Statistical Analysis Plan	
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Phase 1b/2 Study of ATR InhibiTor RP-3500 and PARP Inhibitor Combinations in Patients with Molecularly Selected Cancers (ATTACC)

Statistical Analysis Plan for RP-3500-03

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LIST OF ABBREVIATIONS

Abbreviation or special term	Definition
ADaM	Analysis Data Model
AE	Adverse event
ATM	Ataxia telangiectasia-mutated
ATR	Ataxia telangiectasia-mutated - and rad3-related
ATRi	Ataxia telangiectasia-mutated - and rad3-related inhibitor(s)
AUC_{0-6}	Area under the plasma concentration-time curve 0 to 6 hours post dose
AUC_{ss}	Area under the plasma concentration-time at steady-state
BID	Twice daily
BOIN	Bayesian optimal interval
BOR	Best objective response
BRCA(1/2)	Breast cancer type (1/2) susceptibility protein
BRCA2-KO	Breast cancer type 2 susceptibility protein-knockout
CDISC	Clinical Data Interchange Standards Consortium
CDK12	Cyclin-dependent kinase 12
CI	Confidence interval
C_{max}	Maximum observed plasma concentration
CR	Complete response
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CTMS	Clinical study management system
DCO	Data Cut Off
DLT	Dose-limiting toxicity
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOT	End-of-Treatment
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCIG	Gynecological Cancer Intergroup

Abbreviation or special term	Definition
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GnRH	Gonadotrophin releasing hormone
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	Half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IND	Investigational New Drug
IRT	Interactive response technology
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NGS	Next-generation sequencing
ORR	Objective response rate
OS	Overall survival
PALB2	Partner and localizer of *BRCA2*
PARP	Poly (adenosine diphosphate-ribose) polymerase
PARP1	Poly (adenosine diphosphate-ribose) polymerase 1
PARP2	Poly (adenosine diphosphate-ribose) polymerase 2
PARPi	Poly (adenosine diphosphate-ribose) polymerase inhibitor(s)
PD	Progressive disease
PE	Physical examination
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PK/PD	Pharmacokinetic/pharmacodynamic
PO	Oral(ly)
PODS	Precision Oncology Decision Support

Abbreviation or special term	Definition
PSA	Prostate-specific antigen
PR	Partial response
PT	Preferred Term
QD	Once daily
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
RAD51B	DNA repair protein RAD51 homolog 2
RECIST	Response Evaluation Criteria in Solid Tumors
RNASEH2	Ribonuclease H2
RNASEH2A/B	Ribonuclease H2 subunit A/B
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SDTM	Study Data Tabulation Model
SOC	System Organ Class
SSC	Safety Steering Committee
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum observed concentration
TRAE	Treatment-related adverse event
UDP	Uridine 5’-diphospho
ULN	Upper limit of normal
WHO	World Health Organization

AMENDMENT HISTORY

Version	Date	Brief description of change
2.0		• This version of SAP was updated based on Protocol V8.0, Protocol V8.0 Letter of Amendment #1 (21 June 2024), and Protocol memo 11, 12, 13, and 14. • Definition of Efficacy Population was updated. • Clarification of tumor marker response evaluable was added. • Progression identified by new bone lesion assessment per PCWG3 criteria was added as part of progression of disease to overall response. • Definition of TEAE was updated to include treatment related SAE which are collected indefinitely. • At the time of the database lock Phase 2 dose expansion study was not carried out due to termination of the study, thus any associated analyses will not be performed.

1. INTRODUCTION

This statistical analysis plan (SAP) prospectively describes the planned analyses for Protocol Number RP-3500-03 (IND # 146280). The SAP is written based on Protocol V8.0 Amendment 7 (15 February 2023), Protocol V8.0 Letter of Amendment #1 (21 June 2024), and Protocol memo 11, 12, 13, and 14, and is in full conformity with the most current version of Good Clinical Practices (GCP), the FDA and ICH Guidelines forclinical trials. In addition, the datasets generated for this study will be fully compliant with the latest version of the CDISC standards for the SDTM and ADaM datasets.

This SAP covers the primary and secondary objectives of the study. Exploratory objectives will be addressed outside of the SAP and additional analysis plans may be developed to document the analysis and reporting of the exploratory objectives.

2. STUDY DETAILS

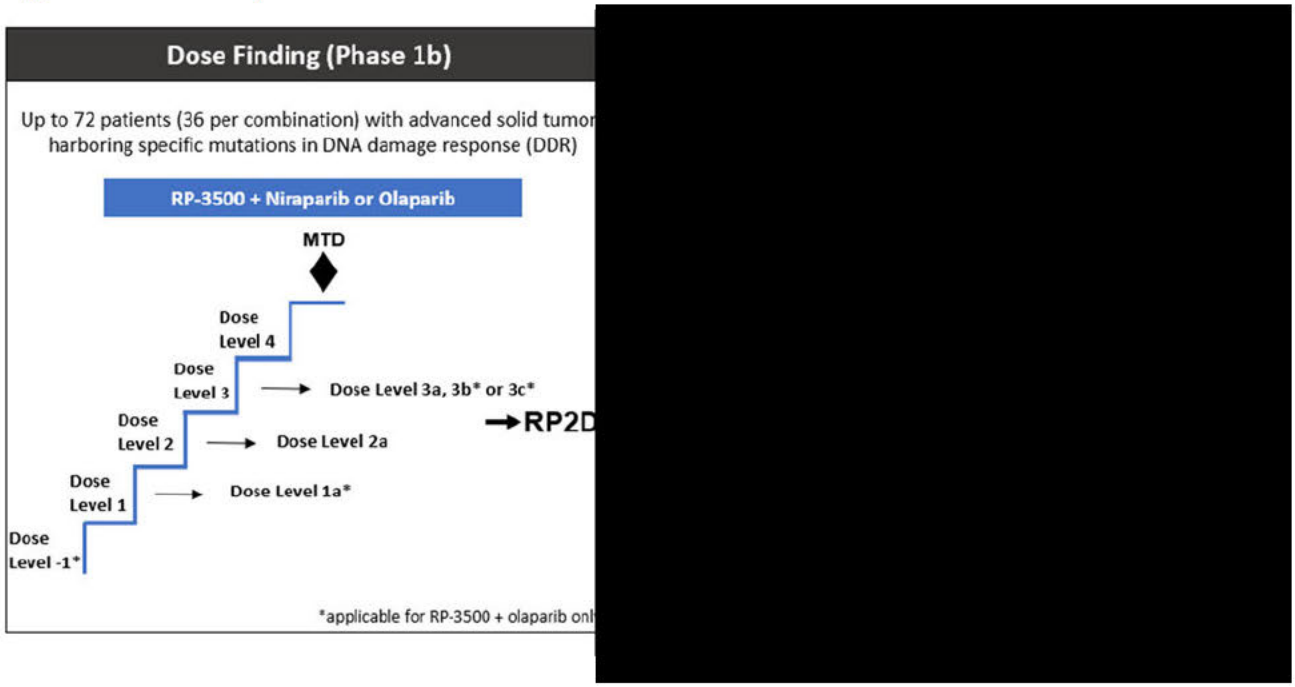
2.1. Study Design

This is a multicenter, open-label Phase 1b/2 study to investigate the safety and efficacy of the combination of the ataxia telangiectasia-mutated- and rad3-related inhibitor (ATRi) RP-3500 with poly adenosine diphosphate-ribose polymerase inhibitor (PARPi) niraparib or olaparib in patients with advanced solid tumors harboring specific deleterious mutations. The study is designed to determine if a reduced exposure to the combination remains well tolerated and results in significant anti-tumor efficacy to warrant further assessment.

The study will be conducted in 2 phases: dose finding and dose expansion (see Figure 1). In Phase 1b, dose finding of the RP-3500 and niraparib combination or the RP-3500 and olaparib combination will be conducted in parallel, using a Bayesian optimal interval (BOIN) design with accelerated titration to identify a tolerable dose for each treatment combination (see Dose Finding Study Schemas in Section 2.1.1). [redacted]

The study is divided into the following 2 phases as described in the diagram below:

Figure 1: Study Schema



2.1.1. Dose Finding Study

The study will begin with accelerated titration by enrolling 1 patient at Dose Level 1 in each arm (RP-3500 in combination with niraparib or olaparib), to minimize the exposure of patients to sub-therapeutic doses. RP-3500 and PARPi will be administered together weekly, following a concomitant 3 consecutive days on and 4 consecutive days off dosing schedule (3/4 schedule) or 2 consecutive days on and 5 consecutive days off dosing schedule (2/5 schedule) in 21-day cycles. Administration of RP-3500 and the PARPi may follow an intermittent weekly schedule (eg, 2 weeks on/1 week off, 1 week on/1 week off, 1 week on/2 weeks off) with a cycle length of 28 days for the 1 week on/1 week off schedule. Patient enrollment to receive RP-3500 in combination with niraparib or olaparib will be guided by the Study (Safety) Steering Committee (SSC).

In the absence of Grade ≥2 drug-related toxicity in Cycle 1 (first 21 days or 28 days, depending on study drug administration schedule), dose escalation will progress to the next dose level, with a cohort size of 1 (Figure 2 or Figure 3). If Grade ≥2 drug-related toxicity is observed at any time during Cycle 1, up to 2 additional evaluable patients will be enrolled at that dose level to further assess safety and tolerability of the dose level. Cohorts of at least 3 patients will be evaluated thereafter.

The starting doses will be RP-3500 50 mg orally (PO) once daily (QD) plus niraparib 100 mg PO QD or olaparib 150 mg PO twice daily (BID). Olaparib may be administered QD as long as the total daily dose does not exceed the BID dose for the respective dose level.

All drugs will be given according to one of the following dosing schedules:

- 3 weeks cycle with 3 days on/4 days off schedule

  Drugs on Days 1-3, 8-10, and 15-17 of each 21-day cycle
- 3 weeks cycle with 2 days on/5 days off schedule

  Drugs on Days 1-2, 8-9, and 15-16 of each 21-day cycle
- 3 weeks cycle with 1 week on/2 weeks off - 3 days on/4 days off

  Drugs on Days 1-3 of each 21-day cycle
- 4 weeks cycle with 1 week on/1 week off - 3 days on/4 days off

  Drugs on Days 1-3 and 15-17 of each 28-day cycle
- 3 weeks cycle with 2 weeks on/1 week off – 2 days on/5 days off

  Drugs on Days 1-2 and 8-9 of each 21-day-cycle

Figure 2: Dose Finding Study Schema for Arm 1

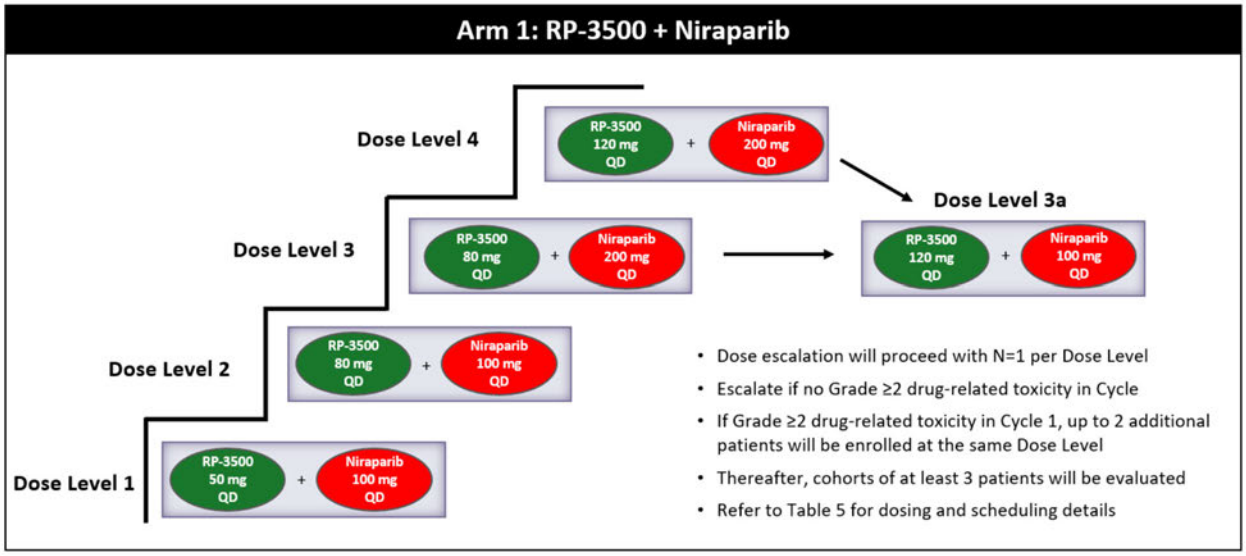
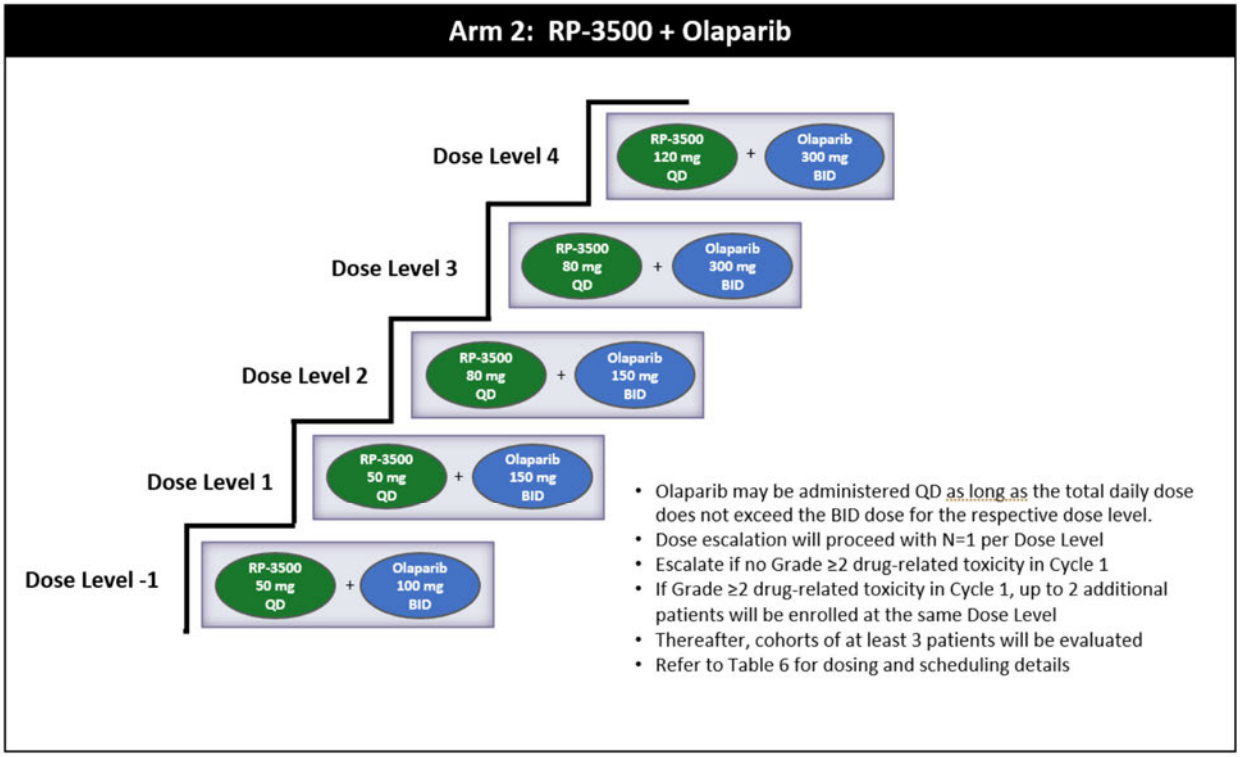
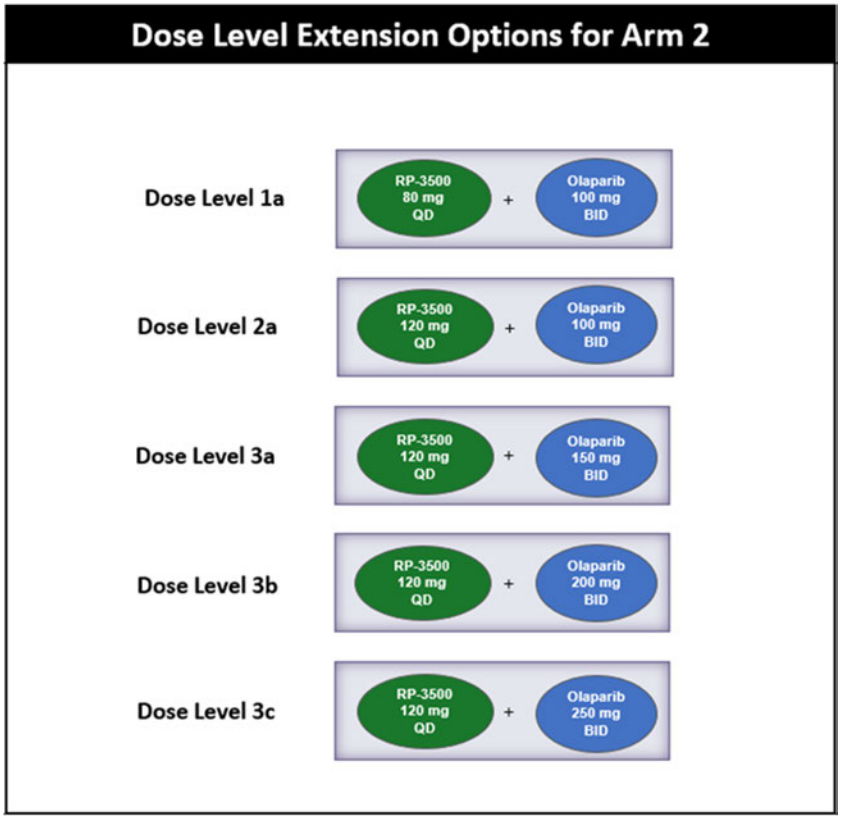


Figure 3: Dose Finding Study Schema for Arm 2





Niraparib and olaparib escalations will progress independently.

2.2. Schedule of Assessment

The study will consist of a Pre-screening Period (within 6 months from time of screening/main informed consent form [ICF] signature, to confirm eligibility of genetic mutation), Screening Period (Day -28 to Day -1, to determine overall study eligibility per inclusion/exclusion criteria), Treatment Period (21-day cycles or 28-day cycles), an End-of-Treatment (EOT) Period (within 30+7 days after the last dose of study drug or 7 days after the last dose of study drug if the patient discontinued due to a treatment-related toxicity), a Safety-Follow-up (within 30 + 14 days of the last dose of study drug; only for the patient discontinued due to a treatment-related toxicity), and a Survival Follow-up (every 3 months ± 2 weeks until the end of the study unless the patient withdraws consent to the study or the study is terminated prior to the 12-month follow-up period). Survival follow-up has been removed according to Letter of Amendment signed on 21-Jun-2024.

Study procedures will occur as outlined in the Schedule of Assessments (Appendix 2). Safety and tolerability will be followed by the Medical Monitor and evaluated by the SSC throughout the study.

The key procedures required in this study include:

- Tumor assessments (based on CT and/or MRI scan) according to RECIST v 1.1 (see Appendix 3), Prostate Cancer Working Group 3 (PCWG3) for patients with prostate cancer (see Appendix 4), or Gynecological Cancer Intergroup (GCIG) for patients

with ovarian cancer (see Appendix 5). Positron emission tomography [PET]/CT may be used as clinically indicated.

- PK samples throughout the study
- Baseline, on-treatment, and end-of-treatment blood samples
- Reporting AEs occurring from the day of signing the main study ICF
- Pre-treatment tumor biomarker data
- Archival tumor tissue
- Paired-tumor biopsies (in a subset of patients)
- Electrocardiograms (ECGs)

2.3. Sample Size

The planned sample size is approximately 160 for the dose finding phase (Phase 1b). This is to achieve at least 100 efficacy evaluable patients in the backfill cohorts. The sample size is not driven by statistics but determined based on number of dose escalations that will potentially be assessed.

[a]

Additionally, up to 8 patients may be enrolled in any of the backfill cohorts in the dose finding phase. Backfill cohorts (up to 8 patients each) may be employed based on agreement with SSC to enable an earlier and better understanding of the variability in drug-related toxicity, clinical benefit, or PK. The objective of backfill cohorts is to (1) aid in the assessment of possible anti-tumor activity in a subset of patients with a specific genomic abnormality or tumor type, (2) allow additional PK/PD evaluation, and (3) further assessment of drug related toxicities.

2.3.1. Dose Finding – BOIN Design

The BOIN design with accelerated titration will be employed to find the MTD of each treatment combination independently. The target toxicity rate is 25%. The maximum sample size will be 36 patients per PARPi combination. DLTs occurring within the first 21- or 28-day cycle will be used for dose finding. DLT criteria are defined in Appendix 1.

BOIN design uses the following rule, optimized to minimize the probability of incorrect dose assignment, to guide dose escalation/de-escalation:

- If the observed DLT rate at the current dose is ≤0.197 (<20%), escalate the dose to the next higher dose level.

- If the observed DLT rate at the current dose is ≥0.298 (>30%), de-escalate the dose to the next lower dose level.
- Otherwise, stay at the current dose

For each treatment combination, dose finding starts at Dose Level 1. The steps to implement the BOIN design are described as follows:

1. Perform accelerated titration as follows: treat the first patient at Dose Level 1. If no Grade ≥2 drug-related toxicity is observed, escalate the dose to the next higher level. Continue this one-patient-per-dose dose escalation process until a Grade ≥2 drug-related toxicity is observed during Cycle 1 (21 or 28 days), or the highest dose level is reached, and then treat up to 2 additional patients at that dose level. Hereafter, cohorts of at least 3 patients will be evaluated, as described in Steps 2 and 3.
2. To assign a dose to the next cohort of patients, conduct dose escalation/de-escalation according to the rule displayed in Table 1 below.
3. Repeat Step 2 until the maximum sample size of 36 patients is reached in Phase 1, or transition to the expansion phase (Phase 2) if the number of patients treated at the current dose reaches 9 and Table 1 below is to stay at the current dose or a decision is made by the SSC to stop.

Table 1: Dose Escalation/De-Escalation Rule for the BOIN Design

	Number of Patients Treated at Current Dose								
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Escalate if # of DLT ≤	0	0	0	0	0	1	1	1	1
Stay at current dose	NA	NA	NA	1	1	NA	2	2	2
Deescalate if # of DLT ≥	1	1	1	2	2	2	3	3	3
Eliminate if # of DLT ≥	NA	NA	3	3	3	4	4	4	5

Abbreviations: BOIN = Bayesian optimal interval; DLT = dose-limiting toxicity
Note: # of DLT is the number of patients with at least 1 DLT. When none of the actions (i.e., escalate, de-escalate or eliminate) is triggered, stay at the current dose for treating the next cohort of patients. "NA" means that a dose cannot be eliminated before treating 3 patients.

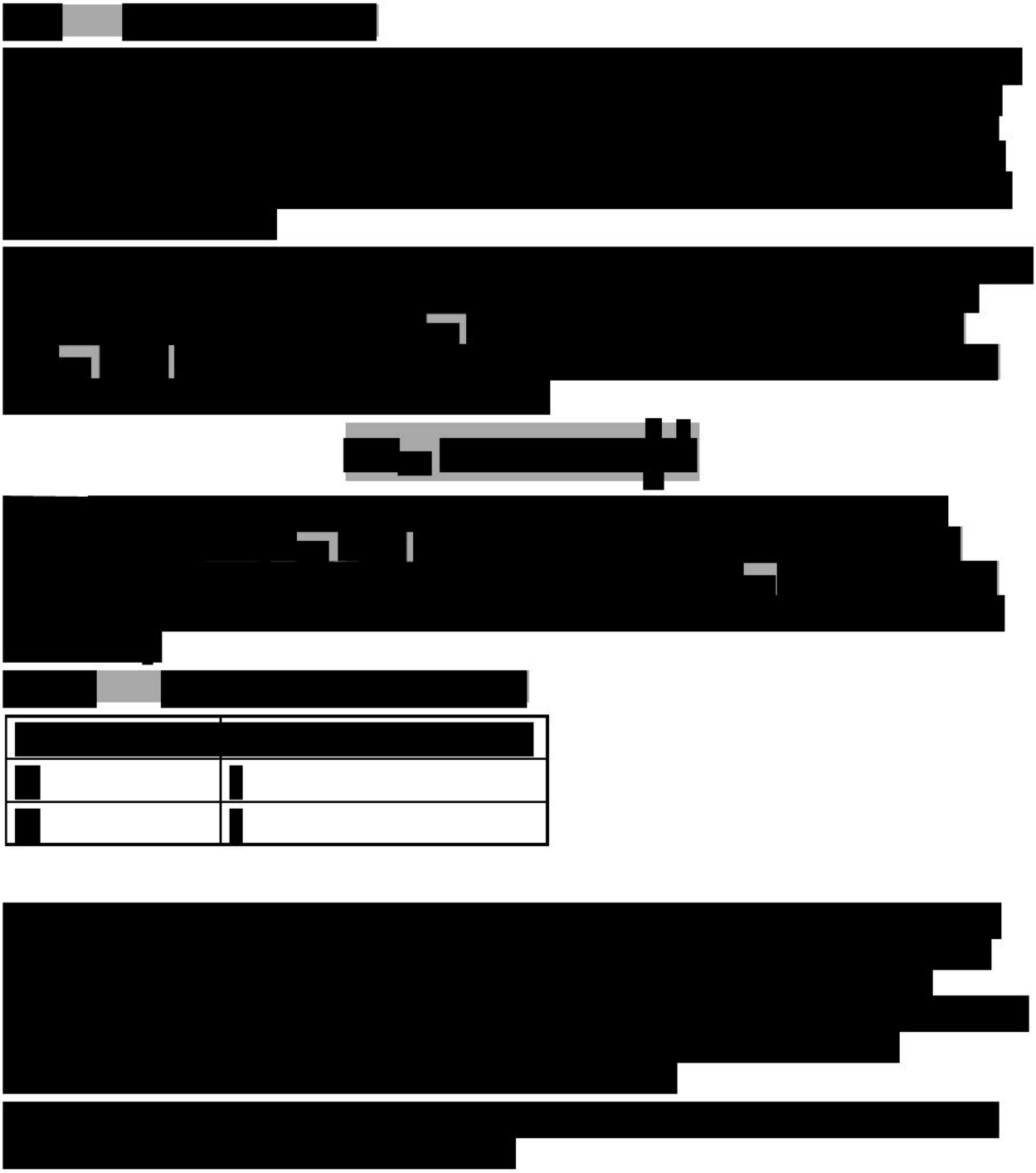
In the event that operational/practical circumstances result in an over-enrollment (i.e., n>3) or under-enrollment (i.e., n=2) for a BOIN cohort, the next dose level decision would be based on the actual number of patients exposed in the cohort and the BOIN criteria.

Final decision to escalate or de-escalate will be made by the SSC based on the dose recommendation by the BOIN method, clinical assessment of toxicity profiles, and PK information observed thus far.

After the study is completed, the dose for which the isotonic estimate of the toxicity rate is closest to and no higher than the target toxicity rate of 25% will be selected as the MTD. The

RP2D for each combination will be based on discussion between the investigators and the sponsor and will be either the established MTD or a dose lower than MTD based on the totality of the safety and tolerability.

[redacted]



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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Objectives

Objectives	Endpoints
Primary Phase 1b	
To determine the safety and tolerability of niraparib or olaparib in combination with RP-3500 in patients with molecularly selected solid tumors	• Incidence and severity of treatment-emergent adverse events (TEAE), dose-limiting toxicities (DLTs), laboratory assessments, vital signs, electrocardiograms (ECGs), physical examinations (PEs), concomitant medications, and exposure
To define the recommended Phase 2 dose (RP2D) of RP-3500 in combination with niraparib or olaparib in patients with molecularly selected solid tumors	• Frequency of DLTs at each dose level during the DLT observation period • RP2D: incidence and severity of treatment-emergent adverse events
[redacted]	

Objectives	Endpoints
[redacted]	[redacted]
Secondary	
To assess the pharmacokinetic (PK) parameters of RP-3500 in combination with niraparib or olaparib	• Plasma concentrations of RP-3500 and niraparib or olaparib with calculation of maximum observed plasma concentration (C_{max}), time to maximum observed plasma concentration (T_{max}), area under the plasma concentration-time curve 0 to 6 hours post dose (AUC_{0-6}), and other parameters as appropriate
[redacted]	
[redacted]	[redacted]

Objectives	Endpoints
[redacted]	[redacted]
[redacted]	[redacted]

3.2. Analysis Endpoints

The objective tables provide information on the study objectives and analysis endpoints, split by primary, secondary and exploratory. The following section summarizes the primary and secondary analysis endpoints split by type of endpoint (safety, efficacy, and PK).

Exploratory endpoints will not be covered as part of this SAP.

3.2.1. Safety Endpoints

- DLTs (Dose Finding Study)
- Incidence of TEAEs, treatment related TEAE, TEAEs leading to death, SAE, treatment related SAE, TEAE leading to study drug discontinuation, TEAE leading to dose modifications summarized by System Organ Class (SOC) and Medical Dictionary for Regulatory Activities (MedDRA) preferred term.
- Changes in clinical laboratory parameters (hematology, chemistry, urinalysis), CTCAE graded laboratory toxicities, vital signs, ECOG performance status, ECG parameters including QTc, PEs and usage of concomitant medications

[redacted]

[redacted]

3.2.3. Pharmacokinetics

PK parameters will be calculated using noncompartmental analysis (NCA) or other compartmental methods as appropriate.

- PK concentrations of RP-3500, niraparib, and olaparib
- C_{max}, AUC_{0-6}, AUC_{ss}, AUC_{0-last}, and T_{max} for RP-3500, niraparib, and olaparib.
- Other PK parameters maybe calculated as needed in order to aid in the interpretation of the overall study.

4. ANALYSIS POPULATIONS

4.1. DLT Evaluable Population

The primary analysis population for dose finding study will be the DLT Evaluable Population consisting of patients who meet the minimum safety evaluation requirements of the study and/or who experience a DLT at any time during the first cycle (21 days or 28 days) of the study. This population will be applied to dose escalation decisions in dosing finding study.

Minimum safety requirements will be met if, during Cycle 1 of treatment, the patient:

- Receives at least 80% of planned total doses of study treatment (both RP-3500 and niraparib/olaparib)
- Completes all required safety evaluations per the Schedule of Assessments and is observed within 21 or 28 days depend on the duration of the cycle following the first dose of study treatment

4.2. Safety Population

The Safety Population, used for the assessment of overall safety and tolerability, will consistof all patients who receive at least one dose of RP3500 and niraparib/olaparib. Patients will be presented based on initial dose assigned.

4.3. Efficacy Population

The Efficacy Population included all patients who received at least 1 dose of RP-3500 and niraparib/olaparib, evaluable for RECIST response or tumor marker response (GCIG criteria for CA-125 or PCWG3 criteria for PSA), and at least 1 post-baseline radiographic tumor assessment or sufficient post-baseline tumor marker assessments meeting GCIG or PCWG3 criteria for evaluation, and without key eligibility criteria deviation.

- Evaluable for RECIST response means patients are required to have measurable disease.
- Evaluable for tumor marker response will apply to ovarian or prostate cancer patients only. Patients with ovarian cancer who had elevated baseline CA-125 levels (>70 kU/L) and two post-baseline CA-125 assessments that are 3 weeks apart will be considered CA-125 response evaluable. Patients with prostate cancer who had elevated baseline PSA (> 2 ng/mL) and two post-baseline PSA assessments that are 3 weeks apart will be considered as PSA response evaluable.

4.4. Pharmacokinetics Population

The Pharmacokinetic Population will consist of all patients who have sufficient RP-3500 or niraparib/olaparib concentration data recorded to derive pharmacokinetic endpoints.

For all analysis populations, patients will be presented by the initial dose received.

5. DATA AND ANALYSIS CONSIDERATIONS

5.1. General Considerations

All demography and safety data will be presented by the Safety Population, with the exception of the DLT reporting which will be based on the DLT evaluable population. Assessment of anti-tumor activity will be based on the Efficacy Population and PK data will be presented by the PK Population.

The majority of the analyses will be descriptive in nature. Unless stated otherwise, continuous variables will be summarized using descriptive statistics (number of patients, mean, standard deviation, median, lower and upper quartile, minimum and maximum values) and the number and percentage of patients will be used for categorical variables. In general, missing data will be considered as missing and will not be imputed. Unless stated otherwise, percentages will be calculated out of the number of patients in the relevant analysis population.

Baseline will be the last assessment of the variable under consideration prior to first dose of study drugs.

5.1.1. Phase 1b - Dose Finding Study

Safety, efficacy and PK will generally be summarized by actual initial dose combination.

In addition, DLTs will also be summarized by the actual initial dose combination.

5.2. Study Day and Analysis Visit

5.2.1. Study Day

Study Day will be calculated from the reference start date (defined as the date of first dose of study drug), and will be used to show start/stop day of assessments/events:

- Study Day = (date of assessments/events - reference start date) if event/assessment is prior to the reference start;
- Study Day = (date of assessments/events - reference start date + 1) if event/assessment is on or after the reference start.

There is no Study Day 0.

5.2.2. Analysis Visit

Baseline value will be the latest non-missing result obtained prior to the start of study treatment. The nominal visits will be used as analysis visits for the purpose of summarizing data over scheduled visit. If visits are clearly defined, no windowing algorithm will be used. If the cycle data are not clearly identifiable, study day with a window will be used to define the visits.

All recorded data will be included in the listings.

5.3. Handling of Missing Data

There will be no imputation of incomplete or missing data other than the dates mentioned below. The imputation below is for analysis purpose only. All the data listings will use the original dates.

5.3.1. Date Imputation Rules

Following date imputation will be applied when needed for derivation of the study day or other analysis variables. However, the original date information will be presented in the data listings.

Initial diagnosis date or other historical dates related to diagnosis/prior treatment (as applicable):

- If year is missing, do not impute.
- If only day is missing, impute day as 15th of the month.
- If day and month are missing, impute as July 1st of the year.

- Note that if the first dose date of study drug is before above imputed date, impute the diagnosis date as the date before the 1st dose date since diagnosis is expected to be confirmed before the study.

Concomitant medication start date:

- If year is missing (or completely missing), do not impute.
- If (year is present and month and day are missing) or (year and day are present and month is missing), impute as January 1st.
- If year and month are present and day is missing, impute day as first day of the month.

Concomitant medication end date:

- If year is missing (or completely missing), do not impute.
- If (year is present and month and day are missing) or (year and day are present and month is missing, impute as December 31st.
- If year and month are present and day is missing, impute day as last day of the *month.*
- If the imputed end date is earlier than the observed/imputed medication start date, the end date will be imputed as the same as the start date.

Post-study therapy/radiotherapy start date:

- If year is missing (or completely missing), do not impute.
- If year is present and month and day are missing:
  - If year is the same as the year of last dose date, impute as the last dose date + 1.
  - If year is greater than the year of last dose date, impute as January 1st.
- If year and day are present and month is missing:
  - If year is the same as the year of last dose date, and day is not greater than the day of last dose date, impute the month as the month of last dose date + 1.
  - If year or day is greater than the year or day of last dose date, impute the month as the month of last dose date.
- If year and month are present and day is missing:
  - If year and month are the same as the year and month of last dose date, impute as first last dose date + 1.
  - If year or month is greater than the year or month of last dose date, impute day as first day of the month.

Post-study therapy/radiotherapy end date:

- If year is missing (or completely missing), do not impute.

- If (year is present and month and day are missing) or (year and day are present and month is missing, impute as December 31st.
- If year and month are present and day is missing, impute day as last day of the *month.*
- If the imputed end date is earlier than the observed/imputed post-study therapy/radiotherapy start date, the end date will be imputed as the same as the start date.

Missing Dates in Adverse Events (only applicable in analysis stage when complete dates are required, not for the purpose of data listing)

Start dates of adverse events will be imputed as follows:

- Completely missing start date will be imputed as the date of first dose
- Start date missing both month and day will be imputed as:
  - the date of first dose if the year of the start date is the same as the date of first dose.
  - otherwise, Jan 1st of the year of the start date will be used.
- Start date missing day will be imputed as:
  - the date of first dose if the year and month of the start date are the same as the dateof first dose.
  - otherwise, the 1st of the month of the start date will be used.

Stop dates of adverse events will be imputed as follows:

- Completely missing stop date will be imputed as the date of last dose.
- Stop date missing both month and day will be imputed as Dec 31st of the year of stopdate.
- Stop date missing day will be imputed as the last date of the month of the stop date.

After imputation, the imputed date will be compared against the date of death, if available. If the planned imputed date is later than the date of death, the date of death will be used as the imputed date instead.

5.3.2. Relationship and Severity Imputation Rules for Adverse Events

For summary of AEs by relationship, missing relationship will be considered as 'Related' if the adverse event started on or after the date of first dose. Imputation will not be made for data listings and datasets. Missing severity will not be imputed. All AEs are expected to have non-missing severity (to toxicity grade) and relationship at the time of database lock.

6. DISPOSITION, DEVIATIONS AND PATIENT CHARACTERISTIC DATA

6.1. Disposition

An overall patient disposition summary will be presented for all subjects to show the number of unique patients who entered the study.

In addition, patient disposition will be presented by Module and by dose/schedule with percentages based on the Safety Population. The following information will be presented for disposition:

- Patients Treated
- Included in each analysis population (DLT evaluation, safety, efficacy and PK)
- Ongoing/discontinued study treatment at the data cut-off.
  - Including reasons for discontinuation of treatment as per the eCRF
- Ongoing/withdrawn/completion from study at the data cut-off
  - Including reasons for study termination as per the eCRF

Disposition data will be listed for all patients and will include patient status, date of discontinuation from treatment, date of withdrawal from study and reason for treatment discontinuation and study withdrawal. In addition, the number and percentage of subjects by site will be summarized.

6.2. Protocol Deviations

Protocol deviations are identified by site staff/PIs, clinical research organization, and the sponsor per Medical Monitoring Plan and Protocol Deviation Guidance. Protocol deviations are documented within the Clinical Trial Management System. After finalization, protocol deviation data will be imported into SDTM and ADaM datasets.

There is no per protocol analysis population defined for this study, therefore, patients will not be excluded from the data analysis and reporting based on deviations.

Any important deviations discovered during the trial either through the data collected on eCRFs or monitoring visits/reports will be listed and summarized.

The following deviations will be considered important deviations:

- Patients who didn’t meet the key eligibility criteria but enrolled and received the study treatment.
- Patient who did not sign a consent or a correct version of the consent prior to the study conduct.
- Patients who received wrong treatment regimen(s).
- Patients who received incorrect dose which resulted in serious adverse events in the dosing cycle during which incorrect dose was received. Note, treatment delays or

changes due to AE management are not consideredtreatment deviations. A review of relevant data may be required to confirm all important deviations in this category.

- Patients who received a prohibited concomitant treatment which resulted in serious adverse events.
- Patients who received any anti-cancer treatments other than the study medication.
- Patients whose baseline tumor scans were conducted outside the protocol window (i.e.,baseline scan date > 28 days from the date of first dose of study treatment).

Following review of all reported deviations and associated data and prior to database lock, other important deviation categories may be added. Only important deviations will be listed and summarized. Other deviations considered minor (such as late visits, missing assessments etc) will not be listed but will be available within the DV Dataset.

6.3. Demographic and Baseline Characteristics

Demographics will be summarized based on the Safety Population. Baseline demographic will include age at informed consent, age group (<65 and ≥65 years), gender, race, ethnicity, height (cm), weight (kg), BMI (kg/m^2). Baseline characteristics will include primary tumor type and ECOG performance status.

A separate listing will also be provided for demographic and baseline characteristics.

6.4. Mutation Status at Enrollment

The following data on the mutation status of patients at enrollment will be listed and summarized:

- Mutations/genes detected and method of detection (IHC or NGS) based on local tests

A patient may test positive for more than 1 enrollment gene and will be summarized under the primary gene curated by central review.

If additional local baseline genomic data with more informative genotypic information with supportive documentation becomes available during the course of the study, the updated genotype information will be used for analyses purposes.

6.5. Disease Characteristics

The following disease characteristics will be summarized based on the Safety Population:

Disease History:

- Time since initial diagnosis (in months)
- Time since presentation of locally advanced or metastatic disease
- Primary tumor type
- Histology and grade of disease at diagnosis

Prior Anti-Cancer Therapy:

- Number of prior lines of treatment as determined by clinical team
- Prior use of PARP inhibitor
- Prior use of platinum containing regimen
- Information on last anti-cancer treatment, if applicable:
  - Best response
  - Time since end of last treatment in months
  - Reason for end of regimen

6.6. Medical History

Medical history will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized for the Safety Population, using System Organ Class (SOC) and preferred term (PT). The table will include the number and percentage of subjects and will be sorted in alphabetical order by SOC and PT. A subject will only be counted once within a class. A listing of medical and surgical history will also be provided.

In particular, cancer related medical history will be summarized by SOC and PT.

6.7. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. The number and percentage of patients will be tabulated by WHO drug generic term for the Safety Population.

Prior medications will include medications which started prior to the date of first dose of study treatment. A summary table will present the numbers and percentages of patients who received prior therapy, including prior systemic anticancer therapy, prior radiation, prior surgery, and best response to the prior therapy, if known. Concomitant medications will include medications which started or were ongoing at the date of first dose of study treatment through to 30 days after the last dose of study treatment, or to the start of subsequent anticancer therapy, whichever occurs first.

7. SAFETY AND EXPOSURE DATA

Safety and tolerability will be assessed in terms of AEs, TEAEs, treatment related TEAEs (TRAEs), SAEs, DLTs, concomitant medications, PEs, vital sign measurements, clinical safety laboratory evaluations (hematology, serum chemistry, and urinalysis), ECOG performance scores, and ECGs including QTc.

Toxicity will be assessed using the NCI CTCAE Version 5.0 unless otherwise specified. A toxicity will be considered dose-limiting if it occurs during the first cycle (first 21 days or 28 days) is deemed to be related to treatment and it meets the criteria defined in Appendix 1. DLTs

will be evaluated during the study to determine dose levels for the dose finding study. DLTs will be listed and summarized based on the DLT Evaluable Population.

DLT criteria are defined in Appendix 1. DLTs will be identified from the AE eCRF where the AE is selected as a DLT. All AEs reported as DLTs on the eCRF will be included even if they were not considered DLTs by the SSC during the study reviews. A listing of AEs considered DLTs by the SSC will be provided for the CSR.

The MTD for this study will be defined as the highest dose with a DLT rate < 25%. Simulations confirm that using this study design to define the MTD is equivalent to employing an isotonic regression with a descending pooled adjacent violators algorithm, which is the recommended method in the publication for BOIN study designs (Yuan et al. 2016).

7.1. Adverse Events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 or higher and graded according to NCI-CTCAE version 5.0. All laboratory test results will be classified for toxicity grade according to the NCI-CTCAE version 5.0 criteria if appropriate.

Treatment emergent adverse events (TEAEs) are those events that occur or worsen on or after the first dose of study drug up through 30 days post the last dose or the start of subsequent anticancer therapy, with exception of treatment related SAEs which were reported indefinitely. Adverse events are considered as related to treatment if the relationship to either RP-3500 or the combination drug in the study regimen is “Related”. TEAEs related to RP-3500 will also be summarized separately.

7.1.1. Overview of Adverse Events

An overview summary table of the number and percentage of patients in each of the categories listed below will be presented.

- All TEAEs
- Treatment-related TEAEs
- RP-3500 related TEAEs
- DLTs
- TEAEs with ≥ CTCAE Grade 3
- Treatment-related TEAEs with ≥ CTCAE Grade 3
- RP-3500 related TEAEs with ≥ CTCAE Grade 3
- Serious TEAEs
- Treatment-related serious AEs
- RP-3500 related serious AEs
- TEAEs with outcome of death

- TEAEs leading to discontinuation of study treatment
- TEAEs leading to dose modification (i.e., dose reduced or dose interrupted) of study treatment

7.1.2. Incidence of TEAEs

A summary of the frequency (number and percentage of participants) of TEAEs will be presented by SOC and PT. Multiple occurrences of the same AE (SOC or PT) will be counted only once when calculating the number and percentage of participants. This summary will be sorted in decreasing order of frequency of SOC, and then in decreasing order of frequency of preferred term within the SOC.

A separate data listing will be provided for all TEAEs.

7.1.3. Most Frequent TEAEs

An AE table of most frequently occurring TEAEs, showing all events in at least 5% of patients across all patients, will be summarized by preferred term, by decreasing frequency based on all patients. This cut-off may be modified after review of the data.

7.1.4. Incidence of TEAEs by Worst Severity

The number and percentage of participants reporting a TEAE will be tabulated by PT and worst severity.

A participant experiencing the same AE multiple times within same PT will be counted only once for that preferred term at the worst severity.

7.1.5. Incidence of Treatment-related TEAEs

Treatment-related TEAEs will be summarized and listed in the same manner described above for TEAEs (Section 7.1.2). In addition to those related to either of the study drugs, a separate summary will be provided for those related to RP-3500 regardless the relationship to niraparib/olaparib.

7.1.6. Incidence of Serious TEAEs

Serious TEAEs will be summarized and listed in the same manner described above for TEAEs (Section 7.1.2). In addition, those non-treatment emergent SAEs will be summarized separately through a summary table or listing (if total events <5).

7.1.7. Incidence of Treatment-related Serious TEAEs

Treatment-related serious TEAEs will be summarized and listed in the same manner described above for TEAEs (Section 7.1.2). In addition to those related to either of the study drugs, a separate summary will be provided for serious TEAEs which are related to RP-3500 regardless the relationship to niraparib/olaparib.

7.1.8. TEAEs Leading to Death

TEAEs and TRAE leading to death will be summarized and listed in the same manner described above for TEAEs (Section 7.1.2).

7.1.9. TEAEs Leading to Discontinuation of Study Treatment

TEAEs and TRAE leading to discontinuation of study treatment will be summarized and listed in the same manner described above for TEAEs (Section 7.1.2).

7.1.10. TRAEs Leading to Dose Modification

TRAEs leading to dose modification will be summarized and listed in the same manner described above for TEAEs (Section 7.1.2).

7.2. Treatment Exposure

Exposure will be derived for RP-3500, niraparib, and olaparib.

Duration of Exposure will be defined as the duration between the first and last dose of study drug

- Duration of exposure = last dose date - first dose date + 1

The last dose date will be obtained from the end of treatment (EOT) CRF page. For the combination regimens, the last dose date will be the later of the 2 drugs' last dose date from the EOT page.

Number of days dosed will be derived as the number of days a patient received a dose of treatment (i.e., excludes off treatment days and any missed doses).

Total dose received (mg) is the total dose the patient received during their time on treatment

- Total dose received = Number of days dose*dose received

If a patient had a dose reduction or change during treatment, then the total dose received will be calculated for each actual dose received and then summed to give the total dose received.

Total dose received:

$$\sum_{i=1}^{k} (number\ of\ days\ dosed\ at\ dose\ x_i * dose\ x_i)$$

for i=1 to k where i represents the number of dose levels received and k = number of distinct dose levels

Maximum expected dose will be derived as the maximum dose a patient could have received without any interruptions or reductions based on the time period between the date of first dose and date of last dose after excluding days when dosing information is not available, accounting for the number of treatment days per week. This is assuming the days without dosing information is missing at random.

Dose intensity will be derived as:

Dose intensity = (total dose received/maximum possible dose)*100%

A dose interruption will be defined as a planned interruption where a decision is made to interrupt the dose temporarily. Dose interruptions will be captured on the eCRF.

A dose reduction is any reduction in dose or schedule compared to the initial dose.

Patients who do not have a final EOT date recorded in the eCRF at the time of analysis and reporting will be considered as still ongoing with treatment. For deriving exposure, ongoing patients will be assumed to be ongoing at the date of the data cut off (DCO) and therefore the DCO date will be used to derive exposure.

Exposure will be listed and summarized by the Safety Population.

The following will be presented for RP-3500, niraparib, and olaparib:

- Duration of exposure (days)
- Number and % of patients exposed to 1-2 cycles, 3-4 cycles...*etc.*
- Number of cycles treated
- Number of cycles completed
- Total dose received (mg)
- Dose intensity (%)
- Number and % or patients with at least one dose interruption reported in dosing log
  - Further broken down by number with 1, 2 or ≥ 3 interruptions
  - Number and % of patients with dose interruption in Cycle 1, 2 or >=3
- Number and percentage of patients with at least one dose reduction reported in doing log
  - Further broken down by number with 1, 2 or ≥ 3 reductions
  - Number and % of patients with dose reduction in Cycle 1, 2 or >=3
- Number of patients with a dose escalation per protocol

Patients with both an interruption and reduction will be included in both the interruption and reduction summaries.

7.3. Laboratory Evaluations

All laboratory data recorded in the eCRF will be listed. Out-of-reference range values will be flagged as high (H) or low (L) in the listings. The results in conventional unit will be used in the summary tables.

Box plots for mean changes from baseline over time for lab parameters will be produced based on the Safety Population and the number of patients with data at the relevant timepoints. Timepoints where there are <3 total observations will not be presented in the box plot.

Selected laboratory assessments will be also presented in shift tables showing baseline grade vs. maximum grade on study for lab assessment with CTCAE grading, based on all post-baseline data including unscheduled assessment. The denominator for each on-treatment maximum grade is the total number of patients in the corresponding row for baseline grade (i.e. the baseline row totals). Shift tables (shift from baseline to worst post-baseline values including assessments from unscheduled visits) will be summarized.

If the worst criteria could be a low or a high value or an increase or decrease (i.e., in both directions) then shift tables should be split to show shift from baseline to worst low/decrease value and then repeated for worst high/increase value. For example, CTCAE grade criteria is given for both lymphocytes count increased and lymphocyte count decreased.

Post-baseline liver function tests including unscheduled assessments will be summarized in the following categories in Safety Population:

- AST > 3 × ULN or 3 × Baseline (if baseline value is >ULN)
- ALT > 3 × ULN or 3 × Baseline (if baseline value is >ULN)
- ALP > 3 × ULN or 3 × Baseline (if baseline value is >ULN)
- Total bilirubin > 2 × ULN

Patients' liver function tests will also be listed if the tests at any timepoint during the study may be to fit the Hy's Law criteria and the status of liver metastasis at baseline will also be included. Liver metastasis at baseline is defined as site of disease located in liver of either the target or the non-target lesion.

Hy's law criteria is considered met if at a certain time point patient's Total bilirubin > 2 x ULN and either of the following at any post baseline tests: 1) AST > 3 x ULN or 3 x Baseline (if baseline value is >ULN); 2) ALT > 3 x ULN or 3 x Baseline (if baseline value is >ULN) is met.

7.4. Vital Signs and Abnormalities

Descriptive statistics of pulse/heart rate, blood pressure (systolic and diastolic) (supine/semi-recumbent), respiratory rate, and body temperature values will be summarized at baseline and post baseline visits, and changes from baseline will be summarized for post baseline visits based on the Safety Population. A separate listing will include all the vital sign measurements, including those from the unscheduled visits.

The following post-baseline vital signs will be summarized based on the Safety Population:

- Maximum post-baseline in SBP:
  - No increase
  - Increase < 20 mmHg
  - Increase ≥ 20 mmHg
    - ≥ 160 mmHg and increase ≥ 20 mmHg

- Maximum post-baseline in DBP:
  - No increase
  - Increase < 20 mmHg
  - Increase ≥ 20 mmHg
    - ≥ 100 mmHg and increase ≥ 20 mmHg

For the number of subjects meeting each category for the post-baseline results or for the change from, the numerator is the number of subjects with meeting the criterion at any post-baseline including the unscheduled and the denominator is the number of subjects with normal baseline and at least one post baseline assessment including unscheduled visits in the Safety Population.

A listing for patients with any post-baseline potentially clinically significant changes listed above will be also presented. Box plots for changes from baseline over time will be produced based on the Safety Population and the number of patients with data at the relevant timepoints. Timepoints where there are <3 observations at dose/schedules will not be presented.

7.5. 12-Lead ECG

Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) of ECG parameters,including heart rate, PR interval, QRS duration, QT interval, and QTcF interval (Fridericia's corrections) will be presented for baseline, each post-baseline visit, and change from baseline to each post baseline visit for Safety Population. All measurements, including those during unscheduled visits, will be provided in data listings, but only the scheduled measurements will be included in the by-visit summary. The average of triplicate 12-lead ECG results will be used for descriptive statistics.

Overall ECG interpretation category (normal, abnormal NCS [not clinically significant], abnormal CS [clinically significant], and not evaluable) is collected in the CRF at baseline and each scheduled post-baseline visit. Shifts tables (shift from baseline to the worst post-baseline values) will be presented. For triplicate 12-lead ECG results collected at a visit, the average of triplicate 12-lead ECG results will be used as the interpretation at baseline as well as post-baseline.

The QTcF will be categorized into the following categories to identify potentially clinically important changes:

- QTc interval >450 msec and ≤480 msec
- QTc interval >480 msec and ≤500 msec
- QTc interval >500 msec

The change from baseline in QTcF will also be categorized separately as follows:

- QTc interval increases from baseline by >30 msec and ≤60 msec
- QTc interval increases from baseline by >60 msec

For the number of subjects meeting each category for the post-baseline results, the numerator is the number of subjects with meeting the criterion at post-baseline and the denominator is the

number of subjects with normal baseline and at least one post baseline assessment in the Safety Population. For the number of subjects meeting each category for the change from baseline, the numerator is the number of subjects with meeting the criterion at post-baseline and the denominator is the number of subjects with baseline and at least one post baseline assessment in the Safety Population.

Box plots for absolute and change from baseline for QTcF will be produced based on the Safety Population and the number of patientswith data at the relevant timepoints. Timepoints where there are <3 observations at a treatment group will not be presented. All ECG parameters will be listed in a data listing. All ECG tables and listings will be reported on the safety analysis set.

7.6. Physical Examinations and ECOG Performance Status

Physical examination results for subjects with abnormalities identified from physical examination will be listed.

Any change in PE findings assessed as clinically significant should be recorded as an AE or SAE.

Shift table of baseline ECOG performance status to worst post-baseline status will be summarized as the number and % of patients in each ECOG category based on the Safety Population.

8. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9. PHARMACOKINETIC DATA ANALYSIS

PK parameters for RP-3500, niraparib, and olaparib will be calculated using non-compartmental analysis or modeling methods. Only plasma concentrations greater than or equal to the validated lower limit of quantitation will be used in the PK analyses. Actual blood sampling times will be

used in all PK analyses (nominal sampling times maybe used in interim analyses). Per-protocol times will be used to calculate mean plasma concentrations for graphical displays.

The C_{max} and time to maximum plasma concentration (T_{max}) will be taken directly from the individual's data.

Calculations including C_{max} and T_{max}, and AUC_{0-6} will be calculated using established methods. Plasma concentrations and derived PK parameters will be summarized using descriptive statistics. Graphs on individual patient and mean plasma concentrations by cohort, will be presented on linear and semi-logarithmic axes.

All PK data will be presented based on the PK population and presented by dose/schedule for RP-3500 and niraparib or olaparib. PK data may be pooled for patients receiving the same dose/schedule of RP-3500 but this will be confirmed prior to analysis depending on the similarity of PK sampling across dose groups and the number of patients.

PK concentrations and parameters will be listed for all patients in the PK population. Individual patient and mean plasma RP-3500 and niraparib or olaparib concentration-time profiles will be plotted for each dose/schedule.

The population PK and exposure-response analyses will be developed and reported separately from the CSR and are out of scope for this SAP.

12. CHANGES OF ANALYSES FROM THE PROTOCOL

- The unconfirmed CR or PR is added as response criteria in addition to protocol defined response criteria in order to identify signal of anti-tumor activity for the treatment.
- Potentially Clinically Significant (PCS) liver functions and blood pressure are summarized which was not described in the protocol.
- Definition of Efficacy Population was updated.
- Progression identified by new bone lesion assessment per PCWG3 criteria was added as progression of disease to overall response.
- [redacted]

13. REFERENCES

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Zhou H, Lee JJ, Yuan Y. 2017. BOP2: Bayesian optimal design for phase II clinical trials with simple and complex endpoints. Stat Med. 36(21):3302–3314. doi:10.1002/sim.7338.

APPENDIX 1. DOSE LIMITING TOXICITIES (DLTS)

DLTs will be defined as follows:

Treatment-related hematologic adverse events (AEs):

- Grade 4 neutropenia lasting at least 7 days
- Febrile neutropenia (defined as absolute neutrophil count <1000/mm^3 with a single temperature of ≥38.3ºC [101°F] or a sustained temperature of ≥38ºC [100.4°F] for >1 hour)
- Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia associated with Grade ≥2 bleeding
- Grade 4 anemia, or Grade 3 anemia requiring blood transfusion

The use of transfusions and hematopoietic growth factors, including thrombopoietin analogues, will be part of the DLT definition if such intervention is required.

Treatment-related non-hematologic AEs:

- Any Grade 3 of >24 hours duration
- Any Grade 4 of any duration
- Grade 4 vomiting/diarrhea of any duration that is refractory to supportive care
- *Exclusions:*
  - *Grade ≥3 laboratory abnormality that are not considered clinically relevant in the opinion of the investigator, or respond to medical intervention*
  - *Grade 3 fatigue with duration of <7 days and resolved to Grade ≤2, unless repeatedly observed and considered drug related upon SSC discussion*
  - *Grade 3 nausea/vomiting/diarrhea unless refractory to supportive care that lasts <3 days*

APPENDIX 2. SCHEDULE OF ASSESSMENTS

Table A1. Schedule of Assessment for 3 Weeks on Schedule, or 2 Weeks on/1Week off Schedule (21-day Treatment Cycle)

Dosing: 3 days on, 4 days off (RP-3500 in combination with niraparib or olaparib)
Dosing: 2 days on, 5 days off (RP-3500 in combination with niraparib or olaparib)

	Pre-Screen	**Screen[a]**	**Cycle 1**				**Cycle 2**			**Additional Cycles**		**EOT/ ET[b]**	**Safety Follow-up[c]**	**Follow-up[d]**
Study Day **Procedures/ Assessments[e]**	**-180 to -1**	**-28 to -1**	**1[a]**	**2/3[w]**	**8**	**17**	**1[f] (+3 days)**	**2/3[w]**	**15**	**1[f] (+3 days)**	**15[g]**	**(30 +7 days)**	**Within 30 (+14) days of last dose**	**Every 3 months (±2 weeks)**
Pre-screen informed consent	X													
Screening/main informed consent		X												
Inclusion/exclusion criteria		X	X											
PODS review[h]	X													
Demographics	X													
Medical/cancer history		X												
PE		X										X		
Abbreviated PE			X				X			X[i]			X	
Height		X												
Weight		X	X				X			X		X	X	
Vital sign measurements[j]		X	X	X	X	X	X	X	X	X	X	X	X	
ECOG performance status		X	X				X			X		X	X	
12-lead ECG[k]		X	X	X				X						
Pregnancy test[l]		X	X				X			X		X	X	

Procedures/ Assessments[e] / Study Day	Pre-Screen	Screen[a]	Cycle 1				Cycle 2			Additional Cycles		EOT/ ET[b]	Safety Follow-up[c]	Follow-up[d]
	-180 to -1	-28 to -1	1[a]	2/3[w]	8	17	1[f] (+3 days)	2/3[w]	15	1[f] (+3 days)	15[g]	(30 +7 days)	Within 30 (+14) days of last dose	Every 3 months (±2 weeks)
Clinical safety labs (including reticulocyte count)[m]		X	X				X			X		X	X	
CBC (with differential) & reticulocyte count				X	X	X			X		X			
ctDNA whole blood[n]		X	X			X	X			X		X		
Tumor tissue for *RNASEH2* IHC testing (archival or fresh biopsy)	X[o]													
Tumor tissue (archival or fresh biopsy)[p]		X												
Study drug administration[q]			*See Section 8.2, Study Drug Dosage and Administration*											
Review of dosing diary[r]				X	X	X	X	X	X	X	X	X		
PK sample collection[s]			X	X[s]				X[s]						
Tumor assessments: RECISTv1.1[t]		X	*To be assessed every 6 weeks (±7 days) from Cycle 1 Day 1 for the first 3 tumor assessments (first ~5 months/22 weeks on treatment). Thereafter, every 9 weeks (±7 days).*											
Serum tumor biomarkers[u]		X	X				X			X		X		
AE assessment		*To be collected from the time of ICF signing through Cycle 1 Day 1 if related to a study procedure and for any AE occurrence from Cycle 1 Day 1 through 30 days after the last dose of the study treatment or start of new anticancer treatment whichever is earlier. SAEs, regardless of relationship, are to be collected from time of ICF until 30 days after the last dose of study drug or start of new anticancer therapy, whichever is earlier. SAEs considered related to the study treatment are to be reported until the end of the survival follow-up period which is up to 12 months after the last dose of IP or until lost to follow-*											X	

Procedures/ Assessments[e] / Study Day	Pre-Screen	Screen[a]	Cycle 1				Cycle 2			Additional Cycles		EOT/ ET[b]	Safety Follow-up[c]	Follow-up[d]
	-180 to -1	-28 to -1	1[a]	2/3[w]	8	17	1[f] (+3 days)	2/3[w]	15	1[f] (+3 days)	15[g]	(30 +7 days)	Within 30 (+14) days of last dose	Every 3 months (±2 weeks)
		up, patient withdrawal of consent, patient death, or whenever the Investigator becomes aware thereafter.												
Concomitant medications and procedures		*To be collected from Screening Visit through the EOT visit.*												
Post-study therapy data collection[v]														X
Survival status														X

Abbreviations: AE = adverse event; BID = twice daily; *BRCA1/2* breast cancer type (1/2) susceptibility protein; CA-125 = cancer antigen 125; CBC = complete blood count; ctDNA = circulating tumor DNA; ECOG = Eastern Cooperative Oncology Group; ECG = electrocardiogram; EOT = End of Treatment; ET = early termination; ICF = informed consent form; MRI = magnetic resonance imaging; NGS = next-generation sequencing; PARPi = poly (adenosine diphosphate-ribose) polymerase inhibitor(s); PE = physical examination; PK = pharmacokinetic; PODS = Precision Oncology Decision Support; PSA = prostate-specific antigen; QTcF = QT interval corrected for heart rate using Fridericia's formula; RECIST = Response Evaluation Criteria in Solid Tumors; *RNASEH2* ribonuclease H2; SAE = serious adverse event

a: **Screening:** Screening Period extends from Day -28 to Day -1. Screening laboratory assessments may be used as Day 1 assessments if performed within 96 hours of the first dose of study drugs, with the exception of vital signs, ctDNA collection, and ECGs. ECOG performance status and abbreviated PE that are completed within 24 hours of first dose of study treatment may be used as Cycle 1 Day 1 assessments. Patients must continue to meet all eligibility criteria prior to first dose of study on Cycle 1 Day 1.

b: **EOT/ET:** An EOT/early termination visit will be conducted within 30 days (+7 days) after the last dose of study drug or within 7 days after the last dose of study drug if discontinued due to a treatment-related toxicity. If a patient is removed from the study due to a treatment-related toxicity, an additional safety follow-up visit will occur within 30 days (+14 days) after the last dose of study drug. The safety follow-up visit may be performed sooner upon resolution of the AE to Grade 1.

c: **EOT Safety Follow-up:** For patients who discontinued treatment due to a drug-related AE. If the EOT/ET visit was done within the last 7 days of last dose for toxicity, the window for the second follow-up safety visit will be within 30 (+14) days from the last dose.

d: **Survival Follow-Up:** Survival follow-up will be conducted approximately every 3 months (±2 weeks) on all patients until the end of the study unless they withdraw consent to the study or the study is terminated prior to the 12-month follow-up. This may be done by telephone contact or standard method used by participating centers and agreed with sponsor.

e: **Procedures/Assessments:** Pre-study procedures and tumor assessment must be performed within 28 days before first dose of study drugs.

f: **Cycle X Day 1:** The start of a new cycle should always coincide with the start of study drug administration for that cycle. A +3-day window is allowed for the start of new cycles, though cycles should never start early and should be at least 21 days in length. A -2 day window is allowed for the assessments scheduled for the Cycle X Day 1 visit to enable flexibility with visit scheduling.

g: **Day 15 of Additional Cycles:** Assessments to be performed ONLY on Day 15 of Cycles 3 and 4.

h: **PODS Review:** NGS reports will be emailed to PODS and Repare Biomarker team for central review and to confirm molecular eligibility or determine if additional testing is required to confirm eligibility.

i: **Abbreviated PE:** Starting at Cycle 2, abbreviated PE to be performed every 2 cycles (unless full PE necessary by investigator judgment).

j: **Vital Signs:** Blood pressure, heart rate, respiratory rate, and temperature must be measured after the patient has been sitting for 5 minutes.

k: **ECG:** 12- lead ECGs to be done in triplicate ≥1 minute apart per Appendix 2 Table C. Patients should be in supine position and resting for at least 10 minutes before study-related ECGs. Only QTcF needs to be recorded.

l: **Pregnancy Test:** For women of childbearing potential, a serum pregnancy test is required at Screening. If pregnancy test was done within 96 hours prior to Cycle 1 Day 1, repeat testing is not required. A serum or urine pregnancy test must be performed on Day 1 of each cycle and at EOT. Pregnancy test can be performed more frequently if required per local regulations.

m: **Safety Laboratory Tests:** Clinical laboratory tests (including serum or plasma chemistry, hematology, and urinalysis) will be performed at local laboratories according to the laboratory's normal procedures. See Section 11.2.1 for a complete listing of laboratory tests to be performed.

n: **ctDNA Whole Blood:** Blood can be collected either pre or post dose for all timepoints except for Cycle 1 Day 1.

o: **Tumor Tissue for *RNASEH2* IHC Testing:** Required *only* if additional central lab testing for *RNASEH2* loss is required to confirm eligibility. If archival tissue is unavailable, a fresh biopsy is required to confirm eligibility. Bone tissue is not acceptable for tumor tissue submission because bone biopsies require a decalcification step that will interfere with downstream processing of the sample.

p: **Tumor Tissue:** Archived tumor samples are required, if available, for participation in the trial. The tumor sample, along with the confirmation of cellularity, must be shipped to the central laboratory prior to C1D1+7. If adequate archived tumor tissue is not available and/or a fresh biopsy cannot be safely performed, the patient may still be eligible with prior sponsor approval. If required archival tumor tissue was provided during pre-screening period, then additional archival tissue is not required during screening. If a subset of archival slides were provided during pre-screening, the remainder must be provided during screening to fulfill tissue requirements. If available, the sponsor will also request archival material from the primary tumor. This is optional and not required for enrollment. If archival tissue does not meet study requirements, a pre-treatment biopsy is mandatory prior to treatment and must be shipped by C1D1+7. If a fresh biopsy was provided during pre-screening, then a biopsy during screening is not required. Bone tissue is not acceptable for tumor tissue submission because bone biopsies require a decalcification step that will interfere with downstream processing of the sample. Contact the sponsor if the biopsy cannot be collected at these timepoints. An optional tumor biopsy will also be requested at disease progression.

q: **Study Drugs (RP-3500 and Olaparib or Niraparib) Administration:** Cycle dosing must start on either Monday, Tuesday, or Wednesday if unable to accommodate weekend visits.

r: **Review of Dosing Diary:** Dosing diary will be reviewed at each visit and collected at each Cycle X Day1 visit and at EOT. Additional details are in the Pharmacy Manual.

s: **PK Blood Samples:** To be collected per Appendix 2 Table B. PK sampling will be done on C1D1 for subjects on all schedules. For subjects on the 2/5 schedule, PK sampling will be done on Day 2 of Cycles 1 and 2. For subjects on the 3/4 schedule, PK sampling will be done on Day 3 of Cycles 1 and 2

t: **Tumor Assessment:** Tumor assessments by disease-appropriate standard criteria (RECIST v1.1) using CT/MRI of known sites of disease as clinically indicated. For patients with prostate cancer, bone scans are required at baseline and at subsequent scheduled timepoints with CT/MRI for patients with bone lesions at baseline. Tumor assessments must be performed at Screening and every 6 weeks (±7 days) from Cycle 1 Day 1 for the first 3 assessments (first ~5 months/22 weeks on treatment), or sooner if clinically indicated. Thereafter, scans must be performed every 9 weeks (±7 days). If a patient discontinues treatment for a reason other than disease progression, withdrawal of consent to study, lost to follow-up, or death, scans should continue at the specified intervals until progression is confirmed or until the start of subsequent anticancer treatment. Per RECIST

v1.1, complete response (CR) or partial response (PR) should be confirmed; tumor imaging for confirmation of response must be performed at least 4 weeks after the first indication of response. The subsequent tumor imaging after the confirmation of response should be obtained per the original scheduled interval from the confirmatory scan (6 weeks ±7 days during the first ~5 months of study treatment or every 9 weeks ±7 days thereafter.

u: **Serum Tumor Biomarkers:** For patients with ovarian and prostate cancer, collection of serum tumor biomarkers is mandatory (CA-125, PSA, or other). For all other tumor types, if being monitored by circulating tumor biomarkers, those serum tumor biomarkers also need to be collected.

v: **Post-study Therapy Data Collection:** All anticancer therapies with start and stop dates should be documented. At a minimum, the start and stop dates and the type of therapy should be collected.

w: **Day 2/3 of Cycle 1 and 2:** For subjects on the 2/5 schedule, only the Day 2 assessments should be completed, however, the C1D2 CBC assessment does not need to be collected. For subjects on the 3/4 schedule, only the Day 3 assessments should be completed.

Table A2. Schedule of Assessment for 1 Week on /2 Weeks off (21-day Treatment Cycle)

Dosing: 3 days on, 4 days off (RP-3500 in combination with niraparib or olaparib)

	Pre-Screen	Screen[a]	Cycle 1				Cycle 2			Additional Cycles		EOT/ET[b]	Safety Follow-up[c]	Follow-up[d]
Study Day **Procedures/Assessments[e]**	**-180 to -1**	**-28 to -1**	**1[a]**	**3**	**8**	**17**	**1[f] (+3 days)**	**3**	**15**	**1[f] (+3 days)**	**8[g]**	**(30 +7 days)**	**Within 30 (+14) days of last dose**	**Every 3 months (±2 weeks)**
Pre-screen informed consent	X													
Screening/main informed consent		X												
Inclusion/exclusion criteria		X	X											
PODS review[h]	X													
Demographics	X													
Medical/cancer history		X												
PE		X										X		
Abbreviated PE			X				X			X[i]			X	
Height		X												
Weight		X	X				X			X		X	X	
Vital sign measurements[j]		X	X	X	X	X	X	X	X	X	X	X	X	
ECOG performance status		X	X				X			X		X	X	
12-lead ECG[k]		X	X	X				X						
Pregnancy test[l]		X	X				X			X		X	X	
Clinical safety labs (including reticulocyte count)[m]		X	X				X			X		X	X	
CBC (with differential) & reticulocyte count				X	X	X			X		X			

Study Day Procedures/Assessments[e]	Pre-Screen	Screen[a]	Cycle 1				Cycle 2			Additional Cycles		EOT/ET[b]	Safety Follow-up[c]	Follow-up[d]
	-180 to -1	-28 to -1	1[a]	3	8	17	1[f] (+3 days)	3	15	1[f] (+3 days)	8[g]	(30 +7 days)	Within 30 (+14) days of last dose	Every 3 months (±2 weeks)
ctDNA whole blood[n]		X	X					X			X	X		
Tumor tissue for *RNASEH2* IHC testing (archival or fresh biopsy)	X[o]													
Tumor tissue (archival or fresh biopsy)[p]		X												
Study drug administration[q]			*See Section 8.2, Study Drug Dosage and Administration*											
Review of dosing diary[r]				X	X	X	X	X	X	X	X	X		
PK sample collection[s]			X	X				X						
Tumor assessments: RECIST[t]		X	*To be assessed every 6 weeks (±7 days) from Cycle 1 Day 1 for the first 3 tumor assessments (first ~5 months/22 weeks on treatment). Thereafter, every 9 weeks (±7 days).*											
Serum tumor biomarkers[u]		X	X				X			X		X		
AE assessment		*To be collected from the time of ICF signing through Cycle 1 Day 1 if related to a study procedure and for any AE occurrence from Cycle 1 Day 1 through 30 days after the last dose of the study treatment or start of new anticancer treatment whichever is earlier. SAEs, regardless of relationship, are to be collected from time of ICF until 30 days after the last dose of study drug or start of new anticancer therapy, whichever is earlier. SAEs considered related to the study treatment are to be reported until the end of the survival follow-up period which is up to 12 months after the last dose of IP or until lost to follow-up, patient withdrawal of consent, patient death, or whenever the Investigator becomes aware thereafter.*										X	
Concomitant medications and procedures		*To be collected from Screening Visit through the EOT visit.*											X	
Post-study therapy data collection[v]														X
Survival status														X

Abbreviations: AE = adverse event; BID = twice daily; *BRCA1/2* breast cancer type (1/2) susceptibility protein; CA-125 = cancer antigen 125; CBC = complete blood count; ctDNA = circulating tumor DNA; ECOG = Eastern Cooperative Oncology Group; ECG = electrocardiogram; EOT = End of Treatment; ET = early termination; ICF = informed consent form; MRI = magnetic resonance imaging; NGS = next-generation sequencing; PARPi = poly (adenosine diphosphate-ribose) polymerase inhibitor(s); PE = physical examination; PK = pharmacokinetic; PODS = Precision Oncology Decision Support; PSA = prostate-specific antigen; QTcF = QT interval corrected for heart rate using Fridericia's formula; RECIST = Response Evaluation Criteria in Solid Tumors; *RNASEH2* ribonuclease H2; SAE = serious adverse event

a: **Screening:** Screening Period extends from Day -28 to Day -1. Screening laboratory assessments may be used as Day 1 assessments if performed within 96 hours of the first dose of study drugs, with the exception of the ctDNA collection and ECGs. ECOG performance status and abbreviated PE that are completed within 24 hours of first dose of study treatment may be used as Cycle 1 Day 1 assessments. Patients must continue to meet eligibility criteria prior to first dose of study on Cycle 1 Day 1.

b: **EOT/ET:** An EOT/early termination visit will be conducted within 30 days (+7 days) after the last dose of study drug or within 7 days after the last dose of study drug if discontinued due to a treatment-related toxicity. If a patient is removed from the study due to a treatment-related toxicity, an additional safety follow-up visit will occur within 30 days (+14 days) after the last dose of study drug. The safety follow-up visit may be performed sooner upon resolution of the AE to Grade 1.

c: **EOT Safety Follow-up:** For patients who discontinued treatment due to a drug-related AE. If the EOT/ET visit was done within the last 7 days of last dose for toxicity, the window for the second follow-up safety visit will be within 30 (+14) days from the last dose.

d: **Survival Follow-Up:** Survival follow-up will be conducted approximately every 3 months (±2 weeks) on all patients until the end of the study unless they withdraw consent to the study or the study is terminated prior to the 12-month follow-up. This may be done by telephone contact or standard method used by participating centers and agreed with sponsor.

e: **Procedures/Assessments:** Pre-study procedures and tumor assessment must be performed within 28 days before first dose of study drugs.

f: **Cycle X Day 1:** The start of a new cycle should always coincide with the start of study drug administration for that cycle. A +3-day window is allowed for the start of new cycles, though cycles should never start early and should at least be 21 days in length. A -2 day window is allowed for the assessments scheduled for the Cycle X Day 1 visit to enable flexibility with visit scheduling

g: **Day 8 of Additional Cycles:** Assessments to be performed ONLY on Day 8 of Cycles 3 and 4.

h: **PODS Review:** NGS reports will be emailed to PODS and Repare Biomarkers for central review and to confirm molecular eligibility or determine if additional testing is required to confirm eligibility.

i: **Abbreviated PE:** Starting at Cycle 2, abbreviated PE to be performed every 2 cycles (unless full PE necessary by investigator judgment).

j: **Vital Signs:** Blood pressure, heart rate, respiratory rate, and temperature must be measured after the patient has been sitting for 5 minutes.

k: **ECG:** 12-lead ECGs to be done in triplicate ≥1 minute apart per Appendix 2 Table C. Patients should be in supine position and resting for at least 10 minutes before study-related ECGs. Only QTcF needs to be recorded.

l: **Pregnancy Test:** For women of childbearing potential, a serum pregnancy test is required at Screening. If pregnancy test was done within 96 hours prior to Cycle 1 Day 1, repeat testing is not required. A serum or urine pregnancy test must be performed on Day 1 of each cycle and at EOT. Pregnancy test can be performed more frequently if required per local regulations.

m: **Safety Laboratory Tests:** Clinical laboratory tests (including serum or plasma chemistry, hematology, and urinalysis) will be performed at local laboratories according to the laboratory's normal procedures. See Section 11.2.1 for a complete listing of laboratory tests to be performed.

n: **ctDNA Whole Blood:** Blood can be collected either pre or post dose for all timepoints except for Cycle 1 Day 1.

o: **Tumor Tissue for *RNASEH2* IHC Testing:** Required *only* if additional central lab testing for *RNASEH2* loss is required to confirm eligibility. If archival tissue is unavailable, a fresh biopsy is required to confirm eligibility. Bone tissue is not acceptable for tumor tissue submission because bone biopsies require a decalcification step that will interfere with downstream processing of the sample.

p: **Tumor Tissue:** Archived tumor samples are required, if available, for participation in the trial. The tumor sample, along with the confirmation of cellularity, must be shipped to the central laboratory prior to C1D1+7. If adequate archived tumor tissue is not available and/or a fresh biopsy cannot be safely performed, the patient may still be eligible with prior sponsor approval. If required archival tumor tissue was provided during pre-screening period, then additional archival tissue is not required during screening. If a subset of archival slides were provided during pre-screening, the remainder must be provided during screening to fulfill tissue requirements. If available, the sponsor will also request archival material from the primary tumor. This is optional and not required for enrollment. If archival tissue does not meet study requirements, a pre-treatment biopsy is mandatory prior to treatment and must be shipped by C1D1+7. If a fresh biopsy was provided during pre-screening, then a biopsy during screening is not required. Bone tissue is not acceptable for tumor tissue submission because bone biopsies require a decalcification step that will interfere with downstream processing of the sample. Contact the sponsor if the biopsy cannot be collected at these timepoints. An optional tumor biopsy will also be requested at disease progression.

q: **Study Drugs (RP-3500 and Olaparib or Niraparib) Administration:** Cycle dosing must start on either Monday, Tuesday, or Wednesday if unable to accommodate weekend visits.

r: **Review of Dosing Diary:** Dosing diary will be reviewed at each visit and collected at each Cycle X Day1 visit and at EOT. Additional details are in the Pharmacy Manual.

s: **PK Blood Samples:** To be collected per Appendix 2 Table B.

t: **Tumor Assessment:** Tumor assessments by disease-appropriate standard criteria (RECIST v1.1) using CT/MRI of known sites of disease as clinically indicated. For patients with prostate cancer, bone scans are required at baseline and at subsequent scheduled timepoints with CT/MRI for patients with bone lesions at baseline. Tumor assessments must be performed at Screening and every 6 weeks (±7 days) from Cycle 1 Day 1 for the first 3 assessments (first ~5 months/22 weeks on treatment), or sooner if clinically indicated. Thereafter, scans must be performed every 9 weeks (±7 days). If a patient discontinues treatment for a reason other than disease progression, withdrawal of consent to study, lost to follow-up, or death, scans should continue at the specified intervals until progression is confirmed or until the start of subsequent anticancer treatment. Per RECIST v1.1, complete response (CR) or partial response (PR) should be confirmed; tumor imaging for confirmation of response must be performed at least 4 weeks after the first indication of response. The subsequent tumor imaging after the confirmation of response should be obtained per the original scheduled interval from the confirmatory scan (6 weeks ±7 days during the first ~5 months of study treatment or every 9 weeks ±7 days thereafter.

u: **Serum Tumor Biomarkers:** For patients with ovarian and prostate cancer, collection of serum tumor biomarkers is mandatory (CA-125, PSA, or other). For all other tumor types, if being monitored by circulating tumor biomarkers, those serum tumor biomarkers also need to be collected.

v: **Post-study Therapy Data Collection:** All anticancer therapies with start and stop dates should be documented. At a minimum, the start and stop dates and the type of therapy should be collected.

Table A3. Schedule of Assessment for 1 Week on /1 Week off (28-day Treatment Cycle)

Dosing: 3 days on, 4 days off (RP-3500 in combination with niraparib or olaparib)

	Pre-Screen	Screen[a]	Cycle 1					Cycle 2			Additional Cycles		EOT/ ET[b]	Safety Follow-up[c]	Follow-up[d]
Study Day **Procedures/Assessments[e]**	**-180 to -1**	**-28 to -1**	**1[a]**	**3**	**8**	**15**	**22**	**1[f] (+3 days)**	**3**	**15**	**1[f] (+3 days)**	**15[g]**	**(30 +7 days)**	**Within 30 (+14) days of last dose[c]**	**Every 3 months (±2 weeks)**
Pre-screen informed consent	X														
Screen/main informed consent		X													
Inclusion/exclusion criteria		X	X												
PODS review[h]	X														
Demographics	X														
Medical/cancer history		X													
PE		X											X		
Abbreviated PE			X					X			X[i]			X	
Height		X													
Weight		X	X					X			X		X	X	
Vital sign measurements[j]		X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG performance status		X	X					X			X		X	X	
12-lead ECG[k]		X	X	X					X						
Pregnancy test[l]		X	X					X			X		X	X	
Clinical safety labs (including reticulocyte count)[m]		X	X					X			X		X	X	
CBC (with differential) & reticulocyte count				X	X	X	X			X		X			
ctDNA whole blood[n]		X	X				X			X		X	X		
Tumor tissue for *RNASEH2* IHC testing (archival or	X[o]														

Study Day **Procedures/Assessments[e]**	**Pre-Screen**	**Screen[a]**	**Cycle 1**					**Cycle 2**			**Additional Cycles**		**EOT/ ET[b]**	**Safety Follow-up[c]**	**Follow-up[d]**
	-180 to -1	**-28 to -1**	**1[a]**	**3**	**8**	**15**	**22**	**1[f] (+3 days)**	**3**	**15**	**1[f] (+3 days)**	**15[g]**	**(30 +7 days)**	**Within 30 (+14) days of last dose[c]**	**Every 3 months (±2 weeks)**
fresh biopsy)															
Tumor tissue (archival or fresh biopsy)[p]		X													
Study drug administration[q]			*See Section 8.2, Study Drug Dosage and Administration*												
Review of dosing diary[r]				X	X	X	X	X	X	X	X	X	X		
PK sample collection[s]			X	X					X						
Tumor assessments: RECIST[t]		X	*To be assessed every 6 weeks (±7 days) from Cycle 1 Day 1 for the first 3 tumor assessments (first ~5 months/22 weeks on treatment). Thereafter, every 9 weeks (±7 days).*												
Serum tumor biomarkers[u]		X	X					X			X		X		
AE assessment			*To be collected from the time of ICF signing through Cycle 1 Day 1 if related to a study procedure and for any AE occurrence from Cycle 1 Day 1 through 30 days after the last dose of the study treatment or start of new anticancer treatment whichever is earlier. SAEs, regardless of relationship, are to be collected from time of ICF until 30 days after the last dose of study drug or start of new anticancer therapy, whichever is earlier. SAEs considered related to the study treatment are to be reported until the end of the survival follow-up period which is up to 12 months after the last dose of IP or until lost to follow-up, patient withdrawal of consent, patient death, or whenever the Investigator becomes aware thereafter.*											X	
Concomitant medications and procedures			*To be collected from Screening Visit through the EOT visit.*												
Post-study therapy data collection[v]															X
Survival status															X

Abbreviations: AE = adverse event; BID = twice daily; *BRCA1/2* breast cancer type (1/2) susceptibility protein; CA-125 = cancer antigen 125; CBC = complete blood count; ctDNA = circulating tumor DNA; ECOG = Eastern Cooperative Oncology Group; ECG = electrocardiogram; EOT = End of Treatment; ET = early termination; ICF = informed consent form; MRI = magnetic resonance imaging; NGS = next-generation sequencing; PARPi = poly (adenosine diphosphate-

ribose) polymerase inhibitor(s); PE = physical examination; PK = pharmacokinetic; PODS = Precision Oncology Decision Support; PSA = prostate-specific antigen; QTcF = QT interval corrected for heart rate using Fridericia's formula; RECIST = Response Evaluation Criteria in Solid Tumors; *RNASEH2* ribonuclease H2; SAE = serious adverse event

a: **Screening:** Screening Period extends from Day -28 to Day -1. Screening laboratory assessments may be used as Day 1 assessments if performed within 96 hours of the first dose of study drugs, with the exception of the ctDNA collection and ECGs. ECOG performance status and abbreviated PE that are completed within 24 hours of first dose of study treatment may be used as Cycle 1 Day 1 assessments. Patients must continue to meet eligibility criteria prior to first dose of study on Cycle 1 Day 1.

b: **EOT/ET:** An EOT/early termination visit will be conducted within 30 days (+7 days) after the last dose of study drug or within 7 days after the last dose of study drug if discontinued due to a treatment-related toxicity. If a patient is removed from the study due to a treatment-related toxicity, an additional safety follow-up visit will occur within 30 days (+14 days) after the last dose of study drug. The safety follow-up visit may be performed sooner upon resolution of the AE to Grade 1.

c: **EOT Safety Follow-up:** For patients who discontinued treatment due to a drug-related AE. If the EOT/ET visit was done within the last 7 days of last dose for toxicity, the window for the second follow-up safety visit will be within 30 (+14) days from the last dose.

d: **Survival Follow-Up:** Survival follow-up will be conducted approximately every 3 months (±2 weeks) on all patients until the end of the study unless they withdraw consent to the study or the study is terminated prior to the 12-month follow-up. This may be done by telephone contact or standard method used by participating centers and agreed with sponsor.

e: **Procedures/Assessments:** Pre-study procedures and tumor assessment must be performed within 28 days before first dose of study drugs.

f: **Cycle X Day 1:** The start of a new cycle should always coincide with the start of study drug administration for that cycle. A +3-day window is allowed for the start of new cycles, though cycles should never start early and should be at least 28 days in length. A -2 day window is allowed for the assessments scheduled for the Cycle X Day 1 visit to enable flexibility with visit scheduling

g: **Day 15 of Additional Cycles:** Assessments to be performed ONLY on Day 15 of Cycles 3 and 4.

h: **PODS Review:** NGS reports will be emailed to PODS and Repare Biomarkers for central review and to confirm molecular eligibility or determine if additional testing is required to confirm eligibility.

i: **Abbreviated PE:** Starting at Cycle 2, abbreviated PE to be performed every 2 cycles (unless full PE necessary by investigator judgment).

j: **Vital Signs:** Blood pressure, heart rate, respiratory rate, and temperature must be measured after the patient has been sitting for 5 minutes.

k: **ECG:** 12- lead ECGs to be done in triplicate ≥1 minute apart per Appendix 2 Table C. Patients should be in supine position and resting for at least 10 minutes before study-related ECGs. Only QTcF needs to be recorded.

l: **Pregnancy Test:** For women of childbearing potential, a serum pregnancy test is required at Screening. If pregnancy test was done within 96 hours prior to Cycle 1 Day 1, repeat testing is not required. A serum or urine pregnancy test must be performed on Day 1 of each cycle and at EOT. Pregnancy test can be performed more frequently if required per local regulations.

m: **Safety Laboratory Tests:** Clinical laboratory tests (including serum or plasma chemistry, hematology, and urinalysis) will be performed at local laboratories according to the laboratory's normal procedures. See Protocol Section 11.2.1 for a complete listing of laboratory tests to be performed.

n: **ctDNA Whole Blood:** Blood can be collected either pre or post dose for all timepoints except for Cycle 1 Day 1.

o: **Tumor Tissue for *RNASEH2* IHC Testing:** Required *only* if additional central lab testing for *RNASEH2* loss is required to confirm eligibility. If archival tissue is unavailable, a fresh biopsy is required to confirm eligibility. Bone tissue is not acceptable for tumor tissue submission because bone biopsies require a decalcification step that will interfere with downstream processing of the sample.

p: **Tumor Tissue:** Archived tumor samples are required, if available, for participation in the trial. The tumor sample, along with the confirmation of cellularity, must be shipped to the central laboratory prior to C1D1+7. If adequate archived tumor tissue is not available and/or a fresh biopsy cannot be safely performed, the patient may still be eligible with prior sponsor approval. If required archival tumor tissue was provided during pre-

screening period, then additional archival tissue is not required during screening. If a subset of archival slides were provided during pre-screening, the remainder must be provided during screening to fulfill tissue requirements. If available, the sponsor will also request archival material from the primary tumor. This is optional and not required for enrollment. If archival tissue does not meet study requirements, a pre-treatment biopsy is mandatory prior to treatment and must be shipped by C1D1+7. If a fresh biopsy was provided during pre-screening, then a biopsy during screening is not required. Bone tissue is not acceptable for tumor tissue submission because bone biopsies require a decalcification step that will interfere with downstream processing of the sample. Contact the sponsor if the biopsy cannot be collected at these timepoints. An optional tumor biopsy will also be requested at disease progression.

q: **Study Drugs (RP-3500 and Olaparib or Niraparib) Administration:** Cycle dosing must start on either Monday, Tuesday, or Wednesday if unable to accommodate weekend visits.

r: **Review of Dosing Diary:** Dosing diary will be reviewed at each visit and collected at each Cycle X Day1 visit and at EOT. Additional details are in the Pharmacy Manual.

s: **PK Blood Samples:** To be collected per Appendix 2 Table B.

t: **Tumor Assessment:** Tumor assessments by disease-appropriate standard criteria (RECIST v1.1) using CT/MRI of known sites of disease as clinically indicated. For patients with prostate cancer, bone scans are required at baseline and at subsequent scheduled timepoints with CT/MRI for patients with bone lesions at baseline. Tumor assessments must be performed at Screening and every 6 weeks (±7 days) from Cycle 1 Day 1 for the first 3 assessments (first ~5 months/22 weeks on treatment), or sooner if clinically indicated. Thereafter, scans must be performed every 9 weeks (±7 days). If a patient discontinues treatment for a reason other than disease progression, withdrawal of consent to study, lost to follow-up, or death, scans should continue at the specified intervals until progression is confirmed or until the start of subsequent anticancer treatment. Per RECIST v1.1, complete response (CR) or partial response (PR) should be confirmed; tumor imaging for confirmation of response must be performed at least 4 weeks after the first indication of response. The subsequent tumor imaging after the confirmation of response should be obtained per the original scheduled interval from the confirmatory scan (6 weeks ±7 days during the first ~5 months of study treatment or every 9 weeks ±7 days thereafter.

u: **Serum Tumor Biomarkers:** For patients with ovarian and prostate cancer, collection of serum tumor biomarkers is mandatory (CA-125, PSA, or other). For all other tumor types, if being monitored by circulating tumor biomarkers, those serum tumor biomarkers also need to be collected.

v: **Post-study Therapy Data Collection:** All anticancer therapies with start and stop dates should be documented. At a minimum, the start and stop dates and the type of therapy should be collected.

Table B. Pharmacokinetic Sample Collection Timepoints

Day of Procedure	**Cycle 1**[a]		**Cycle 2** [a]
	1	**2 or 3**[c]	**2 or 3**[c]
Pre-dose[b] (within 30 min)	X	X	X
Post-dose			
0.5 h (± 5 min)	X	X	
1 h (± 10 min)	X	X	
2 h (± 15 min)	X	X	
4 h (± 15 min)	X	X	
6 h (± 30 min)	X	X	

Abbreviations: QD = once daily; ECG = electrocardiogram; PK = pharmacokinetic
Note: Timepoints are relative to study drug administration.
When ECG coincides with PK, ECG to be done prior to PK blood draws.

a: Cycles must start on either Monday, Tuesday, or Wednesday if unable to accommodate weekend visits.
b: Pre-dose sample to be collected within 30 minutes prior to the administration of the morning doses of study drugs. These doses should be taken in the clinic.
c: Day 2 is only for subjects on the 2/5 schedule and Day 3 is only for subjects on the 3/4 schedule as outlined above

Table C. Electrocardiogram Timepoints

	Screening	Cycle 1[a]		Cycle 2 [a]
Day of Procedure	**Days -28 to -1**	**1**	**2 or 3[c]**	**2 or 3[c]**
Pre-dose[b] (within 30 min)	X	X	X	X
Post-dose				
1 h (± 10 min)		X	X	
2 h (± 15 min)		X	X	
4 h (± 15 min)		X	X	

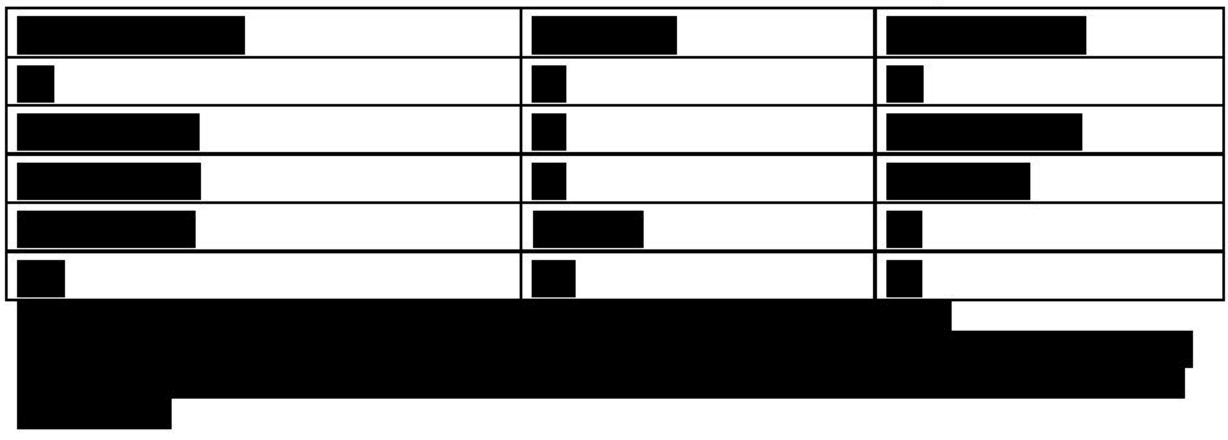
Abbreviations: ECG = electrocardiogram; PK = pharmacokinetic
Note: Timepoints are relative to study drug administration. When ECG coincides with PK, ECG to be done prior to PK blood draws. QTcF only needs to be recorded.

a: Cycles must start on either Monday, Tuesday, or Wednesday, if unable to accommodate weekend visits.
b: Pre-dose ECG performed within 30 minutes prior to study drug administration.
c: Day 2 is only for subjects on the 2/5 schedule and Day 3 is only for subjects on the 3/4 schedule as outlined above.

[redacted]

[redacted]

[redacted]



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