts of the study. The applicable overall response category for each visit that includes disease assessment, based on evaluation of imaging scan, will be recorded in the eCRF. Determination of participant study disposition (i.e., discontinuation or extension of therapy) will be based on disease progression as interpreted from the local evaluation of the imaging scan. Copies of the imaging scans should be available for independent assessment if required.

Bone scans will be performed as described in Table 3, Table 4, Table 5, Table 6, Table 7, and Table 9. In addition, participants with ovarian cancer will have serum CA-125 assessed (Parts A and B), and participants with prostate cancer will have serum PSA assessed (Parts A and B) as described in Table 3, Table 4, Table 5, Table 6, Table 7, and Table 9.

To estimate the antitumor activity of treatment in participants with prostate cancer, who are not evaluable at baseline according to RECIST 1.1, response will be defined on the basis of the following outcomes; if any of these occur, participants will be considered to have responded:

- PSA decline $\geq$ 50% criteria (PCWG2) confirmed 4 weeks or later, and/or
- Confirmed soft tissue objective response (RECIST 1.1) (Scher 2008).

The PCWG2 and RECIST criteria will be used to determine PSA response and soft tissue response. Failure of treatment will be defined as:

- Progression by RECIST 1.1 (Scher 2008) and/or
- Progression of bone scan (Scher 2008).

Parts C

For all Parts C, safety (occurrence of treatment-emergent adverse events [TEAEs] and treatment-related AEs graded according to NCI-CTCAE) and efficacy (i.e. confirmed CR or PR)

are the primary endpoints. In addition to the definitions given above for Parts A, A2, A3, and B1, the following will apply:

Tumor assessment according to RECIST 1.1 will be performed at baseline and at the end of every 2 cycles for the first 6 cycles, then every 3 cycles thereafter until disease progression or start of new anti-cancer treatment line.

All tumor assessments should be made every time with the same methods (CT or MRI) used at the baseline assessment.

In Parts C, participants who discontinue the study treatment for reasons other than disease progression or withdrawal of consent will continue tumor assessments according to the same schedule as participants receiving trial treatment.

Objective response, best overall response, duration of response and progression free survival (PFS) will be derived on the basis of these tumor assessments. The assessment will be performed by the Investigator. Per RECIST 1.1, objective responses need to be confirmed. Confirmation should be determined at a scan no less than 4 weeks after the original assessment of objective response is made; confirmation of response at the next scheduled tumor assessment is acceptable.

Independent review of the imaging-based tumor assessments may be conducted at the discretion of the Sponsor. Copies of the imaging scans should be available to allow for this.

For overall survival, participants will be followed up for survival every 3 months until the study closure.

7.5 Assessment of Safety

The safety profile of the study drug will be assessed through the recording, reporting and analysis of Baseline Medical Conditions, AEs, physical examination findings including vital signs, ECG, and laboratory tests.

Medical history and physical examination information will be collected during the course of the study and will be captured in the source documentation. Physical examinations post-baseline will not be captured for inclusion into the study database. However, any untoward findings identified in physical examinations conducted after the administration of the first dose of study drug will be captured as an AE if those findings meet the definition of an AE.

Comprehensive assessment of any apparent toxicity experienced by each participant will be performed from the time of giving informed consent and throughout the study. The Investigator will report any AEs, whether observed by the Investigator or reported by the participant (see Section 7.5.1.2). The reporting period for AEs is described in Section 7.5.1.3.

7.5.1 Adverse Events

7.5.1.1 Adverse Event Definitions

Adverse Event

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product, regardless of causal relationship with this treatment. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, regardless if it is considered related to the medicinal product.

For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

The Investigator is required to grade the severity or toxicity of each AE.

Investigators will reference the National Cancer Institute – Common Terminology Criteria for AEs (CTCAE), Version 4.0, a descriptive terminology that can be used for AE reporting.

A general grading (severity/intensity; hereafter referred to as severity) scale is provided at the beginning of the above referenced document, and specific event grades are also provided.

If the severity for an AE is not specifically graded by NCI-CTCAE, the Investigator is to use the general NCI-CTCAE definitions of Grade 1 through Grade 5, using his or her best medical judgment.

The 5 general grades are:

- Grade 1 or Mild
- Grade 2 or Moderate
- Grade 3 or Severe
- Grade 4 or Life-threatening
- Grade 5 or Death

Any clinical AE with severity of Grade 4 or 5 must also be reported as an SAE. However, a laboratory abnormality of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets one of the serious criteria specified below.

If death occurs, the primary cause of death or event leading to death should be recorded and reported as an SAE. "Fatal" will be recorded as the outcome of this specific event and death will not be recorded as separate event. Only, if no cause of death can be reported (e.g., sudden death, unexplained death), the death per se might then be reported as an SAE.

Investigators must also systematically assess the causal relationship of AEs to study drug(s)/study treatment (including any other non-study drugs, radiation therapy, etc.) using the following

definitions. Decisive factors for the assessment of causal relationship of an AE to M4344 include, but may not be limited to, temporal relationship between the AE and the study drug known side effects of M4344, medical history, concomitant medication, course of the underlying disease, study procedures.

Unrelated: Not reasonably related to the study drug/study treatment. AE could not medically (pharmacologically/clinically) be attributed to the study drug/study treatment under study in this clinical study protocol. A reasonable alternative explanation must be available.

Related: Reasonably related to the study drug/study treatment. AE could medically (pharmacologically/clinically) be attributed to the study drug/study treatment under study in this clinical study protocol.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (e.g., on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation or are considered otherwise medically important by the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition (e.g., anemia or increased ALT) must be reported as the AE rather than the abnormal value itself.

Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening. "Life-threatening" refers to an event in which the participant is at risk of death at the time of the event, not an event that hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongs an existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is otherwise considered to be medically important. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For the purposes of reporting, any suspected transmission of an infectious agent via a study drug is also considered an SAE, as described in Section 7.5.1.4.

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify study treatment or study procedures (e.g., an overnight stay to facilitate intravenous therapy) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (for example, undesirable effects of any administered treatment) must be documented and reported as SAEs.

Events Not to Be Considered as AEs/SAEs

Medical conditions present at the initial study visit that do not worsen in severity or frequency during the study are defined as Baseline Medical Conditions and are not to be considered AEs.

AE/SAEs Observed in Association with Disease Progression

Progression of the disease/disorder being studied assessed by measurement of lesions on radiographs or other methods as well as associated clinical signs or symptoms (including laboratory abnormalities) should not be reported as an (S)AE, unless the participant's general condition is more severe than expected for the participant's condition and/or unless the outcome is fatal within the adverse event reporting period (as defined in Section 7.5.1.3).

7.5.1.2 Methods of Recording and Assessing Adverse Events

At each study visit, the participant will be queried on changes in his or her condition. During the reporting period, any unfavorable changes in the participant's condition will be recorded as AEs, regardless if reported by the participant or observed by the Investigator.

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the eCRF. All SAEs must be additionally documented and reported using the appropriate Report Form as described in Section 7.5.1.4.

It is important that each AE report includes a description of the event, its duration (onset and resolution dates and also onset and resolution times), when it is important to assess the time of AE onset relative to the recorded treatment administration time, its severity, its causal relationship with the study treatment, any other potential causal factors, any treatment given or other action taken, including dose modification or discontinuation of the study drug, and its outcome. In addition, serious cases should be identified, and the appropriate seriousness criteria documented. If an AE constitutes a DLT this is documented accordingly.

Specific guidance can be found in the eCRF Completion and Monitoring Conventions provided by the Sponsor.

7.5.1.3 Definition of the Adverse Event Reporting Period

The AE reporting period for safety surveillance begins when the participant is initially included in the study (date of first signature of informed consent/date of first signature of first informed consent) and continues until the Safety Follow-up Visit.

Any SAE assessed as related to the study drug must be recorded and reported whenever it occurs, irrespective of the time elapsed since the last administration of study drug.

7.5.1.4 Procedure for Reporting Serious Adverse Events, Adverse Events of Special Interest and Dose Limiting Toxicities

Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (within a maximum of 24 HOURS after becoming aware of the event) inform the Sponsor or its designee in writing. All written reports should be transmitted using the SAE Report Form, which must be completed by the Investigator following specific completion instructions.

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. Names, addresses, and telephone and fax numbers for SAE reporting will be included in the study-specific SAE Report Form.

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 (e.g., 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 Drug Safety department may contact the Investigator directly to obtain further information or to discuss the event.

Dose Limiting Toxicities

Each event meeting the criteria of a DLT (see Section 5.2.6) must be recorded in the eCRF within 24 HOURS after the Investigator becomes aware of the event. Serious DLTs must be reported in an expedited manner as SAEs as outlined above.

7.5.1.5 Safety Reporting to Health Authorities, Independent Ethics Committees/ Institutional Review Boards and Investigators

The Sponsor will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) involving study participants to the IEC/IRB that approved the study.

In accordance with ICH GCP, the Sponsor/designee will inform the Investigator of "findings that could adversely affect the safety of participants, impact the conduct of the study or alter the IEC's/IRB's approval/favorable opinion to continue the study." In particular and in line with respective regulations, the Sponsor/designee will inform the Investigator of AEs that are both serious and unexpected and are considered to be related to the administered product ("suspected unexpected serious adverse reactions" or SUSARs). The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations with regard to Safety Report notifications to Investigators will be considered.

When specifically required by regulations and guidelines, the Sponsor/designee will provide appropriate Safety Reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety Reports provided by the Sponsor/designee and of filing copies of all related correspondence in the Investigator Site File.

For studies covered by the European Directive 2001/20/EC, the Sponsor's responsibilities regarding the reporting of SAEs/SUSARs/Safety Issues will be carried out in accordance with that Directive and with the related Detailed Guidance documents.

7.5.1.6 Monitoring of Participants with Adverse Events

AEs are recorded and assessed continuously throughout the study (see Section 7.5.1.3) and are assessed for final outcome at the Safety Follow-up Visit. All SAEs ongoing at the Safety Follow-up Visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the participant is documented as "lost to follow-up". Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

7.5.2 Pregnancy and In Utero Drug Exposure

7.5.2.1 Pregnancy

The pregnancies considered to be related to the study intervention by the Investigator (e.g., resulting from a drug interaction with a contraceptive method) are AEs. However, all pregnancies

with an estimated conception date during the period defined in Section 7.5.1.3 must be recorded in the AE page/section of the eCRF for both pregnancies in female participants and pregnancies in female partners of male participants. The Investigator must notify the Sponsor/designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted by the same process specified for SAE reporting.

Investigators must actively follow-up, document and report on the outcome of all these pregnancies, even if the participants are withdrawn from the study.

The Investigator must notify the Sponsor/designee of these outcomes using the Pregnancy Report Form. If an abnormal outcome occurs, the SAE Report Form will be used if the participant sustains an event and the Parent-Child/Fetus Adverse Event Report Form if the child/fetus sustains an event. Any abnormal outcome (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) must be reported in an expedited manner, as specified in Section 7.5.1.3, while normal outcomes must be reported within 45 days after delivery.

In the event of a pregnancy in a participant occurring during the study, the participant must be discontinued from study intervention. The Sponsor/designee must be notified without delay and the participant must be followed as indicated above.

Lactation

It is unknown if M4344 is excreted in human breast milk. Because of the potential for serious reactions in breastfeeding infants, women should be advised not to breastfeed while taking M4344 and for 6 months after cessation of treatment.

7.5.2.2 Contraception

Strict use of contraception is required for at least 6 months after the last dose of M4344. Male participants treated with M4344 are advised to use effective contraception and to avoid fathering a child during and up to 3 months after treatment. Participants should be informed that fertility might be impaired long-term and may opt to cryopreserve sperm or ova prior to treatment.

Female participants of childbearing potential (defined below) and male participants with partners of childbearing potential must adhere to contraception guidelines as described below.

Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile, as specified below.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, consider additional evaluation.

A woman of childbearing potential is **not**:

1. Premenarchal

2. A premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

Documentation can come from the site personnel's review of the female's medical records, medical examination, or medical history interview.

For a female with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), Investigator discretion applies to determine study entry.

3. A postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in a female not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, more than 1 FSH measurement is required in the postmenopausal range.
    - A female on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if she wishes to continue HRT during the study. Otherwise, the participants must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Acceptable contraceptive methods must be used from the 28 days (for female participants) or from the Screening Visit (for male participants) before first dose of study drug through 6 months after the last dose of study drug and include the following:

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner: a highly effective contraceptive method provided that the partner is the sole sexual partner of a WOCBP and the absence of sperm has been confirmed. Otherwise, use an additional highly effective method of contraception. The spermatogenesis cycle is approximately 90 days.

Notes:

- Contraceptive use by men or women is consistent with local regulations on the use of contraceptive methods for clinical study participants.

- Highly effective methods are those with a failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
- If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.
- Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception for this study. Male condom and female condom cannot be used together (due to risk of failure with friction).

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

7.5.3 Clinical Laboratory Assessments

Blood samples will be analyzed at a local or central laboratory. On all study days, blood samples should be collected before the first dose of the study drug. Chemistry and hematology testing will be performed on the days specified in the Schedule of Assessments (see Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, Table 7, and Table 9).

The list of analytes for each panel is shown in Table 15. All analytes will be tested at Screening. For other visits, certain analytes will not be assessed at every chemistry or hematology time point. Laboratory test results that are abnormal and considered clinically significant must be reported as AEs.

Table 15 Safety Laboratory Test Panels

Serum Chemistry[a]	Hematology[a]	Urinalysis[a,d]
Glucose	Hemoglobin	Leukocyte esterase
Blood urea nitrogen/Urea[b]	Erythrocytes	Nitrite
Creatinine	Mean corpuscular hemoglobin	Urobilinogen
Sodium	Mean corpuscular hemoglobin concentration	Urine protein
Potassium	Mean corpuscular volume	pH
Calcium	Reticulocytes	Urine blood
Chloride	Platelets	Specific gravity
Magnesium	Leukocytes	Urine ketone
Bicarbonate	Differential (absolute and/or percent[e]):	Urine bilirubin
Inorganic phosphate	Eosinophils	Urine glucose
Total bilirubin	Basophils	
Direct bilirubin	Neutrophils	
Total protein	Lymphocytes	
Albumin	Monocytes	
Creatine kinase[c]	**Coagulation studies[a,c]**	
Alkaline phosphatase	Activated partial thromboplastin time	
Aspartate aminotransferase	Prothrombin time	
Alanine aminotransferase	Prothrombin time International Normalized Ratio	
Lactate dehydrogenase		
Uric acid[c]		
Thyroid stimulating hormone[c]		

a Labs will be performed at Screening (Parts A, A2, A3, and B1: Table 1; Parts C1, C2, and C3: Table 2) and at specified times during the Treatment and Follow-up Period (Table 3, Table 4, Table 5, Table 6, Table 7, and Table 9).

b If blood urea nitrogen cannot be collected, urea may be substituted.

c Creatine kinase, uric acid, thyroid stimulating hormone, and coagulation parameters will only be tested at Screening. Thyroid stimulating hormone not required for Part A3 or Parts C

d If urinalysis results are positive for leukocyte esterase, nitrite, protein, or blood, microscopic examination of urine will be performed, and results provided for leukocytes, erythrocytes, crystals, bacteria and casts.

e Per local laboratory availability.

Safety laboratory tests from Screening must have no clinically significant findings that preclude participation in the study, as judged by the Investigator, in order for a participant to be enrolled.

Urinalysis will be performed at Screening and as clinically indicated.

Serum total testosterone will be measured at Screening and Safety Follow-up in male participants in Parts A and B.

Serologic tumor markers, including PSA or CA-125, will be measured as per the Schedule of Assessments (Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, Table 7, and Table 9) for participants with relevant tumors. Additional serologic tumor CCI may be collected at time points specified in the Schedule of Assessments as deemed appropriate, depending on the participant's primary malignancy (e.g., CEA for participants with colon cancer or CA19-9 for

participants with pancreatic cancer). Of note, serologic tumor marker data should not be used for RECIST response assessments or for treatment decisions.

Pregnancy testing for female participants of childbearing potential (includes those with tubal ligation):

- At Screening, on Day 1 of Cycle 1, and continuing through the Safety Follow-up Visit, female participants of childbearing potential will be followed with urine β-human chorionic gonadotropin (β-hCG) testing and, when there are no scheduled study visits, with urine home pregnancy test kits provided by the site; and
- Bimonthly (approximately every 8 weeks) for 6 months following the last dose of study drug with a urine home pregnancy test kits provided by the 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 participant will be permanently withdrawn from study drug dosing as discussed in Section 7.5.2. If a pregnancy test is positive, the procedures outlined in Section 7.5.2 will be followed.

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

7.5.4 Vital Signs, Physical Examinations, and Other Assessments

7.5.4.1 Physical Examination and Vital Signs

A physical examination of all body systems and vital signs assessment will be performed at Screening and selected study visits (see Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, Table 7, and Table 9). At other visits, symptom-directed physical examination and symptom-directed vital sign assessments can be performed at the discretion of the Investigator or healthcare provider.

A physical examination will include a review of the following systems: head/neck/thyroid; eyes/ears/nose/throat; respiratory; cardiovascular; lymph nodes; abdomen; skin; musculoskeletal; and neurological. For participants in Parts B and C, a hearing assessment will be performed as part of the physical examination at the Screening Visit, on Day 1 of each treatment cycle, and at the Safety Follow-up Visit. Breast, anorectal, and genital examinations will be performed when medically indicated. After Screening, any clinically significant abnormal findings in physical examinations 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.

7.5.4.2 Electrocardiogram

Standard 12-lead ECGs will be performed using a machine with printout according to the Schedule of Assessments (Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, Table 7, and Table 9).

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 participant will be instructed to rest in the supine position for at least 5 minutes before having an ECG performed
- If possible, 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. The ECG machine will compute the PR, QT, and QTc intervals, QRS duration, and heart rate. RR intervals will be calculated later during analysis. 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.

For participants in Stages 1 and 2 of Parts C, triplicate 12-lead ECGs with digital upload for centralized analysis will be measured at the times of M4344 PK sampling on Days 1 and Day 2 of Cycle 1 only.

7.6 Pharmacokinetics

7.6.1 Blood Sampling

For the evaluation of plasma concentrations of M4344 (and metabolites as appropriate), blood samples will be collected from all participants according to the Schedule of Assessments (Table 3, Table 4, Table 5, Table 6, Table 7, Table 8, Table 9, and Table 10). These samples may also be used for evaluations of metabolites of M4344, for further evaluation of the bioanalytical method, and for analyses that provide information on the metabolic pathways used by or affected by M4344.

For the determination of M4344 (and metabolites as appropriate) concentrations at each time point, approximately 4 mL of blood will be collected for plasma PK assays. Blood samples will be collected via direct venipuncture or by an indwelling catheter into Vacutainer® tubes containing K_2EDTA anticoagulant. Detailed PK blood sample collection, processing, handling, and storage instructions 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.

The PK sampling schedule may be modified upon agreement of the clinical pharmacologist and Investigators to optimize the sampling time for M4344 disposition. All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. Actual time of dosing – including last prior dose for predose samples and actual PK sample collection times must be documented at the site and recorded on the eCRF. Acceptable windows for sampling times are shown in Table 16. These windows apply to both the fixed sampling timepoints, as to the boundaries of the sparse sampling windows in Parts C. Samples collected outside of these acceptable windows will be considered protocol deviations. Details of handling these data will be specified in the integrated analysis plan (IAP).

Table 16 Acceptable Pharmacokinetic Sampling Windows

Sampling Time	Time From Scheduled Sampling Allowed
Predose	-120 minutes
From 0.50 up to ≤ 12 hours after dosing	± 15 minutes
From > 12 up to ≤ 24 hours after dosing	± 60 minutes

7.6.1.1 Pharmacokinetic Sampling: Part A

In Part A, M4344 (and metabolites as appropriate) PK will be assessed in plasma as follows:

- Cycle 1, Day 1: 0 (before dosing) and at 0.5, 1, 1.5, 2, 3, 4, 8, and 24 hours (Day 2) after dosing
- Cycle 1, Day 8: 0 (before dosing) and at 0.5, 1, 1.5, 2, 3, 4, 8, and 24 hours (Day 9) after dosing
- Cycle 1, Day 15: 0 hours (before dosing).

7.6.1.2 Pharmacokinetic Sampling: Part A2

In Part A2, M4344 (and metabolites as appropriate) PK will be assessed in plasma as follows:

- Cycle 1, Day 1:
  - 0 hours (before 1st dose) and at 0.5, 1, 1.5, 2, 3, 4, and 8 hours (before 2nd dose, if applicable).
  - For participants undergoing timed-tumor biopsies, M4344 PK will be assessed in plasma as follows: Cycle 1, Day 1: 0 hours (before 1st dose) and at 0.5, 1, 1.5, 4, 8 hours (before 2nd dose, if applicable). If feasible, PK samples should also be collected at 2 and 3 hours after first dosing on Day 1.
  - An optional 12-hour sample (before 2nd dose, if applicable) may also be collected.
- Cycle 1 Day 2: 0 hours (at time of PBMC sample before Day 2 dose).
- Cycle 1, Day 8:
  - 0 hours (before 1st dose) and at 0.5, 1, 1.5, 2, 3, 4, and 8 hours (before 2nd dose, if applicable). An optional 12-hour sample may also be collected (before 2nd dose, if applicable).
- Cycle 1, Day 15: 0 hours (before 1st dosing), 2 hours.
- Subsequent cycles on Day 1: 0 hours (before 1st dosing), 2 hours.

7.6.1.3 Pharmacokinetic Sampling: Part A3

In Parts A3, M4344 (and metabolites as appropriate) PK will be assessed in plasma as follows for each of the potential drug-holiday schedules.

Table 17 Pharmacokinetic Sampling Schedule for Part A3

M4344 Schedule	PK sampling
3 days on/4 days off Or 5 days on/2 days off	M4344 (and metabolites) plasma PK samples will be collected during the following times: -Cycle 1 Day 1: predose at 0 hours, postdose at 0.5, 1, 1.5, 2, 3, 4 and 8 hours. An optional sample may be collected at 12 hours (before 2nd dose, if BID dosing). -Cycle 1 Day 8: predose at 0 hours, postdose at 0.5, 1, 1.5, 2, 3, 4 and 8 hours. An optional sample may be collected at 12 hours (before 2nd dose, if BID dosing). -Cycle 1 Day 15: predose at 0 hours and postdose at 2 hours. -Subsequent cycles on Day 1: predose at 0 hours and postdose at 2 hours For participants undergoing timed-tumor biopsies, PK samples on Cycle 1 Day 1 at 2 and 3 hours after dosing should be collected only if feasible. If Cycle 1, Day 8 occurs during a dose interruption, Cycle 1, Day 8 PK sampling will be collected on Cycle 2, Day 1 instead.
7 days on/7 days off	M4344 (and metabolites) plasma PK samples will be collected during the following times: -Cycle 1 Day 1: predose at 0 hours, postdose at 0.5, 1, 1.5, 2, 3, 4 and 8 hours. An optional sample may be collected at 12 hours (before 2nd dose, if BID dosing). -Cycle 1 Day 15: predose at 0 hours and postdose at 2 hours. -Cycle 2 Day 1: predose at 0 hours, postdose at 0.5, 1, 1.5, 2, 3, 4 and 8 hours. An optional sample may be collected at 12 hours (before 2nd dose, if BID dosing). -Subsequent cycles on Day 1: predose at 0 hours and postdose at 2 hours For participants undergoing timed-tumor biopsies, PK samples on Cycle 1 Day 1 at 2 and 3 hours after dosing should be collected only if feasible.

14 days on/7 days off	This regimen will use the PK sampling schedule from Part A2 with the Cycle 1 Day 2 predose and Cycle 1 Day 15 post dose samples omitted.

7.6.1.4 Pharmacokinetic Sampling: Part B1

In Part B1, for participants not undergoing timed-tumor biopsies, M4344 PK will be assessed in plasma as follows:

- Cycle 1, Day 2: 0 hours (before dosing) and at 0.5, 1, 1.5, 2, 3, 4, 8, and 24 hours (Day 3) after dosing
- Cycle 1, Day 9: 0 hours (before dosing).

In Part B1, for participants undergoing timed-tumor biopsies, M4344 PK will be assessed in plasma as follows:

- Cycle 1, Day 2: 0 hours (before dosing) and at 0.5, 1, 1.5, 4, 8, and 24 hours (Day 3) after dosing. If feasible, PK samples should also be collected at 2 and 3 hours after dosing
- Cycle 1, Day 9: 0 hours (before dosing).

7.6.1.5 Pharmacokinetic Sampling: Parts C

In Parts C1-3, M4344 (and metabolites as appropriate) PK will be assessed in plasma using sparse sampling during sample collection windows as follows:

- Cycle 1, Day 1 (3 samples):
  - 0 (before dosing)
  - between 0.5-2.0 hours after dosing
  - end of visit, at least 1 h after the previous sample
- Cycle 1, Days 8 and 15: at the start and end of the visit, at least 1 hours apart (2 samples)
- Cycle 2, Day 1 and every second cycle until Cycle 8, Day 1: at the start and end of the visit, at least 1 hour apart (2 samples)
- Cycle 12, Day 1 and every fourth cycle: at the start and end of the visit, at least 1 h apart (2 samples)

For drug holiday schedules in Parts C4-6, PK sampling timepoints are provided in the following table, specifically for each schedule.

Table 18 Pharmacokinetic Sampling Schedule for Parts C4, C5, and C6

M4344 Schedule	PK sampling
3 days on/4 days off Or 5 days on/2 days off	M4344 (and metabolites) plasma PK samples will be collected during the following times: -Cycle 1 Day 1: predose at 0 hours, postdose at 0.5 to 2 hours, and end of visit (at least 1 hours after the previous sample). -Cycle 1 Day 8: 2 samples, at the start and end of visit, at least 1 hour apart. -Cycle 1 Day 15: 2 samples, at the start and end of visit, at least 1 hour apart. -Every second cycle during Cycles 2-8 on Day 1: 2 samples, at the start and end of visit, at least 1 hour apart. -Every fourth cycle from Cycle 12 onwards on Day 1: 2 samples, one at start and one at end of visit, at least 1 hour apart.
7 days on/7 days off	M4344 (and metabolites) plasma PK samples will be collected during the following times: -Cycle 1 Day 1: predose at 0 hours, postdose at 0.5 to 2 hours, and end of visit (at least 1 hours after the previous sample). -Cycle 1 Day 15: 2 samples, at the start and end of visit, at least 1 hour apart. -Every second cycle during Cycles 2-8 on Day 1: 2 samples, at the start and end of visit, at least 1 hour apart. -Every fourth cycle from Cycle 12 onwards on Day 1: 2 samples, at the start and end of visit, at least 1 hour apart.
14 days on/7 days off	See PK sampling schedule from Part C1-3.

Time and date of administration of the last dose taken prior to each PK sample is to be recorded on the eCRF. Participants may continue to take drug at their usual schedule and are required to report time of administration when attending their PK visit.

CCI [redacted]

7.6.3 Processing and Handling of Pharmacokinetic Samples

Detailed procedures for the collection of blood and CCI [redacted] samples and further procedures for processing and handling of samples for PK analysis will be provided in the Sample Handling Guidelines. The shipment address and assay laboratory contact information will be provided to the investigational site before initiation of the study.

7.6.4 Bioanalysis

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

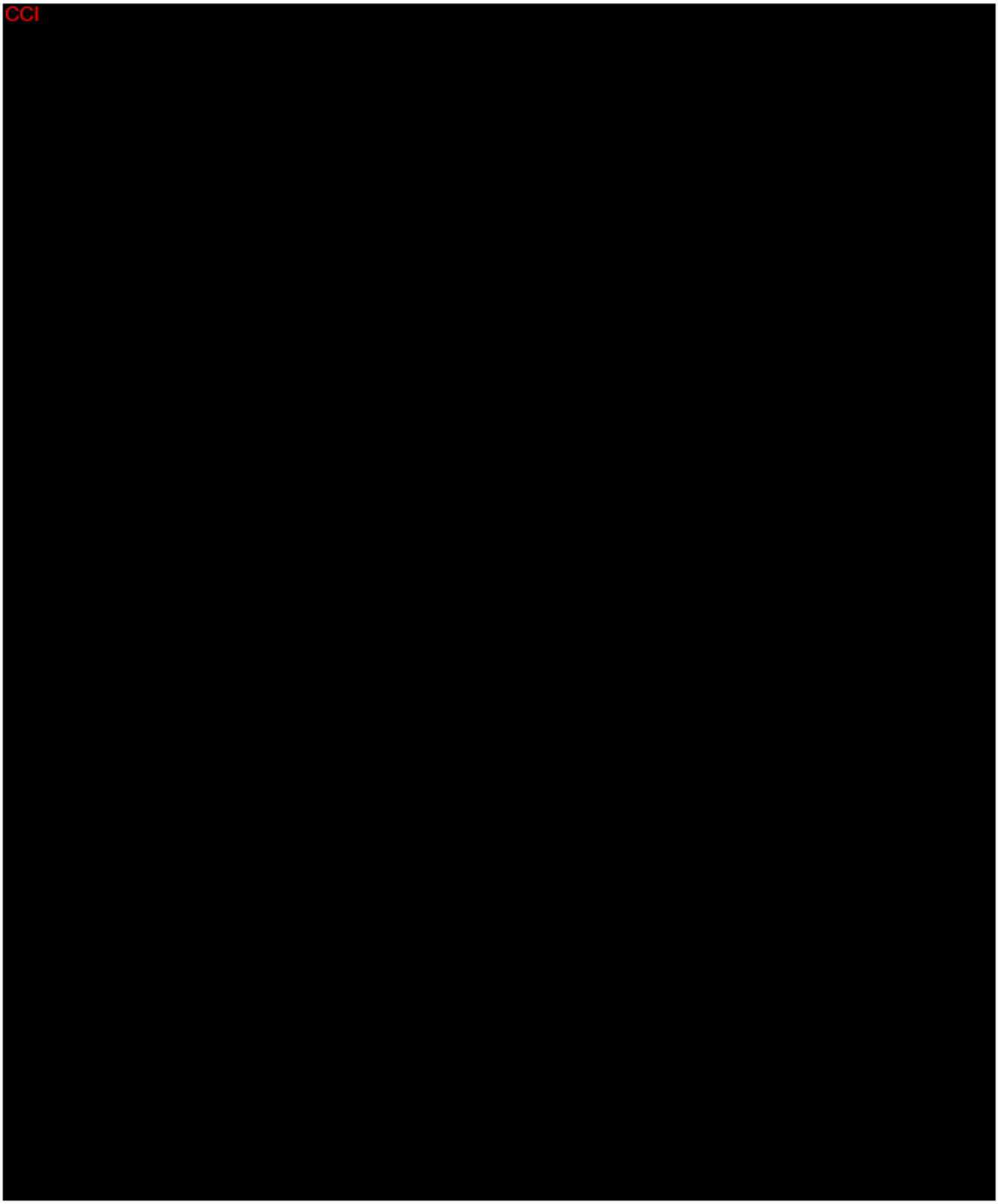
If required, whole blood, plasma, or urine samples may be utilized for assay validation or qualification and may be further analyzed to document the presence of circulation metabolites using qualified research methods. Samples obtained for PK analyses may be used for the future metabolite identification and/or other exploratory evaluations. These data will be used for exploratory purposes and may not be included in the clinical study report. In addition, PK samples may be stored for future analyses of protein binding, other protein related analyses, biochemistry, biomarker, and metabolite profiling. Samples will be analyzed using a noncharacterized assay (nonvalidated). CCI [redacted] Subsequent analyses with validated methods, which were first developed in parallel to the conduct of Part A2, will be reported in the clinical study report.

CCI [redacted]

CCI

[redacted]

CCI



CCI

[redacted]

8 Statistics

Analysis of all data, including safety, 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. A detailed analysis plan for the analysis of safety, efficacy, and PK data will be presented in the IAP before the database is locked for analysis. A detailed plan for the analysis of exploratory biomarker data will be presented in a separate biomarker analysis plan.

8.1 Sequence of Analyses

Parts C

An Independent Data Monitoring Committee (IDMC) will be implemented focusing on the review of safety data after Stage 1 and Stage 2 of each study part. Details will be provided in an IDMC charter.

Interim efficacy analyses after Stage 1

The analyses for Parts C will be performed separately.

The interim analyses will be performed once all participants in Stage 1 have been enrolled. The enrollment for Stage 2 will be started once at least 1 participant in Stage 1 has shown at least 1 confirmed CR/PR. In case no responders are reported, enrollment will be stopped once the last participant is enrolled in Stage 1.

The cutoff date of the interim analysis is defined by the time point at which every participant in Stage 1 has met at least 1 of the following criteria:

- Have progressed according to RECIST 1.1,
- Have shown an objective response,
- Have stopped planned on-study tumor assessment for any reason,
- Started treatment at least 6 months ago.

Interim efficacy analyses after Stage 2

The (interim) analysis for each study part will be performed after all participants in Stage 2 of that part have been enrolled. The enrollment for Stage 3 will not start until at least 4 participants in Stage 1 and 2 have shown a confirmed CR/PR. In case 3 or fewer responders are reported, enrollment will be stopped when the last participant is enrolled in Stage 2.

The cutoff date of the interim analysis is defined by the time point when all participants in Stage 1 and 2 meet at least 1 of the following criteria:

- Have progressed according to RECIST 1.1,
- have shown an objective response,
- Stopped planned on-study tumor assessment for any reason,
- Started treatment at least 6 months ago.

Primary analysis

The primary analysis is planned to occur once all enrolled participants have met at least 1 of the following criteria:

- Shown a confirmed Best Overall Response of PR or CR,
- Have progressed according to RECIST 1.1,
- Stopped planned on-study tumor assessment for any reason
- Started treatment at least 12 months ago.

Follow-Up analyses

The follow-up analysis will be performed at the end of the study. Details will be provided in the IAP.

The overall safety profile of M4344 will be assessed in terms of the following safety endpoints:

- Incidence of DLTs,
- Incidence of TEAEs, including AEs leading to dose modifications or discontinuations,
- Clinical laboratory values,
- ECG outcomes,
- Vital signs.

CCI

CCI

[redacted]

CCI [redacted]

8.3 Randomization

Not applicable.

8.4 Endpoints

8.4.1 Primary Endpoints

8.4.1.1 Part A

- Safety parameters, including AEs, clinical laboratory values (serum chemistry and hematology), vital signs, and ECG assessments
- MTD and/or RP2D of single agent M4344 administered BIW.

8.4.1.2 Parts A2 and A3

- Safety parameters, including AEs, clinical laboratory values (serum chemistry and hematology), vital signs, and ECG assessments
- MTD and/or RP2D of single agent M4344 administered with a dose dense schedule.

8.4.1.3 Part B1

- Safety parameters, including AEs, clinical laboratory values (serum chemistry and hematology), vital signs, and ECG assessments
- MTD and/or RP2D of M4344 administered in combination with carboplatin.

8.4.1.4 Parts C

- Occurrence of:
    - TEAEs and treatment-related AEs graded according to NCI-CTCAE (Version 5)
    - Laboratory abnormalities
    - Clinically significant abnormal vital sign
    - Clinically significant abnormal ECG
- Objective response (i.e. confirmed CR or PR) according to RECIST 1.1 as assessed by the Investigator.

8.4.2 Secondary Endpoints

8.4.2.1 Part A

- PK parameter estimates of single agent M4344 administered BIW, derived from plasma concentration-time data
- OR and disease stabilization as evaluated by RECIST 1.1.

8.4.2.2 Parts A2 and A3

- PK parameter estimates of single agent M4344 (and metabolites as appropriate) administered with a twice daily or once daily schedule, derived from plasma concentration-time data
- OR and disease stabilization as evaluated by RECIST 1.1

8.4.2.3 Part B1

- PK parameter estimates of M4344 administered in combination with carboplatin derived from plasma concentration-time data
- OR as evaluated by Response Criteria Evaluation RECIST 1.1.

8.4.2.4 Parts C

- Confirmed Best Overall Response (response assessment according to RECIST 1.1 as assessed by the Investigator will be used)
- Duration of response assessed from CR or PR until progression of disease (PD), death, or last tumor assessment
- Progression-free survival
- Overall survival
- PK parameter estimates of M4344 (and metabolites as appropriate) in individual participants with loss-of-function mutations.

CCI [redacted]

CCI

8.4.3.5 Analysis Sets

Parts A, A2, A3, and B1

The Safety Analysis Set

Defined as all enrolled participants who received at least 1 dose of study drug. The safety analysis set will be used for safety analyses.

The DLT Evaluable Set

Defined as all participants enrolled in Parts A or B who either:

- Experienced a DLT before the end of Cycle 1 or

- Received all scheduled assessments through the end of Cycle 1 (including Day 1 of Cycle 2) and received doses of M4344 and/or carboplatin, as specified in Section 5.2.7 with compliance to study prohibited medicine and dietary restrictions (Table 13).

The Full Analysis Set

For Parts A and B, the full analysis set is defined as all enrolled participants who received at least 1 dose of study drug, have a baseline scan and have at least 1 disease assessment on treatment.

Part C

The analysis populations are specified below. The final decision to exclude participants from any analysis population will be made during the data review meeting prior to database lock.

Analysis Set	Description
Enrolled	All participants, who signed informed consent
Full Analysis Set (FAS)	All participants, who received at least one dose of M4344.

8.5 Description of Statistical Analyses

This section presents a summary of the planned statistical analyses of efficacy and safety for this study. Methodological details (e.g., missing data handling) will be provided in the IAP for this study, which will be finalized before clinical database lock.

8.5.1 Part C

All efficacy analyses will be performed on the full analysis set (FAS).

Analysis on baseline characteristics and demographics as well as the safety analysis will be performed on the safety analyses set (SAF).

The statistical analysis of PK, CC and CCI data will be performed on the respective analysis sets.

8.5.1.1 Sequence of analyses

Interim analysis is planned after Stage 1 and after Stage 2.

The primary analysis will take place when all participants are enrolled (for details see Section 8.1), whereas the final FU-analysis is planned when all participants have completed the study.

8.5.1.2 Data Cutoff

The cutoff dates for all analyses are defined in Section 8.1.

8.5.1.3 Significance level

A nominal significance level of 5% will be used. No adjustment for multiplicity will be made.

8.5.1.4 Summary statistics and confidence intervals

Continuous variables will be summarized using descriptive statistics, i.e., number of participants (N), mean, median, standard deviation, 2-sided 95% CIs where appropriate, 25th and 75th percentiles, minimum, and maximum.

Qualitative variables and rates will be summarized by counts and percentages along with 2-sided exact Clopper-Pearson 95% CIs. Unless otherwise stated, the calculation of proportions will be based on the sample size of the analysis set of interest. Counts of missing observations will be included in the denominator and presented as a separate category.

8.5.1.5 Baseline measurement

The last measurement prior to first administration of M4344 will serve as the baseline measurement.

8.5.1.6 On-treatment period

The On-treatment period is defined by the start of treatment until 28 days after the last administration of M4344.

8.5.1.7 Pooling across centers

To provide overall estimates of the treatment effects, data will be pooled across centers. The factor center will not be considered in statistical models or for subgroup analyses because of the high number of participating centers and the anticipated small number of participants enrolled at each center.

No further analyses are planned.

8.5.2 General Considerations

For all parts, continuous data will be summarized by dose and visit using the following descriptive summary statistics: the number of observations (n), mean, SD, standard error (SE), median, minimum value, and maximum value. Categorical data will be summarized using counts and percentages. All participant data, including those derived, will be presented in the participant data listings; listings will display all participants who were enrolled, regardless of whether or not they received the study drug.

8.5.3 Background Characteristics

8.5.3.1 Participant Disposition

The number and percentage of participants in each disposition category (e.g., randomized, included in safety analysis set, DLT Evaluable Set, full analysis set, completing treatment period, completing the 14-day Safety Follow-up Visit, and discontinuing study [with a breakdown of the reasons for discontinuation]) will be summarized by dose group.

8.5.3.2 Demographics and Baseline Characteristics

For all study parts, demographics and baseline characteristics will be summarized by treatment group for the safety analysis set. Demographics will include variables such as sex, race, ethnicity, age, weight, height, body mass index, and body surface area. Baseline characteristics will include variables such as type of cancer, tumor stage, WHO performance status, time elapsed since cancer diagnosis, and prior chemotherapy.

Statistical tests of baseline characteristics to check for imbalance between treatment groups will not be performed.

8.5.3.3 Prior and Concomitant Medicine

Medications taken 14 days before the Screening Visit and up to the 14-Day Safety Follow-up Visit will be summarized by Preferred Name using the World Health Organization-Drug Dictionary (WHO-DDE) for the full analysis set frequency tables in 2 parts:

- Prior medication: medication that started before the first dose of study drug, regardless of when dosing of the medication ended
- Concomitant medication: medication received at or after the first dose of study drug, or medication that was received before initial dosing and continued after initial dosing of study drug, or 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.

8.5.3.4 Study Drug Exposure Compliance

Study drug exposure will be summarized based on the safety analysis set. Total number of cycles is defined as the maximum number of treatment cycles that a participant receives. Total cumulative dose is defined as the sum of the actual doses that a participant receives across cycles. The total number of cycles and total cumulative dose will be summarized for each component of the dosing regimen for all Parts of this study.

8.5.4 Efficacy Analysis in Parts A, A2, A3 and B1

Efficacy data will be summarized by treatment group and study part, and overall. Efficacy data may also be summarized by type of cancer, tumor stage, WHO performance status, time elapsed since cancer diagnosis, and prior chemotherapy. Efficacy analysis will be based on the full analysis set.

8.5.4.1 Analysis of Primary Variables

Not applicable.

8.5.4.2 Analysis of Secondary Efficacy Variables

All efficacy endpoints are secondary.

The proportion of participants achieving a given categorical efficacy endpoint will be summarized by treatment group and study part. For each proportion, a 90% confidence interval will be provided using the exact method.

- Objective response by visit: CR or PR demonstrated by visit
- Disease control rate by visit: CR, or PR, or stable disease demonstrated by visit
- Best overall response: CR or PR demonstrated at any time after initiation of treatment.

Tumor response will also be depicted via waterfall plots. Time to event endpoints such as progression-free survival (PFS) and response duration will be estimated using the Kaplan-Meier method if the number of events is adequate.

8.5.5 Efficacy Analysis in Parts C

All efficacy analyses will be performed on the FAS.

Objective response is defined as a confirmed assessment of CR or PR by the Investigator using RECIST 1.1.

Confirmed Best Overall Response is defined as the best confirmed response from start of treatment. Tumor assessments performed after start of further anticancer treatment line will not be used in the determination of the best overall response.

Duration of response is defined as the time from the earliest assessment of confirmed CR or PR until PD, death, or last adequate tumor assessment.

Progression-free survival is defined as the time between the start of study treatment to PD or death (in case PD is not observed prior to death). Death is only taken into account, if observed within 2 consecutive missed planned tumor assessments. after the last tumor assessment showing CR, PR, or SD.

If the death is observed after more than two consecutive missed planned tumor assessments after the last tumor assessment showing CR, PR, or SD, PFS will be censored at the last tumor assessment.

Response assessment by the Investigator will be used for the calculation of efficacy endpoints.

Endpoint	Statistical Analysis Methods
Primary: • Objective response	• Objective response rate, incl. 95% 2-sided Clopper-Pearson Confidence interval
Secondary • BOR	• Count and percentage per BOR category
• DoR • PFS • Overall survival	• Kaplan-Meier plot • Kaplan-Meier estimates and corresponding statistics

No adjustment for multiplicity will be made.

Selected subgroup analyses will be performed per indication with each study part.

Secondary efficacy endpoints will be analyzed descriptively only.

Details of all analysis will be provided in the IAP.

8.5.6 Clinical Pharmacology Analysis

8.5.6.1 Pharmacokinetic Analysis

Upon receipt of bioanalytical data, M4344 PK will be assessed on an ongoing basis during the dose escalation phase in Parts A, A2, A3, and B1, using standard noncompartmental analysis methods. When possible, PK results for M4344 will be reviewed along with safety data to inform dose escalation.

Further details of the PK analyses for M4344 in Parts A, A2, A3, B1, and C will be provided in the IAP.

Population PK Analysis

Sparse PK samples collected in Parts C will be combined with PK data from other study parts (and/or additional future studies) in a population PK analysis to develop a population PK model for M4344 and derive individual participant exposure estimates.

Further details of the PK analyses for M4344 in Parts A, A2, A3, B1, and C will be provided in the IAP.

CCI [redacted]

8.5.6.3 Exposure - QTc Analyses

Time matched PK and ECG samples from Parts A, A2, A3, and C will be used to assess the relationship between concentration of M4344 (and metabolites, if applicable) and QT/QTc interval. The relationship(s) will be explored graphically initially and may be further explored mathematically. Further details will be provided in the IAP.

CCI [redacted]

8.5.7 Analysis of Safety and Other Endpoints

8.5.7.1 Safety in Parts A and B1

The overall safety profile of M4344 will be assessed in terms of the following primary (safety) endpoints:

- Incidence of treatment-emergent AEs (including AEs leading to dose modifications or discontinuations)
- Incidence of DLTs (Parts A, B1)
- Clinical laboratory values (including serum chemistry, hematology, and coagulation studies)
- ECG outcomes
- Vital signs

Safety data will be summarized by treatment group and study part, and overall.

In general, safety analyses will be based on the safety analysis set. The summary of DLTs will be based on the DLT evaluable set.

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

Adverse events will be coded according to Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of participants 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 pretreatment or treatment-emergent.

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

Treatment-emergent adverse events (TEAEs) are defined as AEs that were reported or worsened on or after start of study drug dosing through the 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 participant with multiple occurrences of the same AE or continuing AEs 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. Treatment emergent adverse events leading to study drug dose modification or permanent discontinuation will be summarized.

AEs leading to death, SAEs, dose interruption of study drug, or permanent discontinuation of study drug, and SAEs will be listed separately. Pretreatment AEs and TEAEs will be listed in individual participant data listings. Unresolved, ongoing AEs reported through the 14-Day Safety Follow-up will be listed separately in an individual participant data listing.

8.5.7.2 Safety in Parts A2 and A3

Analyses to decide on dose escalation will be based on safety and preliminary PK/Pd data as available.

CCI

For the lowest dose level, the stopping criteria are based on the posterior probability that the true MTD is greater than the target probability. If this posterior probability is 90% or higher for the lowest dose level the dose escalation will be stopped.

In case the posterior probability that the true MTD is greater than the target probability for the current dose level is at least 95%, the current dose level and all higher doses will be eliminated from the set of planned dose levels, i.e. these dose levels cannot be chosen for any further cohort.

After the completion of the dose escalation, the MTD will be determined based on isotonic regression (Liu and Yuan, 2015).

Analyses for the BOIN model will be performed on the DLT Evaluable Set.

8.5.7.3 Safety in Parts C

All analysis of safety will be based on the SAF analysis set defined as all participants who were administered at least 1 dose of M4344.

Adverse Events

Adverse events will be coded according to the latest available version of the MedDRA. Severity of AEs will be graded by the Investigator using the NCI-CTCAE (Version 5) toxicity grades. Adverse events related to trial medication will be defined as any AE considered as related to M4344. Missing classifications concerning study intervention will be considered related to the trial treatment.

Any treatment-emergent AEs will be summarized, i.e. those events that:

- are emergent during on-treatment period having been absent pretreatment or
- worsen relative to the pretreatment state and with onset dates occurring in the on-treatment period.

For laboratory values, vital signs and other safety parameter only the baseline value and values during the on-treatment period will be summarized.

Laboratory variables

Laboratory results will be classified by grade according to NCI-CTCAE v 5.0.
Results for variables that are not part of NCI-CTCAE will be presented as below, within, or above normal limits.

Endpoint	Statistical Analysis Methods
• TEAEs • SAE • Related TEAEs • Related SAEs • TEAE of Grade ≥ 3 • Related TEAE of Grade ≥ 3 • TEAEs leading to treatment interruptions or modifications	Incidence of TEAE overall and by SOC and PT

• TEAEs leading to permanent treatment discontinuation • TEAEs leading to deaths • AESIs.	
• Death	Count and percentage of deaths overall and by primary reason of death • Deaths after start of treatment • Deaths within 30 days after the last dose of trial intervention • Deaths within 60 days after the first dose of trial intervention
• Laboratory variables	Parameter with CTC grading: Summary statistics • Worst on-treatment grade • Shifts from baseline to worst on-treatment • Box-plot (Laboratory values over time)
• Vital signs	Summary statistics • Highest increase from baseline • Highest decrease from baseline • Shifts from baseline to highest increase on-treatment • Shifts from baseline to highest decrease on-treatment

8.6 Clinical Laboratory Assessment

All statistical analyses of laboratory values will be performed using SI units. Continuous-valued serum chemistry, hematology, and coagulation results will be summarized by treatment group, by study part, and overall at each scheduled time point. Change from baseline results will also be summarized.

The number and percentage of participants with shift changes based on CTCAE toxicity grades will be tabulated.

A listing of individual participant hematology, serum chemistry, and coagulation values outside the reference ranges will be provided. This listing will include data from scheduled and unscheduled time points.

Grade 3 and above toxicity laboratory values will be provided in individual participant data listings. Clinically significant abnormal laboratory findings will be reported as AEs.

8.7 Electrocardiogram

A summary of raw values and change from baseline values by treatment group and study part for each scheduled visit will be provided for the following ECG parameters: PR, QT, QRS, and QTc intervals, and heart rate. In addition, the number and percentage of participants 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.

8.8 Vital Signs

A summary of values and change from baseline values by treatment group and study part, and overall for each scheduled visit will be provided for the following vital sign parameters: 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.

8.9 Physical Examination

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

8.10 Interim and Additional Planned Analyses

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

For all Parts C, interim analyses are planned after each stage, see Section 8.1.

9 Ethical and Regulatory Aspects

9.1 Responsibilities of the Investigator

The Investigator is responsible for the conduct of the study at the site and will ensure that the study is performed in accordance with this protocol, the ethical principles outlined in the Declaration of Helsinki, ICH GCP, and any other applicable regulations. The Investigator must ensure that only participants who have given informed consent are included in the study.

According to United States Code of Federal Regulations Part 54.2 (e), for studies conducted in any country that could result in a product submission to the United States Food and Drug Administration for marketing approval and could contribute significantly to the demonstration of efficacy and safety of a study drug (which are considered "covered clinical studies" by the FDA), the Investigator and all sub-Investigators are obliged to disclose any financial interest which they, their spouses or their dependent children may have in the Sponsor or the Sponsor's product under

study. This information is required during the study and for 12 months following completion of the study.

9.2 Participant Information and Informed Consent

An unconditional prerequisite for each participant prior to participation in the study is written informed consent, which must be given before any study-related activities are carried out. Adequate information must therefore be given to the participant by the Investigator or an appropriate designee (if local regulations permit) before informed consent is obtained.

A participant information sheet must be prepared in the local language in accordance with ICH GCP and will be provided by the Sponsor for the purpose of obtaining informed consent. In addition to providing this written information to a potential participant, the Investigator or a designate will inform the participant verbally of all pertinent aspects of the study, using language chosen so that the information can be fully and readily understood by laypersons. The participant will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification.

If permitted by national regulations, a person other than the Investigator may inform the participant about the study and sign the ICF, as above.

After the information is provided by the Investigator, the Informed Consent Form must be signed and dated by the participant and the Investigator.

The signed and dated declaration of informed consent will remain at the Investigator's site, and must be safely archived so that the forms can be retrieved at any time for monitoring, auditing and inspection purposes. A copy of the signed and dated information and ICF should be provided to the participant prior to participation.

Whenever important new information becomes available that may be relevant to informed consent, the Investigator will revise the participant information sheet and any other written information to be provided to the participants and submit them to the IRB for review and opinion. Using the approved revised participant information sheet and other written information, The Investigator will explain the changes to the previous version to each study participant and obtain new written consent for continued participation in the study. The participant will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification about the changes.

9.3 Participant Identification and Privacy

A unique number will be assigned to each participant, immediately after informed consent has been obtained. This number will serve as the participant's identifier in the study as well as in the clinical study database. If a participant is screen failure and is re-screened or consents for participation in a different part of the study, that participant will be assigned a new unique number. All participant data collected in the study will be stored under the appropriate participant number. Only the Investigator will be able to link study data to an individual participant via an identification list kept at the site. For each participant, original medical data will be accessible for the purposes

of source data verification by the Monitor, audits and regulatory inspections, but participant confidentiality will be strictly maintained.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing participant data. Participants will be informed accordingly and will be requested to give their consent on data handling procedures in accordance with national regulations.

Blood and tumor tissue samples for CCI and CCI will be stored for up to 10 years after study completion. During this time, the samples may be reanalyzed for newly identified CCI or with new or improved technology. After 10 years, the samples will be destroyed or fully anonymized or a new IEC/IRB approval and informed consent will be requested to keep the samples for an additional period. If tumor tissue remains, the site will be notified, and the tumor tissue will be returned to the site upon request. If the site does not request the return of the tumor tissue, it will be destroyed.

9.4 Emergency Medical Support and Participant Card

Participants will be provided with Emergency Medical Support cards supplied by the Sponsor for use during study participation in order to provide clinical study participants with a way of identifying themselves as participating in a clinical study and to give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the participant. The information provided on the Emergency Medical Support card may include the process for emergency unblinding (if applicable).

The first point of contact for all emergencies will be the clinical study Investigator caring for the affected participant. The Investigator agrees to provide his or her emergency contact information on the card for this purpose. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action (for example, unblinding) will follow the standard process established for Investigators.

In cases where the Investigator is not available, the Phase I facility will provide the appropriate means to contact a physician. This includes the provision of a 24-hour contact number at the facility, whereby the health care providers will be given access to an appropriate physician to assist with the medical emergency and to provide support for the potential unblinding of the participant concerned.

9.5 Clinical Study Insurance and Compensation to Participants

Insurance coverage will be provided for each country participating to the study. Insurance conditions shall meet good local standards, as applicable.

9.6 Independent Ethics Committee or Institutional Review Board

Prior to commencement of the study at a given site, this clinical study protocol will be submitted together with its associated documents (protocol, Investigator's Brochure, sample ICF, advertisements [if applicable], written information given to the participants [including diary cards], safety updates, annual progress reports, and any revisions to these documents) to the responsible

Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for its favorable opinion or approval, which will be filed in the Investigator Site File. A copy will be filed in the Sponsor Trial Master File at the Sponsor.

The IEC or IRB will be asked to document the date of the meeting at which the favorable opinion or approval was given and the members and voting members present. Written evidence of favorable opinion or approval that clearly identifies the study, the clinical study protocol version and the Participant Information and ICF version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

Amendments to this clinical study protocol will also be submitted to the concerned IEC or IRB, before implementation of substantial changes (see Section 10.5). Relevant safety information will be submitted to the IEC or IRB during the course of the study in accordance with national regulations and requirements.

9.7 Health Authorities

The clinical study protocol and any applicable documentation (for example, Investigational Medicinal Product Dossier, Participant Information and ICF) will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

10 Study Management

10.1 Case Report Form Handling

Refer to the Manual of Operations for eCRF handling guidelines.

The main purpose of the eCRF is to obtain data required by the clinical study protocol in a complete, accurate, legible and timely. The data in the eCRF should be consistent with the relevant source documents.

The Investigator or designee is responsible for ensuring that the data collected in the course of this study is accurate and documented appropriately on all applicable forms. They will then be processed, evaluated, and stored in anonymous form in accordance with applicable data protection regulations. The Investigator must ensure that the eCRFs and any other associated documents forwarded to Sponsor or its designated organization contain no mention of any participant names.

The data will be entered into a validated database. The Sponsor or its designee will be responsible for data processing, in accordance with the Sponsor's data management procedures. Database lock will occur once quality control and quality assurance procedures have been completed. PDF files of the eCRFs will be provided to the Investigators at the completion of the study.

10.2 Source Data and Participant Files

The Investigator must keep a file (medical file, original medical records) on paper or electronically for every participant in the study. It must be possible to identify each participant by using this

participant file. This file will contain the demographic and medical information for the participant listed below and should be as complete as possible.

- Participant's full name, date of birth, sex, height, weight
- Medical history and concomitant diseases
- Prior and concomitant therapies (including changes during the study)
- Study identification, that is, the Sponsor study number for this clinical study, and participant number
- Dates for entry into the study (informed consent) and visits to the site
- Any medical examinations and clinical findings predefined in this clinical study protocol
- All AEs
- Date that the participant left the study including any reason for early withdrawal from the study or study drug (if applicable).

All documents containing source data must be filed, including, but not limited to CT or MRI scan images, ECG recordings, and laboratory results. Such documents must bear the participant number and the date of the procedure. If possible, this information should be printed by the instrument used to perform the assessment or measurement. As necessary, medical evaluation of such records should be performed; all evaluations should be documented, signed, and dated by the Investigator.

Electronic participant files will be printed whenever the Monitor performs source data verification. Printouts must be signed and dated by the Investigator, countersigned by the Monitor and kept in a safe place at the site. Printing the files will not be necessary if the monitor is permitted to access and review electronic participant files or other electronic study records at Investigator sites, provided that they are given their own unique access and is "Read Only."

10.3 Investigator Site File and Archiving

Upon initiation of the study, the Investigator will be provided with an Investigator Site File containing all necessary study documents, which will be completed throughout the study and updated as necessary. The file must be available for review by the Monitor, during Sponsor audits and for inspection by Health Authorities during and after the study, and must be safely archived for at least 15 years (or longer, per local requirements or as otherwise notified by the Sponsor) after the end of the study. The documents to be archived include the Participant Identification List and the signed participant ICFs. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor/designee.

All original participant files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

10.4 Monitoring, Quality Assurance and Inspection by Health Authorities

This study will be monitored in accordance with the ICH GCP, and any other applicable regulations. The site Monitor will perform visits to the study site at regular intervals.

The clinical study protocol, each step of the data capture procedure, and the handling of the data, including the final clinical study report, will be subject to independent Quality Assurance activities. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data. Representatives of the Quality Assurance unit from the Sponsor or a designated organization, as well as Health Authorities, must be permitted to access all study documents and other materials at the site, including the Investigator Site File, the completed eCRFs, all study drug and study drug accountability records, and the original medical records or files for each participant.

10.5 Changes to the Clinical Study Protocol

Changes to the clinical study protocol will be documented in writing. Substantive amendments will usually require submission to the Health Authorities and to the relevant IEC/IRB for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

Minor (nonsubstantial) protocol amendments, including administrative changes, will be filed by the Sponsor and at the site. They will be submitted to the relevant IEC/IRB or to Health Authorities only where requested by pertinent regulations. Any amendment that could affect the participant's agreement to participate in the study requires additional informed consent prior to implementation following the process as described in Section 9.2.

10.6 Clinical Study Report and Publication Policy

10.6.1 Clinical Study Report

A clinical study report, written in accordance with the ICH E3 Guideline by the Sponsor in consultation with the Coordinating Investigator, will be submitted in accordance with local regulations.

10.6.2 Publication

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows Merck to protect proprietary information and to provide comments. The Sponsor will comply with the requirements for publication of study results. Per standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by agreement. Authorship will be determined by agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Posting of results from this trial on ClinicalTrials.gov and EudraCT is planned and will occur 12 months after the last clinic visit of the final study participant or another appropriate date to meet applicable requirements.

11 References Cited in the Text

American Cancer Society. Cancer facts and figures 2012. Atlanta: American cancer society; 2011.

Cancer Genome Atlas Research Network. Comprehensive molecular portraits of human breast tumours. Nature. 2012;490:61-70.

Carboplatin. Summary of Product Characteristics [Internet].

Cimprich KA, Cortez D. ATR: an essential regulator of genome integrity. Nature Reviews Molecular Cell Biology. 2008;9:616-27.

Cisplatin. Summary of Product Characteristics [Internet].

Creasy DM, Foster PMD (2002). Male Reproductive System. In WM Haschek, CG Rousseaux, MA Wallig (Eds.), Handbook of Toxicologic Pathology (pp.785). San Diego, California: Elsevier Science.

Ding L, Getz G, Wheeler DA, et al. Somatic mutations affect key pathways in lung adenocarcinoma. Nature. 2008;455:1069-75.

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer. 2009;45:228-47.

Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010;127:2893-2917.

Flynn RL, Cox KE, Jeitany M, et al. Alternative lengthening of telomeres renders cancer cells hypersensitive to ATR inhibitors. Science. 2015;347(6219):273-7.

Further analysis of the data in the CrownBio report entitled "Evaluation of efficacy and safety of Vertex's test compound VXc-803 and in combination with carboplatin in the treatment of subcutaneous MDA-MB-468 human breast cancer xenograft model". Report K243. Report date 19 August 2014.

Gemcitabine. Summary of Product Characteristics [Internet].

Gilad O, Nabet BY, Ragland RL, et al. Combining ATR suppression with oncogenic Ras synergistically increases genomic instability, causing synthetic lethality or tumorigenesis in a dosage-dependent manner. Cancer Research. 2010;70:9693-702.

Greenman C, Stephens P, Smith R, et al. Patterns of somatic mutation in human cancer genomes. Nature. 2007;446:153-58.

Hammond EM, Dorie MJ, Giaccia AJ. Inhibition of ATR leads to increased sensitivity to hypoxia/reoxygenation. Cancer Research. 2004;64:6556-62.

Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. New England Journal of Medicine. 2005;352:997-1003.

Howlader N, Noone AM, Krapcho M, et al (eds). SEER Cancer Statistics Review, 1975-2011, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2011/, based on November 2013 SEER data submission, posted to the SEER web site, April 2014.

ITR Laboratories. VRT-1228692: A 14-day oral range finding toxicity and toxicokinetic study in Sprague-Dawley rats. Vertex study number: VRT-1228692-TX-001. ITR study number: 72171. Report date: 15 November 2013.

ITR Laboratories. VRT-1228692: A 14-day oral range finding toxicity and toxicokinetic study in Beagle dogs. Vertex study number: VRT-1228692-TX-002. ITR study number: 61388. Report date: 18 November 2013.

Ivanova A. Escalation, group and A+B designs for dose-finding trials. Statist Med. 2006;25:3668-78.

Jiang H, Reinhardt HC, Bartkova J, et al. The combined status of ATM and p53 link tumor development with therapeutic response. Genes & Development. 2009;23:1895-909.

Kastan MB, Bartek J. Cell-cycle checkpoints and cancer. Nature. 2004;432:316-23.

Li J, Zhao, T, Zhang Y, et al. Performance evaluation of pathogenicity-computation methods for missense variants. Nucleic Acids Res. 2018;46(15):7793-804.

Min A, Im SA, Jang H, et al. AZD6738, A Novel Oral Inhibitor of ATR, Induces Synthetic Lethality with ATM Deficiency in Gastric Cancer Cells. Mol Cancer Ther. 2017;16(4):566-577.

MPI Research. VRT-1228692: A 28-day oral (gavage) toxicity and toxicokinetic study in rats with a 14-day recovery period. Vertex study number: VRT-1228692-TX-004. MPI study number: 863-165. Report date: 28 August 2014.

MPI Research. VRT-1228692: A 28-day oral (gavage) toxicity and toxicokinetic study in dogs with a 14-day recovery period. Vertex study number: VRT-1228692-TX-005. MPI study number: 863-166. Report date: 28 August 2014.

Murga M, Bunting S, Montana MF, et al. A mouse model of ATR-Seckel shows embryonic replicative stress and accelerated aging. Nature Genetics. 2009;41:891-8.

Murga M, Campaner S, Lopez-Contreras AJ, et al. Exploiting oncogene-induced replicative stress for the selective killing of Myc-driven tumors. Nature Structural & Molecular Biology 2011;18:1331-5.

NCCN Clinical Practice Guidelines in Oncology for Non-Small Cell Lung Cancer. Version 2. 2013. Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp

Liu S, Yuan, Y. Bayesian Optimal Interval Designs for Phase I Clinical Trials. Journal of the Royal Statistical Society: Series C, 64, 507-23.

Nghiem P, Park PK, Kim Y, et al. ATR inhibition selectively sensitizes G1 checkpoint-deficient cells to lethal premature chromatin condensation. Proceedings of the National Academy of Sciences of the United States of America. 2001;98:9092-7.

Nghiem P, Park PK, Kim Ys, et al. ATR is not required for p53 activation but synergizes with p53 in the replication checkpoint. Journal of Biological Chemistry. 2002;277:4428-34.

Norquist B, Wurz KA, Pennil CC, et al. Secondary somatic mutations restoring BRCA1/2 predict chemotherapy resistance in hereditary ovarian carcinomas. Journal of Clinical Oncology. 2011;29:3008-15.

Olaussen KA, Dunant A, Fouret P, et al. DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy. New England Journal of Medicine. 2006;355:983-91.

Pires IM, Olcina MM, Anbalagan S, et al. Targeting radiation-resistant hypoxic tumour cells through ATR inhibition. British Journal of Cancer. 2012;107:291-9.

Reaper PM, Griffiths MR, Long JM, et al. Selective killing of ATM- or p53-deficient cancer cells through inhibition of ATR. Nature Chemical Biology. 2011;7:428-30.

Rustin GJ, Quinn M, Thigpen T, et al. Re: New guidelines to evaluate the response to treatment in solid tumors (ovarian cancer). Journal of the National Cancer Institute. 2004;96:487-8.

Ruzankina Y, Pinzon-Guzman C, Asare A, et al.Deletion of the developmentally essential gene ATR in adult mice leads to age-related phenotypes and stem cell loss. Cell Stem Cell. 2007;1:113-26.

Sangster-Guity N, Conrad BH, Papadopoulos N, et al. ATR mediates cisplatin resistance in a p53 genotype-specific manner. Oncogene. 2011;30:2526-33.

Scher HI, Halabi S, Tannock I, et al: Design and endpoints of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: Recommendations of the Prostate Cancer Clinical Trials Working Group. Journal of Clinical Oncology. 2008;26:1148-59.

Schoppy DW, Ragland RL, Gilad O, et al. Oncogenic stress sensitizes murine cancers to hypomorphic suppression of ATR. The Journal of Clinical Investigation 2012;122:241-52.

Toledo LI, Murga M, Zur R, et al. A cell-based screen identifies ATR inhibitors with synthetic lethal properties for cancer-associated mutations. Nature Structural & Molecular Biology. 2011;18:721-7.

Williamson CT, Miller R, Pemberton HN, et al. ATR inhibitors as a synthetic lethal therapy for tumours deficient in ARID1A. Nat Commun. 2016;7:13837

12 Appendices

Appendix I: Signature Pages and Responsible Persons for the Study

Signature Page – Protocol Lead

Study Title:	An Open-Label Study of the Safety, Tolerability, and Pharmacokinetic/Pharmacodynamic Profile of M4344 (formerly VX-803) as a Single Agent and in Combination with Cytotoxic Chemotherapy in Participants with Advanced Solid Tumors
IND Number:	CCI
EudraCT Number:	2014-003838-86
Clinical Study Protocol Date / Version:	29 January 2020 / Version 8.0

Protocol Lead:

PPD

I approve the design of the clinical study

PPD

PPD

Signature

PPD

Date of Signature

Name, academic degree:	PPD
Function / Title:	Senior Medical Director
Institution:	PPD
Address:	Merck KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany
Telephone number:	PPD
Fax number:	
E-mail address:	

Signature Page –Coordinating Investigator

Study Title	An Open-Label Study of the Safety, Tolerability, and Pharmacokinetic/Pharmacodynamic Profile of M4344 (formerly VX-803) as a Single Agent and in Combination with Cytotoxic Chemotherapy in Participants with Advanced Solid Tumors
IND Number	CCI
EudraCT Number	2014-003838-86
Clinical Study Protocol Date / Version	29 January 2020 / Version 8.0

I approve the design of the clinical study and I understand and will conduct the study according to the clinical study protocol, any approved protocol amendments, International Council for Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

PPD

Signature

PPD

Date of Signature

Name, academic degree:	PPD
Function / Title:	
Institution:	
Address:	
Telephone number:	
E-mail address:	

Signature Page – Principal Investigator

Study Title	An Open-Label Study of the Safety, Tolerability, and Pharmacokinetic/Pharmacodynamic Profile of M4344 (formerly VX-803) as a Single Agent and in Combination with Cytotoxic Chemotherapy in Participants with Advanced Solid Tumors
IND Number	CCI [redacted]
EudraCT Number	2014-003838-86
Clinical Study Protocol Date / Version	29 January 2020 / Version 8.0
Center Number	
Principal Investigator	

I, the undersigned, am responsible for the conduct of the study at this site and affirm that I understand and will conduct the study according to the clinical study protocol, any approved protocol amendments, International Council for Harmonisation (ICH) good Laboratory Practice (GCP) (Topic E6) and all applicable Health Authority requirements and national laws.

I also affirm that I understand that Health Authorities may require the Sponsors of clinical studies to obtain and supply details about ownership interests in the Sponsor or Investigational Medicinal Product and any other financial ties with the Sponsor. The Sponsor will use any such information solely for the purpose of complying with the regulatory requirements. I therefore agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties including those of my spouse and dependent children, and to provide updates as necessary to meet Health Authority requirements.

_____ _____

Signature Date of Signature

Name, academic degree:

Function / Title:

Institution:

Address:

Telephone number:

Fax number:

E-mail address:

Appendix II: Protocol Amendment History

The information for the current amendment is on the title page.

Protocol History

Version and Date of Protocol	Comments
Version 7.0, 28 April 2019	<u>Change of Study Design and Plan</u> • The development of M4344 in combination with cytotoxic agents like carboplatin, gemcitabine, and cisplatin was deprioritized, and consequently the initially planned Parts B2, B3, and C were removed. • 3 new study parts (Parts C1, C2, and C3) were added to investigate the potential antitumor efficacy in participants whose tumors have certain biomarkers that have been identified to sensitize to ATR inhibition in preclinical models and for whom no standard treatment options are available. The recommended Phase II dose (RP2D) determined in Part A or A2 will be used in Parts C1, C2, and C3. • Part A2: Once Protocol Version 7.0 (28 April 2019) has been approved and implemented at all participating centers, a Bayesian optimal interval design will replace the 3+3 design if any change in the schedule of M4344 administration occurs (e.g., to a once daily administration, or a drug holiday schedule). • Text was modified to allow participants who require concomitant treatment with proton pump inhibitors (PPI) to continue treatment in the trial. • The rationale for introduction of BID dosing in Part A2 (in the previous amendment) was improved for clarity. <u>Change in Number and Location of Sites Expected to Participate</u> • The number of sites and countries participating in the study was updated to reflect current expectations. <u>Change in Pharmacodynamic/Biomarker text</u> • Added assessment of treatment-related changes in pharmacodynamic markers in PBMC in Part A2 to expand the assessment of treatment-related changes in pharmacodynamic markers.

	Update to Contraception Methods • Details and definitions for appropriate and acceptable methods of contraception were updated. Editorial Changes • Furthermore, this amendment incorporated clarifications and changes to allow investigative sites additional ease in enrolling and adhering to the protocol. • Date of last participant out was changed from 2019 to 2021 to reflect change in study parts.
Version 6.0, 02 February 2018	Change of Study Design and Plan • Generally, Ataxia telangiectasia mutated and Rad3-related protein (ATR) signaling is required to enable cancer cells to progress through to S/G2-phase, and inhibition of ATR lethally compromises this process. Repeated or prolonged ATR inhibition is expected to result in increased antitumor efficacy (VX-970 Investigator Brochure 2017). For M4344 monotherapy, preclinical murine xenograft studies of M4344 in alternative lengthening of telomeres (ALT+) models demonstrate that increased frequency of dosing is associated with, and possibly required, for optimal antitumor activity in the monotherapy setting (Vertex Report E0453-U1607 2016) while maintaining tolerability based on body weight and mortality. These data suggest that prolonged or repeated inhibition of ATR not only potentiates the cytotoxic effects of deoxyribose nucleic acid (DNA) damage, but it may also be efficacious as monotherapy in cancers which are reliant on ATR signaling (Flynn 2015). Of note, similar antitumor activity was observed for the same total weekly dose when administered once daily or twice daily in the preclinical study (Vertex Report E0453-U1607 2016). Therefore, twice daily (BID), daily dosing was selected as the initial schedule for Part A2 to sustain ATR inhibition and minimize potential for maximum concentration (C_{max}) related adverse events. • A 100-mg single dose administered BID (200 mg daily) was selected as starting dose for Part A2. • This starting dose is based on the available clinical experience in 36 participants treated with up to the 1200 mg twice weekly dosing schedule in Part A. As of December 2017, in total 10 participants have completed the dose limiting toxicity (DLT) period at the 1200 mg dose

	level. One DLT of Grade 3 fever was observed and the criteria for MTD were not yet fulfilled. The 1200 mg twice weekly schedule results in a total weekly dose of 2400 mg. A 100-mg dose administered twice daily results in a total weekly dose of 1400 mg and is therefore expected to be a tolerable starting dose. • The target dose for optimal activity as monotherapy in humans is approximately 400 mg BID daily based on preclinical studies. At this dose, the majority of participants are predicted to have an average weekly concentration of M4344 that meets or exceeds the optimal average concentration identified from preclinical models. Since the terminal half-life of M4344 is approximately 2 hours, minimal drug accumulation is expected with the twice daily or once daily schedules. • When M4344 is administered twice daily, the second daily dose is hypothesized to be optimally administered at 12-hour intervals to provide sustained ATR inhibition. However, a 4-hour window (8 to 16 hours) is permitted for participant convenience. <u>Clarification of Pharmacodynamic/Biomarker text</u> • Some changes in pharmacodynamic/biomarker exploratory objectives and endpoints, the Part B and Part C schedule of assessments, and other biomarker text were made in order to provide clarity and correctness of concepts and reduce redundancies. <u>Editorial Changes</u> • Minor editorial changes (including the change from "subject" or "patient" to "participant", where applicable) were made for readability, clarity, and flow, and, along with new references, are not included in the following comparison table.

Version 5.0, 16 August 2017	Change of Sponsor • The study will transition from Vertex Pharmaceuticals Incorporated, to Merck KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany for sites in the UK and The Netherlands, and to EMD Serono Research & Development Institute, Inc., 45A Middlesex Turnpike, Billerica, MA, USA for sites in the USA. Change of Drug name • The drug name VX-803, used in the Vertex studies, changed to M4344 during the transition to Merck. Delete 10 mg tablets of study drug Only 50 mg tablets of M4344 will be supplied.
Version 4.0, 03 June 2016	The following changes to the overall study design were made that affected multiple sections in the protocol: • Due to sponsor decision to focus on solid tumors, subjects with lymphomas will no longer be included in the study. • In order to evaluate the safety and tolerability of VX-803 in combination with gemcitabine and with cisplatin, dose escalation of VX-803 in combination with gemcitabine (Part B2) and in combination with cisplatin (Part B3) were added. Parts B2 and B3 are optional and may be pursued depending on the safety and tolerability data from the initial dose levels explored in Part B1 and sponsor decision. • On-treatment tumor biopsy substudy was added to Part B in an effort to demonstrate ATR inhibition in response to VX-803 in combination with carboplatin (Part B1), gemcitabine (Part B2), and cisplatin (Part B3). • Subject numbers in Parts A and B were updated to reflect changes in the study design. • Part C was updated to include the option of dosing VX-803 in combination with cisplatin if this combination is felt to be more appropriate for a patient than the combination of VX-803 with carboplatin. Food-effect study was deleted from Part C as it was determined from modeling that dosing in the fed state is unlikely to improve the systemic exposure of VX-803.
	• To further evaluate the pharmacokinetic (PK) of VX-803 and its metabolites, urine PK collection was added to Part B1.

	• In order to follow subjects after the 2-week Safety Follow-up Visit, a Radiologic Follow-up Visit was added to Part B. Also, additional imaging scans were added to Part C for subjects who complete at least 6 cycles of treatment and discontinue treatment for reasons other than disease progression.
	• Fluorothymidine positron emission tomography [^{18}F]-FLT-PET scans were deleted from Part B and circulating tumor cells (CTCs) were deleted from Parts B and C. [^{18}F]-FLT-PET scans were removed because sites indicated that 3 scans in one cycle are not feasible. Collection of CTCs were removed because, in a separate clinical study, we have demonstrated that the numbers of traditional CTCs/mL of blood are extremely low (approximately 1-5 CTCs/mL), making assessment of gH2AX levels in CTCs challenging as a target engagement readout.
	• Intrasubject dose escalation was added to Part A and is permitted only if VX-803 study drug at that dose level is no longer available for the subject who is continuing dosing, responding to treatment, and has no significant toxicity.
	• Based on review of the available clinical and nonclinical data and outside expert opinion, the following changes were made to the DLT definition: o Exclude transient elevations in liver function tests. • Exclude Grade 3 or 4 increase in bilirubin, if the increase is assessed as arising from inhibition of bilirubin glucuronidation. If the increase in bilirubin is assessed as arising from inhibition of bilirubin glucuronidation, then only bilirubin levels above 15 mg/dL (257 µmol/L) will be considered DLTs.
	• Inclusion criterion 6f was updated to include minimum serum albumin value needed at Screening.
	• Exclusion criterion 11c was updated to exclude subjects who have been diagnosed with Li-Fraumeni Syndrome or ataxia telangiectasia. This change was made because in cell studies, depletion of ataxia telangiectasia mutated (ATM) or p53 in non-cancer cells leads to marked sensitization to the combination of an ATR inhibitor and the DNA damaging drug cisplatin. This may indicate the potential for normal tissue to be sensitive to the combination of an ATR inhibitor and the DNA damaging drug in the event either p53 or ATM is functionally impaired.

	• Clarification was added in Parts B and C that magnetic resonance imaging (MRI) may be used as an alternative to computed tomography (CT) scans for disease assessment, but each subject should be followed using the same scan technique for assessing response throughout the study if possible.
	• Dose modification section was updated to provide more details for dose escalations for the different chemotherapeutic agents.
	• The definition of Full Analysis Set was updated.
	• Protocol synopsis was updated to align with changes made throughout the protocol.
Version 3.0, 31 August 2015	• Part A was revised to allow enrollment of up to 2 additional subjects (3 per cohort) at the discretion of the Investigators and Sponsor, in the single subject cohort at any dose level, irrespective of the toxicity, to further explore safety and/or PK. • Clarification was added that VX-803 doses will be escalated by up to 50% during dose escalation in Parts A and B. • The Safety Follow-up Visit window for all Parts was extended from 3 days to 7 days and the Radiologic Follow-up Visit for Part C was changed from 4 weeks to 5 weeks following the last cycle of treatment to allow subjects additional flexibility. • Whole blood (all Parts) and peripheral blood mononuclear cell (PBMC) collection (Parts B and C) for potential exploratory evaluation of correlations between biomarkers and PK, pharmacodynamic (PD) were deleted because of technical difficulties with the planned assays. • In response to regulatory feedback, a hearing assessment at the Screening Visit, on Day 1 of each treatment cycle, and at the Safety Follow-up Visit was added as part of the physical examination in Parts B and C. • In response to regulatory feedback, Exclusion Criterion 13 was updated to specify that subjects receiving treatment with ototoxic or nephrotoxic medications that cannot be discontinued at least 7 days before the first dose of study drug and for the duration of the study, will be excluded in Parts B and C.
Version 2.0, 14 November 2014	• Added footnote to the Schedule of Assessments for Parts A, B, and C to provide guidance on missed assessments • Clarified eligibility criteria related to the disease status of subjects in Parts A and B

	• Revised text related to Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 or greater drug-related toxicities to include any CTCAE Grade 2 or greater toxicity that is possibly, probably, or definitely related to study drug. • Clarified dose escalation of VX-803 for subjects in the single subject cohort in Part A who experience a CTCAE Grade 2 toxicity that is possibly, probably, or definitely drug-related and does not qualify as a dose-limiting toxicity (DLT). • Decreased the number of additional subjects evaluated in the initial expansion cohort when a single DLT occurs from 5 subjects to 2 subjects. An additional 3 subjects would be included at the same dose only if no DLTs occur in the 2 additional subjects. • Updated duration of long-term follow-up for subjects in Part C without documented disease progression at last study visit to every 3 months to make consistent with Section 3 and Section 8.1.10. • Modified the definition of a DLT to no longer exclude Grades 3 or 4 mucositis in subjects who have not received optimal therapy; Grades 3 or 4 mucositis would now be considered a DLT. • Clarified that in addition to all safety data, review of available pharmacokinetic (PK) data would be conducted during dose escalation in Part A. • Inclusion criteria were made more specific: 1. Subjects with known or suspected Gilbert's syndrome are exempted from serum bilirubin exclusion 2. Alkaline phosphatase must be of liver origin • Updated hemoglobin and estimated glomerular filtration rate values required for administration of VX-803 or chemotherapy on Day 1 of Cycle 1 in Table 10-1 for consistency with inclusion criteria specified in Section 9.1. In response to investigator feedback, estimated glomerular filtration rate values required for administration of VX-803 or chemotherapy on Day 1 of all cycles beyond Cycle 1 in Table 10-1 was changed from "≥ 20 mL/min" to "Does not meet DLT criteria." • Modified Exclusion Criterion 2 to allow for the inclusion of subjects in Part B1 who have received more than 6 cycles of prior therapy with carboplatin if discussed with and approved by the Vertex medical monitor.

	• Clarified that interruption of treatment is required, and was not at the discretion of the investigator, for Grade 3 or greater toxicity beyond Cycle 1. • Clarified details regarding study drug supply and handling. • Clarified the definition of an adverse event. • Clarified the serious adverse event criteria related to hospitalizations and moved this text from Section 13.1.1.1 to Section 13.1.2.1.
Version 1.0, 19 September 2014	Original version