STATISTICAL ANALYSIS PLAN

A PHASE 1 TRIAL OF THE SAFETY, PHARMACOKINETICS, PHARMACODYNAMICS, AND PRELIMINARY CLINICAL ACTIVITY OF RP-1664 IN PARTICIPANTS WITH ADVANCED SOLID TUMORS

Protocol Number:	RP-1664-01
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SIGNATURE PAGE

Protocol Title:	*A PHASE 1 TRIAL OF THE SAFETY, PHARMACOKINETICS, PHARMACODYNAMICS, AND PRELIMINARY CLINICAL ACTIVITY OF RP-1664 IN PARTICIPANTS WITH ADVANCED SOLID TUMORS*
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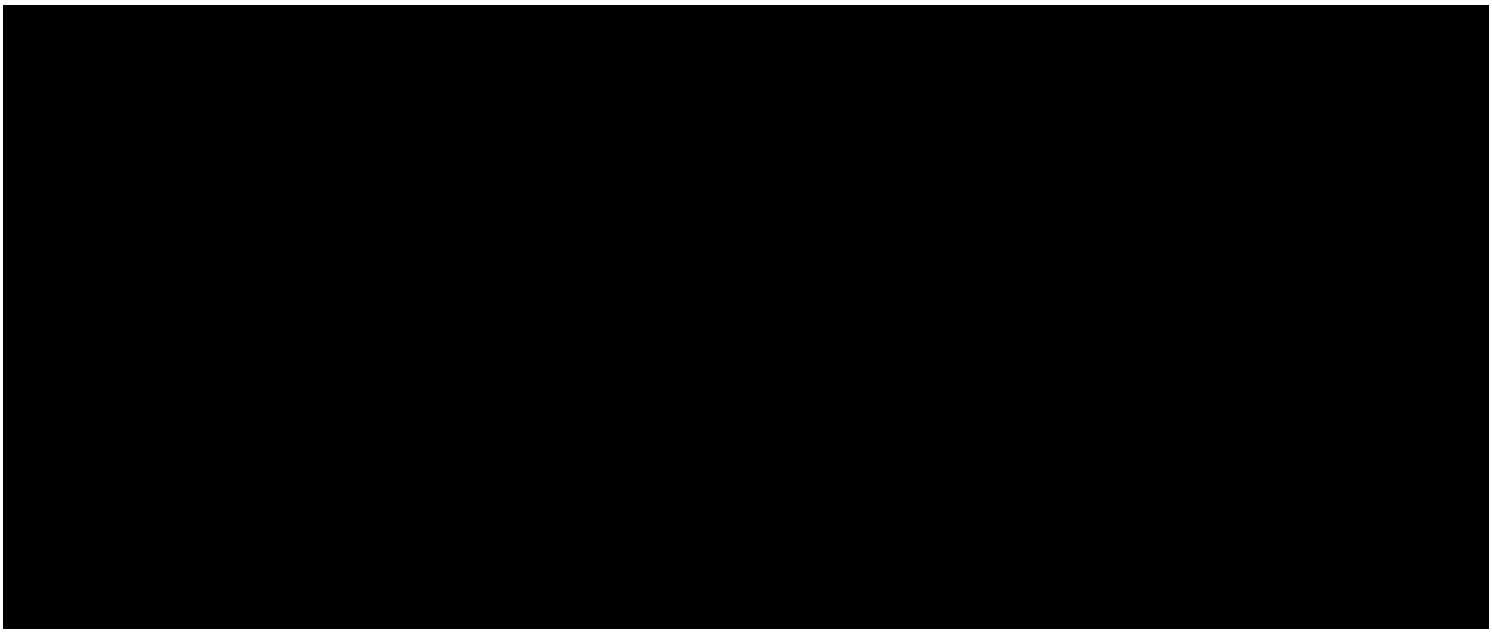

Version History

Version and Date	Description
Version 1.0, 10SEPT2025	Original Version

<< Additional versions may be added as additional rows if applicable. >>

1. Table of Contents

2. ABBREVIATIONS AND ACRONYMS

Abbreviation or Specialist Term	Explanation
AE	Adverse event
ADI	Actual Dose Intensity
ALT	Alaine Aminotransferase
ANC	Absolute neutrophile count
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Class
AUC	Area under
BID	Twice-daily
BOIN	Bayesian optimal interval
BOR	Best overall response
CA-125	Cancer antigen 125
CBR	Clinical benefit rate

Abbreviation or Specialist Term	Explanation
CI	Confidence Interval
CR	Complete response
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Event
CYP	Cytochrome P450
C_{max}	Maximum observed plasma concentration
C_{min}	Minimum observed plasma concentration
ctDNA	Circulating tumor DNA
DOR	Duration of response
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	End-of-treatment
eCRF	Electronic case report form
FISH	DNA fluorescent in situ hybridization
GCIG	Gynecologic Cancer Intergroup criteria
ICF	Informed consent Form
IHC	Immunohistochemistry
INRC	International Neuroblastoma Response Criteria
LLOQ	Lower limit of quantitation
MTD	Maximum Tolerated Dose
MR	Minor Response
MedDRA	Medical Dictionary for Regulatory Activities
NCA	Non-compartmental analysis
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	Not evaluable
NGS	Next generation sequencing
OHC	4β-hydroxycholesterol
ORR	Objective response rate

Abbreviation or Specialist Term	Explanation
PCWG3	Prostate Cancer Working Group criteria
PD	Progressive disease
PDI	Planned Dose Intensity
PFS	Progression-free survival
PLK4	Polo-Like Kinases 4
PK	Pharmacokinetic
PR	Partial response
PSA	Prostate specific antigen
PT	Preferred Term
QD	Daily
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable disease
SOC	System organ classification
SRC	Safety Review Committee
TEAE	Treatment-emergent adverse events
TL	Target lesion
T_{max}	Time to maximum observed plasma concentration
$t_{1/2}$	Elimination half-life
ULN	Upper limit of normal
VAF	Variant allele frequency
WHODrug	World Health Organization Drug

3. INTRODUCTION

This document describes the statistical methods to be implemented in the statistical analysis of data collected under clinical study Protocol RP-1664-01, titled: “Phase 1 Trial of the Safety, Pharmacokinetics (PK), Pharmacodynamics, and Preliminary Clinical Activity of RP-1664 in Participants with Advanced Solid Tumors”. This Statistical Analysis Plan (SAP) contains definitions of analysis populations, derived variables, statistical methods for the analyses of baseline, efficacy, and safety data and the data listings and summary tables which will be produced. Details will be described to ensure the results are complete and appropriate to allow valid conclusion regarding the study objectives.

The analysis details for pharmacokinetic, pharmacodynamics, and biomarker analyses are not described within this SAP. A separate analysis plan may be implemented for those analyses.

This document has been prepared based on Protocol Version 3.0, dated March 24, 2025.

4. STUDY OVERVIEW

This is a multicenter, open-label Phase 1 trial to investigate the safety, PK, pharmacodynamic, and preliminary efficacy of the PLK4 inhibitor RP-1664 in participants with molecularly selected advanced solid tumors. The trial is estimated to enroll approximately 80 evaluable participants with solid tumors harboring any one of the following:

[redacted]

4.1 Study Design

The trial will follow a Bayesian Optimal Interval (BOIN) design to guide escalation and de-escalation decision, establish a maximum tolerated dose (MTD), and identify a dose and schedule of RP-1664 that is tolerable.

All participants will undergo a PK evaluation period starting at Cycle 0 Day 1. Participants will be assigned to receive either a single dose of RP-1664 at the highest Safety Review Committee (SRC) approved dose level with PK collection over the subsequent 48 hours to characterize the half life (t1/2) of RP-1664 in the fasted state or enrolled into a cohort to investigate the effect of food on RP-1664 PK.

The starting dose (Dose Level 1) is 10 mg once daily (QD). RP-1664 will initially be given QD on a 2 weeks on 1 week off schedule to allow 1 week for bone marrow recovery.

The first escalation (Dose Level 2) will be up to 30 mg to limit the number of participants receiving a potentially sub-therapeutic dose. After Dose Level 2, escalation will proceed with up to 100% increases in RP-1664 after evaluation of tolerability by the SRC until Dose Level S. Dose Level S is defined as the dose level at which any of the following safety signals occur during Cycle 0 or Cycle 1:

- Any ≥ Grade 3 hematological toxicity
- >50% decrease in platelets or neutrophils from Cycle 0 Day 1
- >2 g/dL decrease in hemoglobin from Cycle 0 Day 1
- Any ≥ Grade 2 drug-related non-hematological toxicity lasting >5 days or requiring clinical intervention, except Grade 2 fatigue, nausea, vomiting, diarrhea, or constipation
- Any adverse event (AE) of any grade limiting tolerability as assessed by the SRC

At Dose Level S, the cohorts will be expanded to a minimum of 3 participants to further evaluate safety, PK, and pharmacological activity. Evidence of pharmacologic activity can include Grade ≥ 2 drug-related toxicity at any cycle, PK

data demonstrating exposure levels predicted to be efficacious based on nonclinical studies, or other evidence of treatment-related activity as agreed on by the SRC. Dose decisions will be based on assessments in 2 or more dose-limiting toxicity (DLT) evaluable participants completing the DLT evaluation period. Any escalation of RP-1664 after Dose Level S will be in increments up to 75% as agreed upon by the SRC and will enroll cohort sizes of N ≥ 3.

RP-1664 Escalation Dose Level	**Escalation Plan**
	Daily (mg) or % of previous dose increment
1	10 mg
2	Up to 30 mg
3 to S	Up to 100% increases until Dose Level S
S	Expand cohort at same dose
S1 to MTD or tolerated and pharmacologically active dose	Up to 75% increases until MTD or tolerated and pharmacologically active dose

Evaluation of the PK data after at least 6 participants, with sufficient data to derive PK parameters, may trigger adjustment of the daily dosing frequency of RP-1664 to allow for twice-daily (BID) dosing. BID dosing may be initiated based on observed participant outcomes and PK parameters such as, but not limited to, t1/2 is < 12 hours or the C_{max}:C_{min} ratio is > 10. Any decision to move from QD to BID dosing during the trial will be made after consultation with the SRC. If BID dosing is initiated, the Sponsor in agreement with SRC, can elect to continue or cease enrollment in QD dosing cohorts based on available data.

Additional treatment schedules, including daily dosing, 3 days on/4 days off, 1 week on/1 week off, or 2 weeks on/2 weeks off may also be explored to mitigate AEs and/or improve efficacy. If an additional schedule is tested, the starting dose of RP-1664 may be as high as the highest total daily dose that cleared DLT evaluation. The decision to test one or more of these schedules and set the starting dose level will be agreed upon by the SRC and will take into consideration all available safety, efficacy, pharmacodynamic, and PK data.

The food effect portion of the trial will be conducted at selected centers and may start at Dose Level 3 or once Dose Level S is reached. The fasting recommendation for RP-1664 in the general trial population may be revised to allow dosing with food after at least 4 participants have been evaluated in the food effect portion of the trial.

Expansion cohorts may be opened if at least one safe dose and schedule at which clinical activity is identified and agreed upon by the SRC. Up to 20 efficacy evaluable participants in each expansion cohort can be enrolled to further evaluate the safety, PK, pharmacodynamic, and preliminary efficacy of RP-1664 at the selected dose level(s). Enrollment in expansion cohorts may be limited to specific tumor types and/or genomic profiles based on assessment of clinical activity by the Sponsor in the dose escalation portion and other emerging preclinical, translational, and clinical data external to the trial.

4.2 Study Procedure and Assessment

The trial will consist of a Pre-Screening Period (within 6 months from time of the Screening/Main Informed Consent Form [ICF] signature, to confirm molecular eligibility), Screening Period, Treatment Period (including PK evaluation period starting at cycle 0 Day 1, and continuing in 21- or 28- Day cycles), an End of Treatment (EOT) Visit (occurring within 7 days after the last dose of trial treatment), a Safety Follow-up Visit (occurring within 30 days ± 14 days after the last dose of trial treatment), and a Survival Follow-up Period (survival follow-up assessments will be done every 90 days [± 14 days] after the date of treatment discontinuation until the end of trial [for up to 6 months after EOT] unless the participant

withdraws consent to the trial, the trial is terminated, the participant dies or is lost to follow-up), The end of Trial is defined as the date of the last visit (including all follow-up visit) of the last participant in the trial.

4.3 Sample Size

The approximate total number of participants exposed to RP-1664 will be 80. This will include approximately 40 DLT evaluable participants in dose escalation and 40 efficacy evaluable participants to be included in cohort expansion.

The sample size for dose escalation is not driven by statistics but determined based on number of dose escalations that will potentially be assessed. The sample size for the food effect and PK bridging portions of the trial were considered adequate to enable a preliminary assessment of potential food and formulation effect.

After one or more tolerated and clinically active doses/schedules are identified, based on discussion between the investigators and the sponsor, up to 2 expansion cohorts will be added to enroll selected tumor types or genotypes to further confirm the dose levels or establish a range for acceptable doses and assess efficacy required for a proof of concept. Up to approximately 20 efficacy evaluable participants will be enrolled in each expansion cohort (up to approximately 40 total evaluable participants). With the targeted response rate (Objective Response Rate [ORR]) of $\geqslant$ 30%, this sample size (n=20) will provide approximately 80% power to reject the null hypothesis of ORR $\leqslant$ 10%, with 1-sided type I error of 0.05. Specifically, at least 5 responses (out of 20 evaluable participants) are required for rejecting the null hypothesis.

5. STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objectives

- To assess the safety and tolerability of RP-1664 in participants with eligible, advanced solid tumors
- To define a dose and schedule of RP-1664 that is tolerated and has clinical activity.

[redacted]

5.2 Primary Endpoints

- Incidence and severity of treatment-emergent adverse events (TEAEs)

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- [redacted]
- [redacted]
- [redacted]

[redacted]

6. ANALYSIS POPULATIONS

The following analysis populations will be used for statistical analysis.

6.1 DLT Evaluable Population

The DLT Evaluable Population will consist of participants who have met the minimum safety evaluation requirements of the trial and /or who experience a DLT at any time during the DLT evaluation period (from the start of treatment through the end of Cycle 1). Minimum safety requirements will be met if, during Cycle 1 of treatment, the participant receives at least 75% of their planned total dose of RP-1664, completes required safety evaluations, and is observed through the end of Cycle 1. This analysis set will be used for DLT analyses, unless otherwise specified.

6.2 Safety Population

The Safety Population, used for the assessment of overall safety and tolerability, will consist of all participants who receive at least 1 dose of RP-1664. The analysis set will be used for individual listings, disposition summary table and all safety analyses, unless otherwise specified.

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7. DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

All analyses will be performed using SAS® Version 9.4 or higher.

Unless specified otherwise, the analyses of data collected will be descriptive and summaries will be presented separately for each dose level, dose schedule and in total for the specified analysis population. Statistical analysis will be purely descriptive and no formal hypothesis testing or comparative analysis between dose level and dose schedule will be performed. Confidence intervals (CIs) will be constructed at two-side 95% level where appropriate.

Frequency distributions for categorical variables will be provided as the number of subjects in the category and the percentages of the total number of subjects in the given population as noted. Percentages will be reported to one decimal place.

The descriptive statistics for continuous variables will be the number of subjects, mean, standard deviation, median, lower and upper quartile, minimum and maximum. Mean and median will be reported to 1 decimal place, while the standard deviation will be reported to 2 decimal places . Minimum and maximum will be reported the same as the original data.

Summary tables may be replaced with listings when appropriate. For instance, an AE Frequency table may be replaced with a listing if it only contains a few unique preferred terms (PTs) reported on relatively few subjects.

Shift tables will be utilized to summarize clinical laboratory tests and neurological exams when applicable.

All tables will be summarized by study cohorts, treatment, dose level and dose schedule and include an overall column unless otherwise specified.

All listings will be sorted by study cohorts, dose level and dose schedule, subject ID and, if applicable, by visit date unless otherwise specified in the text.

7.1 Definition of Baseline

For all evaluations unless otherwise noted, baseline is defined as the most recent non-missing measurement within 28 days prior to the first administration of RP-1664.

- Change from baseline is calculated as (Value at a visit - Baseline value).
- Percent change from baseline is calculated as (Value at a visit - Baseline value)/Baseline value * 100.

7.2 Definition of Study Days

Unless otherwise noted, study days of an evaluation are defined as the number of days relative to the first dose date which is designated as Day 1, and the preceding day is Day -1, the day before that is Day -2, etc.

Study days are calculated as

- (Date of assessment – first dose date + 1) for assessments on/after first dose date.
- (Date of assessment – first dose date) for assessments before first dose date.

7.3 Analysis Visit Window

Data will be analyzed by scheduled visits, where appropriate. Data that are collected from an unscheduled visit will not be included in the by-visit summary tables but will be presented in the listings. However, data collected at unscheduled visits will also be considered for toxicity grading for laboratory assessments. Both unscheduled and out-of-window imaging assessments will be included in efficacy analysis.

7.4 Handling of Partial Dates for Adverse Events

If the year of the start date is missing or the start date is completely missing, the first dose date will be used. If the year of the end date is missing or the end date is completely missing, the event will be regarded as ongoing and do not impute. Impute AE end date first if both AE start date and end date are partially missing.

If end date of an adverse event is partially missing, impute as follows:

- If the day of the month is missing, the onset day will be set to the last day of the month.
- If the onset day and month are both missing, the day and month will be assumed to be December 31.
- If the imputed end date > death date, then set to death date.

If start date of an adverse event is partially missing, impute as follows:

- If the day of the month is missing, the onset day will be set to the first day of the month unless it is on or after the same month and year as study treatment. In this case, the onset date will be assumed to be the first dose date of treatment.
- If the onset day and month are both missing, the day and month will be assumed to be January 1 when the year is on or after the year of study treatment. If the year is prior to year of first dose, December 31st will be used. The event onset will be coded to the first dose date of treatment if year is the same as the year of first dose date to conservatively report the event as treatment-emergent.
- If the imputed AE start date is after the AE end date (maybe imputed), then update the AE start date with the AE end date as the final imputed AE start date.
- If the imputed start date > death date, then set to death date
- If the imputed end date is before imputed start date, the AE event will be treated as treatment emergent AE and report it as data issue.

Imputation of partial dates is used only to determine whether an event is treatment-emergent; data listings will present the partial date as recorded in the eCRF.

7.5 Handling of Partial Dates for Medications/Procedures/Therapy

When the start date or end date of a medication/therapy/procedure is partially missing, the date will be imputed to determine whether the medication/therapy/procedure is prior or concomitant. The following rules will be applied to impute partial dates for medications.

If the start date of a medication/procedure/therapy is partially missing, impute as follows:

- Medication/procedure/therapy start dates with a missing day and non-missing month will be assumed to have occurred on the first day of the non-missing month if the month and year is after first dose date. If the month and year are prior to the first dose date, the last day of the month will be assigned to the missing day. If the month and year are the same as the first dose date, the first dose date will be used.
- Medication/procedure/therapy start dates with missing day and month will be assumed to have occurred on the first day of the non-missing year (i.e., 01 January) if the year is after the year of first dose date. If the year is prior to the year of first dose date, December 31 will be assigned to the missing fields. If the year is the same as the year of the first dose date, the first dose date will be used.
- If the imputed start date > death date, then set to death date and report it as data issue

If the end date of a medication/procedure/therapy is partially missing, impute as follows:

- Medications/procedure that are not ongoing and have a medication/procedure/therapy stop date with a missing day and non-missing month will be assumed to have stopped on the last day of the non-missing month.
- Medications/procedure that are not ongoing and have a medication/radiotherapy stop date with a missing month will be assumed to have stopped on the last day of the non-missing year (i.e., 31 December).
- If the imputed end date > death date, then set to death date and report it as data issue.
- If the imputed end date is before imputed start date, report it as data issue.

If the year of the start date or the year of the end date of a medication/procedure/therapy is missing, or the start date or end date is completely missing, do not impute.

7.6 Handling of Missing/Partial Dates during Screening Visit

The following rules apply to partially missing dates recorded during the screening visits (e.g. initial diagnosis), If date is completely missing, no imputation is needed:

- If the day of the month is missing, the first day of the month will be used if the year and the month are the same as the first dose of study days. Otherwise, the 15th will be used.
- If the day and month are both missing, the day and month will be assumed to be January 1 when the year is on the year of study treatment. If the year is prior or after the year of first dose date, the date of the first of July will be used, unless other data indicates the date is earlier.

7.7 Handling of Missing/Partial Dates for Prior Anticancer Therapy/Procedures

The following rules will be applied to impute partial dates such as prior systemic anticancer therapy or radiotherapy date (start/end date), or surgery date etc.

Impute end date first. If end date is partially missing, impute as follows:

- If both month and day are missing, then set to December 31

- If only day is missing, then set to the last day of the month
- For prior systemic therapy for cancer, if imputed end date > the first study drug date, then set to the first study drug date
- For prior radiotherapy, if imputed end date > the first study drug date, then set to the first study drug date - 1

If start date is partially missing, impute as follows:

- If both month and day are missing, then set to January 01
- If only day is missing, then set to the first of the month
- If the imputed start date > end date, then set to the end date

If the year of start date or year of end date of a medication/therapy/procedure is missing, or the start date or end date is completely missing, do not impute.

7.8 Handling of Missing/Partial dates for Post-study Anticancer Therapy/Radiotherapy

For records with completely missing start date, end of treatment date will be used as the start date of post-study therapy/radiotherapy. If the start date of post-study anticancer therapy/radiotherapy is partially missing, impute as follows:

- If the day of the month is missing, the start day will be set to the last day of the month unless it is on the same month and year as last dose of the study treatment. In this case, the start date will be assumed to be the last dose date + 1.
- If the day and month are both missing, the start date will be set to January 1st unless it tis on the same year as the last dose date of the study treatment. In this case, the start date will be assumed to be the last dose date + 1.
- If only month is missing, year and day are present, set the missing month to the month of the last dosing date of the study drug unless the day is prior to the last dose day. In this case, impute the missing month as the month of last dose date + 1

No imputation is needed for post-study therapy/radiotherapy end date.

7.9 Handling of Partial Dates for Other Data

Other data with partial dates will be listed as collected. For other calculations of time intervals, the dates will be imputed with the first day of the month (if the day is missing) or with January 1 (if both day and month are missing).

7.10 Handling of Missing Data

Missing data will not be imputed, except for:

- missing date parts, i.e., partial dates, discussed above.
- missing efficacy assessments discussed in Section 9.
- missing AEs relationship to study drug, discussed in Section 12.2.

8. STUDY SUBJECTS

8.1 Subject Enrollment

The number of subjects in each analysis set will be summarized for all patients. Analysis set flag for each subject will be listed together with the dose level and dose schedule for all patients.

8.2 Subjects Disposition

Subjects disposition will be summarized by, dose level and dose schedule, and overall for the Safety Population including:

- Number of subjects in each analysis population
- Number of subjects treated.
- Number of subjects who discontinued RP-1664 and primary reasons of discontinuation.
- Number of subjects who completed the study as per protocol.
- Number of subjects who discontinued study and primary reasons of discontinuation.

The primary reason for treatment discontinuation and study discontinuation will be summarized by categories in eCRF. Subjects' disposition will be listed for the Safety Population.

8.3 Protocol Deviations

Major protocol deviations are protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a patient's rights, safety, or well-being. Protocol deviations will be identified and classified prior to any database snapshot or database lock. Only major and critical protocol deviations will be summarized in a CSR for the Safety Population.

8.4 Demographics and Other Baseline Disease Characteristics

Demographic, baseline characteristics and baseline disease characteristics will be tabulated using descriptive statistics for the Safety Population. The following variables will be included:

- Age at Consent (years)
- Sex at birth
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- BMI (body mass index, kg/m^2), defined as weight (kg) / height $(m)^2$
- ECOG at Screening
- Lansky Performance Status

- Time from initial diagnosis to first dose (Months) and time from diagnosis at Screening to first dose (months), calculate as (Date of Informed Consent – Date of diagnosis + 1)/30.4375
- Tumor types
- Genotypes (TRIM37, Genomically unaltered TP53, RAD51C, PPM1D, BRIP1, RNF43, Chromosome region 17q23, Others)
- Histological Categories (Andenocarcinoma, Squuamous Cell, and other)
- Histology Subtypes (Adrenal and other neuroendocrine histology, central nervous system histology, breast histology, etc)
- Grade at disease diagnosis (Gx, G1, G2, G3, G4, Unknown, Other)
- Time from first presentation of locally advance disease to enrollment (months), calculate as (Date of Informed Consent – Date of diagnosis + 1)/30.4375
- Time from diagnosis of disease to metastasis (months), calculated as (Date of diagnosis for metastatic disease – Date of diagnosis + 1)/30.4375

Conversions for height and weight are as follows:

Height (cm) = Height (inches) x 2.54

Weight (kg) = Weight (lb) x 0.4536

Demographics and baseline disease characteristics will be tabulated and listed in the Safety Population.

8.5 Prior Anti-Cancer Systemic Therapy

Prior Anti-cancer systemic therapy will be summarized, including

- Prior systemic therapy (Yes, No)
- Number of lines of prior systemic therapy
- Time from the most recent prior systemic therapy to the first dose of the study drug (months), calculated as: (Date of first dose of study drug – End date of most recent prior systematic therapy +1)/30.4375
- Best overall response (BOR) from last prior systemic therapy
- Reason for therapy ended from last prior systemic therapy (Completion of therapy as planned, Progressive Disease, Toxicity, Other)

Prior anti-cancer systemic therapy will be summarized and listed for Safety Population.

8.6 Prior Anti-Cancer Radiotherapy

Prior Anti-cancer radiotherapy will be summarized, including

- Prior radiation therapy (Yes, No)
- Radiotherapy Site

- Reason for Administration
- Time from most recent radiotherapy to first dose of the study drug (months), calculated as: (Date of first dose of study drug – End date of most recent prior radiotherapy+1)/30.4375

Prior anti-cancer radiotherapy will be summarized and listed for Safety Population.

8.7 Medical History

Medical history will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) version available.

The frequency count and percentage of subjects experiencing any medical conditions will be tabulated by System Organ Classifications (SOC) and Preferred Term (PT). If a PT or SOC was reported more than once for a subject, the subject would only be counted once in the incidence for that preferred term or system organ class.

Medical history data will be summarized and listed for the Safety Population.

8.8 Prior and Concomitant Medications and Procedures

Prior and concomitant medications and procedures will be coded using the latest World Health Organization Drug (WHODrug) Dictionary version available. Unless specified otherwise, summaries of prior and concomitant medications will be presented by Anatomical Therapeutic Class (ATC) Level 2 and PT with numbers and percentages for subjects in the Safety Population.

A subject who takes more than one medication will be counted only once if these medications belong to the same ATC Level 2 classification.

In the summary tables, prior medications and concomitant medications and procedures will be presented by decreasing frequency of subjects overall within each ATC Level 2 class and then similarly by decreasing frequency of subjects overall within each preferred term. In cases of ATC Level 2 classes or preferred terms with equal frequencies, medications will be sorted alphabetically.

Prior medications/procedures are defined as those medications/procedures that started prior to the first administration of the study drug. Concomitant medications/procedures are defined as those medications/procedures taken on or after the first administration of the study drug till 30 days after the last dose of study treatment, or the start of subsequent anticancer therapy, whichever occurs first.

A prior medication/procedure could also be classified as "both prior and concomitant medication/procedure" if the end date is on or after first dose of study treatment. In the listing, it will be indicated whether a medication is prior-only, concomitant-only, or both prior and concomitant medication.

8.9 Study Drug Exposure and Compliance

RP-1664 exposure will be summarized and grouped by dose level and dose schedule, and overall for overall treatment period and treatment cycles for the Safety Population by the following parameters:

- Duration of treatment (week)
- Number of cycles treated

- Number and percentage of patients treated for 1-2 Cycles, 3-4 Cycles, 5-6 Cycles, 7-8 Cycles, 9-10 Cycles, 11-20 Cycles, >20 Cycles
- Any dose interrupted
- Any dose increases from the initial assigned dose
- Actual cumulative dose
- Actual and Relative dose intensity.

The PK lead-in period (Cycle 0) will not be considered as part of the treatment exposure window for the purpose of exposure analysis.

8.9.1 Duration of Treatment

Duration of treatment will be calculated as:

Duration of treatment (weeks) = (min (last dose date of study drug, death date, data cutoff date) – first dose of study drug +1)/7

For participants who have discontinued study treatment, the last dose date will be used as the treatment end date. For participants with ongoing treatment at the time of data extraction, the data cutoff date will be used.

If a participant has a recorded date of death that precedes both the last dose date and the data cutoff date, the death date will be used as the treatment end date.

8.9.2 Dose Reduction

Dose reduction is defined as 1) decreased in the total daily dose level or, 2) a decrease in the number of consecutive day (e.g., from 2 weeks on/1 week off to 3 days on/4 days off) or weeks (e.g. 2 weeks on/1 week off to 2 weeks on/2 weeks off).

8.9.3 Actual Cumulative Dose

The actual cumulative dose of RP-1664 is defined as the sum of all actual doses administered taking into consideration of any dose change during the study treatment exposure

8.9.4 Actual Dose Intensity

The actual dose intensity (ADI) is defined as the actual cumulative dose during a cycle, calculated as :

$$\text{RP-1664 ADI (mg/cycle)} = \frac{Actual\ Cumulative\ Dose\ (mg)}{\frac{Duration\ of\ exposure\ (days)}{planned\ cycle\ length\ (days/cycle)}}$$

8.9.5 Relative Dose Intensity

The Relative Dose Intensity is defined as the percent dose taken in a cycle, derived as the ADI divided by Planned Dose Intensity (PDI). The PDI is derived as the initial dose of the study drug multiplied by planned number of dosing days per cycle according to the protocol at the start of the planned dose regimen.

Details of study treatment exposure will be listed for Safety Population and swimmer plot for duration of treatment for individual participants by dose level and dose schedule will be presented.

9. EFFICACY ANALYSIS

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12.SAFETY ANALYSIS

12.1 Dose Limiting Toxicities

The number of DLTs will be summarized by treatment arms for the DLT Evaluable Population. A toxicity will be considered a DLT if it occurs from the first dose to the end of Cycle 1 (including the PK evaluation period), meets the pre-defined criteria for DLTs, is deemed at least possibly related to trial treatment, and is not clearly and incontrovertibly due to disease progression or extraneous cause. Toxicity will be assessed using CTCAE v 5.0, unless other specified. Details of DLTs will be listed.

DLTs will be defined as any of the following:

- Any death not clearly due to the underlying disease or extraneous causes

Hematologic TEAES:

- Grade 4 neutropenia
- Febrile neutropenia (defined as absolute neutrophil count (ANC) <1000 cells/µL with a single temperature of 38.3ºC [100.4℉] for > 1 hour).
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia associated with Grade ≥ 2 bleeding.
- Grade 4 anemia or Grade 3 anemia requiring red blood cell (RBC) transfusion given to participants with documented anemia-related symptoms.

Non-Hematologic TEAEs:

- Any Grade ≥ 3 TEAE except the below
    1. Grade ≥ 3 non-hematologic laboratory abnormalities that are asymptomatic and respond to medical intervention or resolve to grade 1 in ≤72 hours.
    2. Grade 3 fatigue with duration < 7 days
    3. Grade ≥ 3 nausea/vomiting/diarrhea that lasts ≤ 72 hours and resolves with or without optimal supportive care.
    4. Grade ≥ 3 amylase or lipase elevation not associated with symptoms or clinical manifestations of pancreatitis.
    5. The use of red blood cell transfusion for anemia Grade <3 or the use of G-CSF for Grade <4 neutropenia
- Symptomatic Grade ≥ 3 QTc prolongation (QTcF ≥ 501 msec on at least two separate electrocardiogram (ECGs)), or asymptomatic Grade ≥ 3 QTc prolongation that has been confirmed by repeat testing and reevaluation by a qualified person and persists after correction of reversible causes such as electrolyte abnormalities or hypoxia.
- Drug-induced liver injury meeting Hy's Law criteria defined as:
    1. ALT or AST ≥3-fold above the Upper Limit of Normal (ULN) or 5.0 x ULN in the case of liver metastases at baseline and
    2. Serum total bilirubin ≥ 2-folde above ULN (without findings of cholestasis) and
    3. Alkaline phosphatase < 2 x ULN and
    4. No other overt reason for liver injury

12.2 Adverse Events

All reported AEs will be coded using the MedDRA with the most current version for the purposes of summarization. NCI CTCAE Version 5.0 will be used for grading AEs. AEs will be collected and recorded for each patient from the day of signing the ICF until 30 days after last trial intervention administration or until participant started alternative anticancer

therapy, whichever is sooner. Prior to receiving trial intervention, only AEs considered related to trial procedures, and all serious adverse events (SAEs) will be summarize by study phase and treatment arms.

A treatment-emergent adverse event (TEAE) will be defined as any event that was not present prior to the initiation of trial intervention(s) or any event that worsens in either intensity or frequency following exposure to trial intervention(s) through 30 days after cessation of trial treatment or until the participant starts alternate anti-cancer therapy, whichever is sooner, with exception of treatment related SAEs which were reported until the end of survival follow-up and will be included as TEAE regardless of time of onset.

All TEAEs reports will summarize by dose levels and dose schedules unless otherwise specified.

Overall TEAE summaries will be presented for the Safety Population. The summaries will include the following categories:

- All TEAEs
- TEAE by CTCAE grade
- TEAEs with CTCAE Grade ≥ 3
- TEAE leading to study treatment discontinuation
- TEAE leading to death
- TEAE related to study treatment
    - TEAEs related to study treatment are defined as ‘definitely related’, ‘probably related’, or ‘possibly related’, to study drug as assessed by the Investigator.
- TEAE related to study treatment with CTCAE Grade ≥ 3
- TEAE related to study treatment leading to treatment discontinuation
- TEAE related to study treatment leading to study treatment interruption
- TEAE related to study treatment leading to study treatment reduction
- TEAE related to study treatment leading to death
- Serious TEAE
- Serious TEAE leading to treatment discontinuation
- Serious TEAE leading to death
- Serious TEAE related to study treatment
- Serious TEAE related to study treatment leading to study treatment discontinuation
- Serious TEAE related to study treatment leading to death

Any missing onset date, causality, or severity must be queried for resolution. Unresolved missing causality will be handled according to the following rules:

An unresolved missing causality will be considered “Related”.

The following summaries by SOC and PT will be sorted by decreasing frequency of subjects within each SOC and then similarly by decreasing frequency of subjects within each PT. In the case of equal frequency of number of subjects in SOCs or PTs, summaries will be sorted descending order.

- TEAEs by SOC and PT
- TEAEs with Grade ≥ 3 by PT
- TEAEs leading to study treatment discontinuation by SOC and PT
- TEAEs leading to death by SOC and PT

- TEAEs by maximum NCI-CTCAE grade by SOC and PT
- Treatment-related TEAEs by SOC and PT
- Treatment-related TEAEs with Grade ≥ 3 by PT
- Treatment-related TEAEs leading to treatment discontinuation by SOC and PT
- Treatment-related TEAEs leading to death by SOC and PT
- Serious TEAEs by SOC and PT
- Most frequent TEAE (>= 10% in total) by PT
- Most frequent treatment-related TEAE (>= 5% in total) by PT

If a SOC or PT was reported more than once for a subject, the subject would only be counted once in the incidence for that SOC or PT.

All AEs will be listed by patient, along with information regarding onset, duration, relationship and severity to study drug, action taken with study drug, treatment of event, and outcome.

12.3 Clinical Laboratory Tests

Selected hematology and serum chemistry parameters including Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Creatinine, Total Bilirubin, Hemoglobin, Neutrophiles and Platelets Count will be summarized for Safety population. All other laboratory results, including pregnancy test results, will be listed only.

For all quantitative parameters, the actual value and the change from baseline by scheduled time of evaluation will be summarized by dose levels and dose schedule for each study visit using descriptive statistics. Both scheduled and unscheduled visits will be considered for baseline derivation.

Laboratory parameters are also graded according to CTCAE v5.0 for the selected parameters listed above. A shift table, presenting the 2-way frequency tabulation for baseline and the worst post-treatment value according to the NCI-CTCAE grade, will be provided. Laboratory parameters with CTCAE grading in both high and low directions will be summarized separately. Both scheduled and unscheduled post-treatment visits will be considered in tabulation of the worst post-treatment value. Additionally, the number and percentage of participants with the following potentially clinically significant abnormal liver function test will be presented:

- ALT >3xULN, ≥5xULN, ≥10xULN, and ≥20xULN
- AST >3xULN, ≥5xULN, ≥10xULN, and ≥20xULN
- Total bilirubin ≥2xULN

12.4 Vital Signs

The observed value and changes from baseline of blood pressure, heart rate, and temperature will be summarized and listed by visit for Safety Population.

12.5 12-lead ECG

Descriptive statistics of actual value and change from baseline value for ECG parameters, including heart rate, PR interval, QRS duration, QT interval, and QTcF interval (Fridericia's corrections) will be presented for baseline visit and scheduled

post-treatment visit. The average of triplicate 12-lead ECG results at each timpoint will be used for descriptive statistics. Standard and triplicate 12-lead ECG data will be listed for each participant and time point for Safety population.

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.

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 patients with data at the relevant timepoints. Timepoints where there are <3 observations at a treatment group will not be presented. All ECG tables and listings will be reported on the safety population.

12.6 Performance Status

ECOG score or Lansky Play-performance score will be presented in listings.

13.INTERIM ANALYSIS

Due to the exploratory nature of this Phase 1 trial, data will be assessed descriptively on an ongoing basis after each dose cohort based on safety and clinical activity information to inform the dose selection. No formal statistical inference will be made to these interim evaluations.

14.APPENDIX

14.1.1 Schedule of Activities

Table 1 Schedule of Activities for Participants Enrolled on 2 Weeks On/1 Week Off Dosing (21-Day Cycles)

	Pre-screening	Screening[a]	Cycle 0									Cycle 1			Cycle 2			Additional Cycles		EOT/ ET[c]	Safety Follow-up Visit[d]	Survival Follow-up[e]
			PK Cycle For Food Effect or PK Bridging Cohorts								PK Cycle[b]											
			Fed (Food Effect) or Formulation 1 (PK Bridging)				Fasted (Food Effect) or Formulation 2 (PK Bridging)				Fasted											
Trial Days **Procedures/ Assessments[f]**	**-180 to -1**	**-28 to -1**	**1[a]**	**2**	**3**	**4**	**5** (+5)	**6**	**7**	**8**	**1[a]**	**1**	**8** (+2)	**15** (+2)	**1** (+3)	**8** (+2)	**15** (+2)	**1** (+3)[g]	**8** (+2)[h]	**Within +7 days of Disc of Trt date**	**30 days after last dose (+14 days)**	**Every 90 days (±14 days)**
Pre-screen informed consent	X																					
Screening/main informed consent		X																				
Inclusion/ exclusion criteria		X	X								X											

	Pre-screening	Screening[a]	Cycle 0									Cycle 1			Cycle 2			Additional Cycles		EOT/ ET[c]	Safety Follow-up Visit[d]	Survival Follow-up[e]
			PK Cycle For Food Effect or PK Bridging Cohorts								PK Cycle[b]											
			Fed (Food Effect) or Formulation 1 (PK Bridging)				Fasted (Food Effect) or Formulation 2 (PK Bridging)				Fasted											
Trial Days **Procedures/ Assessments[f]**	**-180 to -1**	**-28 to -1**	**1[a]**	**2**	**3**	**4**	**5** (+5)	**6**	**7**	**8**	**1[a]**	**1**	**8** (+2)	**15** (+2)	**1** (+3)	**8** (+2)	**15** (+2)	**1** (+3)[g]	**8** (+2)[h]	**Within +7 days of Disc of Trt date**	**30 days after last dose (+14 days)**	**Every 90 days (±14 days)**
Molecular eligibility[i]	X																					
Demographics	X																					
Medical/cancer history		X																				
Physical examination		X	X								X									X		
Abbreviated PE[j]															X[j]			X[j]			X	
Height[k]		X																X[k]				
Weight		X	X								X				X			X		X	X	
Vital sign measurements[l]		X	X								X	X	X	X	X	X	X	X	X[h]	X	X	

	Pre-screening	Screening[a]	Cycle 0									Cycle 1			Cycle 2			Additional Cycles		EOT/ ET[c]	Safety Follow-up Visit[d]	Survival Follow-up[e]
			PK Cycle For Food Effect or PK Bridging Cohorts								PK Cycle[b]											
			Fed (Food Effect) or Formulation 1 (PK Bridging)				Fasted (Food Effect) or Formulation 2 (PK Bridging)				Fasted											
Trial Days **Procedures/ Assessments[f]**	**-180 to -1**	**-28 to -1**	**1[a]**	**2**	**3**	**4**	**5** (+5)	**6**	**7**	**8**	**1[a]**	**1**	**8** (+2)	**15** (+2)	**1** (+3)	**8** (+2)	**15** (+2)	**1** (+3)[g]	**8** (+2)[h]	**Within +7 days of Disc of Trt date**	**30 days after last dose (+14 days)**	**Every 90 days (±14 days)**
ECOG or Lansky performance status		X	X								X				X			X		X	X	
12-lead ECG[m]		X	X				X				X		X		X			X				
Pregnancy test[n]		X	X								X				X			X		X	X	
Clinical safety lab tests[o]		X	X								X				X			X		X	X	
CBC with diff. (included in safety lab tests)													X	X		X	X		X[h]			
ctDNA whole blood[p]		X	X								X		X			X		X[h]	X[h]	X		
Tumor biopsy[q,r,s]		X[q]														X[r]				X[s]		

	Pre-screening	Screening[a]	Cycle 0									Cycle 1			Cycle 2			Additional Cycles		EOT/ ET[c]	Safety Follow-up Visit[d]	Survival Follow-up[e]
			PK Cycle For Food Effect or PK Bridging Cohorts								PK Cycle[b]											
			Fed (Food Effect) or Formulation 1 (PK Bridging)				Fasted (Food Effect) or Formulation 2 (PK Bridging)				Fasted											
Trial Days **Procedures/ Assessments[f]**	**-180 to -1**	**-28 to -1**	**1[a]**	**2**	**3**	**4**	**5** (+5)	**6**	**7**	**8**	**1[a]**	**1**	**8** (+2)	**15** (+2)	**1** (+3)	**8** (+2)	**15** (+2)	**1** (+3)[g]	**8** (+2)[h]	**Within +7 days of Disc of Trt date**	**30 days after last dose (+14 days)**	**Every 90 days (±14 days)**
Central testing for molecular eligibility[t]	X																					
Archival tumor tissue[u]	X[t]	X																				
RP-1664 dispensed/collected			*Dispensed and collected according to Pharmacy Manual*																			
RP-1664 administration[v]			X				X				X	*See Section* ***Error! Reference source not found.****, Dosing and Administration*										
Review of dosing diary[w]												X	X	X	X	X	X	X		X		
PK sample collection[x]			X	X[y]	X[y]	X[y]	X[y]	X[y]	X[y]	X[y]	X[z]	X[z]	X[z]		X[z]	X[z]		X[z]				

	Pre-screening	Screening[a]	Cycle 0									Cycle 1			Cycle 2			Additional Cycles		EOT/ ET[c]	Safety Follow-up Visit[d]	Survival Follow-up[e]
			PK Cycle For Food Effect or PK Bridging Cohorts								PK Cycle[b]											
			Fed (Food Effect) or Formulation 1 (PK Bridging)				Fasted (Food Effect) or Formulation 2 (PK Bridging)				Fasted											
Trial Days **Procedures/ Assessments[f]**	**-180 to -1**	**-28 to -1**	**1[a]**	**2**	**3**	**4**	**5** (+5)	**6**	**7**	**8**	**1[a]**	**1**	**8** (+2)	**15** (+2)	**1** (+3)	**8** (+2)	**15** (+2)	**1** (+3)[g]	**8** (+2)[h]	**Within +7 days of Disc of Trt date**	**30 days after last dose (+14 days)**	**Every 90 days (±14 days)**
Blood collection (4β-OHC/total cholesterol)[aa]		X	X											X		X			X			
Urine collection[bb]							X															
Tumor assessments: RECIST or INRC[cc]		X[dd]										*To be assessed every 6 weeks (±7 days) from Cycle 1 Day 1 for the first 3 tumor assessments. Thereafter, every 9 weeks (±7 days).*										
Serum tumor markers[ee]		X	*To be assessed at least once per cycle from Cycle 0 Day 1 and at EOT (or as per standard of care schedule).*																			
AE assessment		*To be collected from the time of ICF signing; see Section* **Error! Reference source not found.**																				

	Pre-screening	Screening[a]	Cycle 0									Cycle 1			Cycle 2			Additional Cycles		EOT/ ET[c]	Safety Follow-up Visit[d]	Survival Follow-up[e]
			PK Cycle For Food Effect or PK Bridging Cohorts								PK Cycle[b]											
			Fed (Food Effect) or Formulation 1 (PK Bridging)				Fasted (Food Effect) or Formulation 2 (PK Bridging)				Fasted											
Trial Days **Procedures/ Assessments[f]**	**-180 to -1**	**-28 to -1**	**1[a]**	**2**	**3**	**4**	**5** (+5)	**6**	**7**	**8**	**1[a]**	**1**	**8** (+2)	**15** (+2)	**1** (+3)	**8** (+2)	**15** (+2)	**1** (+3)[g]	**8** (+2)[h]	**Within +7 days of Disc of Trt date**	**30 days after last dose (+14 days)**	**Every 90 days (±14 days)**
Concomitant medications/ procedures (transf. and growth factors included)		*To be collected from the time of Screening Visit through the Safety Follow-up visit*																				
Post-trial therapy data collection[ff]																						X
Survival status																						X

AE = adverse event; BID = twice daily; CA-125 = cancer antigen 125, CBC = complete blood count; CT = computed tomography; ctDNA = circulating tumor DNA; CXDX = Cycle X Day X, Disc of Trt = Discontinuation of treatment; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; ET = early termination; FISH = fluorescent in situ hybridization; ICF = informed consent form; INRC = International Neuroblastoma Response Criteria; MRI = magnetic resonance imaging; NGS = next-generation sequencing; OHC = hydroxycholesterol; PE = physical examination; PK = pharmacokinetic; PSA = prostate-specific antigen; QD = once daily; QTcF = Fridericia formula for correct QT interval; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SNP = single nucleotide polymorphism; US = United States

a. **Screening:** Screening Period extends from Day -28 to Day -1. Screening assessments may be used as Cycle 0 Day 1 assessments if performed within 96 hours of the first dose of RP-1664 except for the ctDNA blood draw, vital signs, and ECGs. ECOG or Lansky performance status and PE that are completed within 24 hours of first dose of RP-1664 may be used a Cycle 0 Day 1 assessments. Participants must continue to meet eligibility criteria prior to first dose of RP-1664 on Cycle 0 Day 1.
b. **Cycle 0:** The 2-day PK Cycle 0 is not required for participants in the food effect or PK bridging portion of the trial.
c. **EOT/ET:** A post-treatment/ET visit will be conducted following the last dose of trial intervention and within 7 days after the date of treatment discontinuation but prior to the start of the next anticancer therapy.
d. **Safety Follow-Up:** Required for all participants who discontinued from the trial for whatever reason.
e. **Survival Follow-Up:** Survival follow-up will be conducted approximately every 90 days (±14 days) after date of treatment discontinuation until the end of trial (for up to 6 months), participant withdrawal of consent to trial, or death. This follow-up may be conducted by telephone contact or standard method used by participating centers and agreed by the Sponsor.
f. **Procedures/Assessments:** Pre-screening for molecular eligibility can take place up to 180 days before first dose of RP-1664. Screening procedures and tumor assessment must be performed within 28 days before first dose of RP-1664.
g. **CXD1:** The start of a new additional cycle should always coincide with the start of RP-1664 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 CXD1 visit to enable flexibility with visit scheduling.
h. **Day 8 of Additional Cycles:** CBC and vital signs to be assessed only on C2 and C3. Labs and vital signs can be done locally at these timepoints as long as they are reviewed by the research team on the day of draw. For Cycle 3, ctDNA should be collected on Day 8 and not on Day 1, however for Cycles 4 and up, ctDNA should be collected on Day 1. Blood samples for 4β-OHC and total cholesterol are only collected up to Cycle 3.
[redacted]
j. **Abbreviated PE:** Starting at Cycle 2, abbreviated PE to be performed every 2 cycles (unless full PE necessary by Investigator judgment).
k. **Height:** Pediatric participants will have their height measured every 3 cycles.
l. **Vital Signs:** Blood pressure, heart rate, and temperature to be measured after the participant has been sitting for 5 minutes.
m. **ECG:** 12-lead ECGs to be done in triplicate ≥ 1 minute apart per Table 2. The triplicate ECG measurements must occur within a 30 minute time period. Participants should be in supine position and resting for at least 10 minutes before trial-related ECGs. QTcF should be recorded (QTcB is not required). Participants in the food effect or PK bridging portion of the trial should have ECGs collected per Table 11 and Table 12, respectively.
n. **Pregnancy Test:** For women of childbearing potential, a serum pregnancy test is required at Screening. If pregnancy test was done within 96 hours of Cycle 0 Day 1, repeat testing is not required. A serum or urine pregnancy test must be performed on Day 1 of each cycle starting on Cycle 2, at EOT, and at the Safety Follow-up visit. A pregnancy test can be performed more frequently if required per local regulations.
o. **Clinical Safety Laboratory Tests:** Clinical laboratory tests (including serum or plasma chemistry, hematology [including reticulocyte count], and urinalysis) will be performed at local laboratories according to the laboratory's normal procedures. See Section **Error! Reference source not found.** for a complete listing of laboratory tests to be performed.
[redacted]

q. **Baseline Tumor Biopsy:** If archival tissue does not meet trial requirements, a pre-treatment biopsy during Screening is mandatory. If a biopsy cannot be safely performed, the participant may still be eligible with prior Sponsor approval. If the participant is providing paired biopsies, a pre-treatment and an on-treatment biopsy are mandatory. Biopsy tissue must be shipped to the Sponsor-designated lab during Screening or by Cycle 1 Day 1 (+7 days). 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. *US only:* Participants 12 to 17 years of age are not required to provide a biopsy.

r. **On-treatment Tumor Biopsy**: This assessment applies only to participants providing a paired tumor biopsy. Biopsy should be collected on Cycle 2 Day 8 (+2), 2 to 6 hours after dosing of RP-1664. Participants must have taken a minimum of 7 consecutive days of RP-1664 prior to on-treatment biopsy collection. If biopsy collection at this timepoint is not possible, please contact the Sponsor to schedule an appropriate time for on-treatment biopsy.

s. **Post-Progression Tumor Biopsy:** An optional tumor biopsy will be requested post-progression for participants with prior confirmed responses or stable disease ≥ 16 weeks.

t. [redacted]

[redacted] **Mandatory Archival Tumor Tissue:** Archival tissue is to be submitted to the Sponsor-designated lab during Screening. Refer to Laboratory Manual for further details. If adequate archived tumor tissue is not available and/or a fresh biopsy cannot be safely performed, the participant may still be eligible with prior Sponsor approval. The Sponsor prefers archival material from the primary tumor if available.

v. **RP-1664 Administration:** Cycle 0 dosing should start Monday to Wednesday, if unable to accommodate weekend visits. A +5-day window is allowed prior to initiating the Cycle 0 Day 5 Fasted PK or PK bridging blood collection.

w. **Review of Dosing Diary:** Dosing diary will be reviewed at each participant visit and collected at each CXD1 visit and at EOT. Additional details are in the Pharmacy Manual.

x. [redacted]

bb. **Urine Collection:** Urine collection is only required for participants in the food effect portion of the trial. Urine samples will be collected (0 to 3, 3 to 6, and 6 to 12 hours) while participants are in the clinic on Cycle 0 Day 5.

cc. **Tumor Assessment:** Tumor assessments by disease-appropriate standard criteria (e.g., RECIST v1.1 or INRC) using CT/MRI of known sites of disease as clinically indicated. Tumor assessments must be performed at Screening and every 6 weeks (±7 days) from C1D1 for the first 3 assessments, or sooner if clinically indicated). Thereafter, assessments must be performed every 9 weeks (±7 days). Per RECIST v1.1, complete response or partial response 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 trial treatment or every 9 weeks thereafter). If a participant discontinues treatment for a reason other than radiographic disease progression, withdrawal of consent to trial, lost to follow-up, or death, scans should continue at the specified intervals until progression is confirmed or until start of subsequent anticancer treatment. All radiographic images/scans at the timepoints specified as well as any unscheduled images/scans should be archived by the trial sites for potential future evaluation.

dd. **Tumor Assessment at Screening:** Scans performed prior to signing of the ICF as part of routine clinical management are acceptable for use as baseline tumor imaging if they are of diagnostic quality and performed within 28 days prior to the first dose on Cycle 0 Day 1.

ee. **Serum Tumor Markers:** This assessment applies only to participants with cancers being monitored by circulating tumor markers (e.g., CA-125 or PSA). The baseline assessment should be performed within 96 hours of the first dose on Cycle 0 Day 1. If the assessment is done during Screening prior to this time, it should be repeated within the allotted time frame. It should then be collected on Day 1 of each subsequent cycle starting at Cycle 2, or per standard of care, through end of treatment.

ff. **Post-trial Therapy Data Collection:** All anticancer therapies with start and stop dates should be recorded for 6 months after treatment discontinuation.

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Table 3: Schedule of Activities for Participants Enrolled on a 3 Days On/4 Days Off Dosing (RP-1664 Days 1-3, 8-10, 15-17: 21-Day Cycles; if Needed)

	Pre-screening	Screening[a]	Cycle 0										Cycle 1			Cycle 2				Additional Cycles		EOT/ ET[c]	Safety Follow-up Visit[d]	Survival Follow-up[e]
			PK Cycle for Food Effect or PK Bridging Cohorts								PK Cycle[b]													
			Fed (Food Effect) or Formulation 1 (PK Bridging)				Fasted (Food Effect) or Formulation 2 (PK Bridging)				Fasted													
Trial Days	**-180 to -1**	**-28 to -1**	**1[a]**	**2**	**3**	**4**	**5** (+5)	**6**	**7**	**8**	**1[a]**	**2**	**1**	**8** (+2)	**15** (+2)	**1** (+1)	**3**	**10** (+2)[g]	**17** (-1)	**1** (+3)[h]	**8** (+2)[i]	**Within +7 days of Disc of Trt date**	**30 days after last dose (+14 days)**	**Every 90 days (±14 days)**
Procedures/ Assessments[f]																								
Pre-screen informed consent	X																							
Screening/main informed consent		X																						
Inclusion/ exclusion criteria		X	X								X													
Molecular eligibility[j]	X																							
Demographics	X																							
Medical/cancer history		X																						
Physical examination		X	X								X											X		

	Pre-screening	Screening[a]	Cycle 0										Cycle 1			Cycle 2				Additional Cycles		EOT/ ET[c]	Safety Follow-up Visit[d]	Survival Follow-up[e]
			PK Cycle for Food Effect or PK Bridging Cohorts								PK Cycle[b]													
			Fed (Food Effect) or Formulation 1 (PK Bridging)				Fasted (Food Effect) or Formulation 2 (PK Bridging)				Fasted													
Trial Days **Procedures/ Assessments[f]**	**-180 to -1**	**-28 to -1**	**1[a]**	**2**	**3**	**4**	**5** (+5)	**6**	**7**	**8**	**1[a]**	**2**	**1**	**8** (+2)	**15** (+2)	**1** (+1)	**3**	**10** (+2)[g]	**17** (-1)	**1** (+3)[h]	**8** (+2)[i]	**Within +7 days of Disc of Trt date**	**30 days after last dose (+14 days)**	**Every 90 days (±14 days)**
Abbreviated PE[k]																X[k]				X[k]			X	
Height[l]		X																		X[l]				
Weight		X	X								X					X				X		X	X	
Vital sign measurements[m]		X	X								X		X	X	X	X		X	X	X	X[i]	X	X	
ECOG or Lansky performance status		X									X					X				X		X	X	
12-lead ECG[n]		X	X				X				X			X			X			X				
Pregnancy test[o]		X	X								X					X				X		X	X	
Clinical safety lab tests[p]		X	X								X					X				X		X	X	
CBC with diff (included in safety lab tests)														X	X			X	X		X[i]			
ctDNA whole blood[q]		X	X								X				X				X	X	X[i]	X		

	Pre-screening	Screening[a]	Cycle 0										Cycle 1			Cycle 2				Additional Cycles		EOT/ ET[c]	Safety Follow-up Visit[d]	Survival Follow-up[e]
			PK Cycle for Food Effect or PK Bridging Cohorts								PK Cycle[b]													
			Fed (Food Effect) or Formulation 1 (PK Bridging)				Fasted (Food Effect) or Formulation 2 (PK Bridging)				Fasted													
Trial Days **Procedures/ Assessments[f]**	**-180 to -1**	**-28 to -1**	**1[a]**	**2**	**3**	**4**	**5** (+5)	**6**	**7**	**8**	**1[a]**	**2**	**1**	**8** (+2)	**15** (+2)	**1** (+1)	**3**	**10** (+2)[g]	**17** (-1)	**1** (+3)[h]	**8** (+2)[i]	**Within +7 days of Disc of Trt date**	**30 days after last dose (+14 days)**	**Every 90 days (±14 days)**
Tumor biopsy[r,s,t]		X[r]																	X[s]			X[t]		
Central testing for molecular eligibility[u]	X																							
Archival tumor tissue[v]	X[u]	X																						
RP-1664 dispensed/collected			*Dispensed and collected according to Pharmacy Manual*																					
RP-1664 administration[w]			X				X				X		*See Section* ***Error! Reference source not found.****, Dosing and Administration*											
Review of dosing diary[x]													X	X	X	X		X	X	X		X		
PK sample collection[y]			X	X[z]	X[z]	X[z]	X[z]	X[z]	X[z]	X[z]	X[a,a]	X[aa]	X[a,a]	X[aa]			X[a,a]		X[aa]	X[aa]				
Blood collection (4β-OHC/total cholesterol)[bb]		X	X												X		X	X			X			

	Pre-screening	Screening[a]	Cycle 0										Cycle 1			Cycle 2				Additional Cycles		EOT/ ET[c]	Safety Follow-up Visit[d]	Survival Follow-up[e]
			PK Cycle for Food Effect or PK Bridging Cohorts								PK Cycle[b]													
			Fed (Food Effect) or Formulation 1 (PK Bridging)				Fasted (Food Effect) or Formulation 2 (PK Bridging)				Fasted													
Trial Days **Procedures/ Assessments[f]**	**-180 to -1**	**-28 to -1**	**1[a]**	**2**	**3**	**4**	**5** (+5)	**6**	**7**	**8**	**1[a]**	**2**	**1**	**8** (+2)	**15** (+2)	**1** (+1)	**3**	**10** (+2)[g]	**17** (-1)	**1** (+3)[h]	**8** (+2)[i]	**Within +7 days of Disc of Trt date**	**30 days after last dose (+14 days)**	**Every 90 days (±14 days)**
Urine collection[cc]							X																	
Tumor assessments: RECIST or INRC[dd]		X[ee]											*To be assessed every 6 weeks (±7 days) from Cycle 1 Day 1 for the first 3 tumor assessments. Thereafter, every 9 weeks (±7 days).*														
Serum tumor markers[ff]		X	*To be assessed at least once per cycle from Cycle 0 Day 1 and at EOT (or as per standard of care schedule).*																					
AE assessment		*To be collected from the time of ICF signing; see Section* **Error! Reference source not found.**																						
Concomitant medications/ procedures (transf. and growth factors included)		*To be collected from the time of Screening Visit through the Safety Follow-up visit*																						
Post-trial therapy data collection[gg]																								X
Survival status																								X

AE = adverse event; BID = twice daily; CA-125 = cancer antigen 125, CBC = complete blood count; CT = computed tomography; ctDNA = circulating tumor DNA; CXDX = Cycle X Day X, Disc of Trt = Discontinuation of treatment; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; ET = early termination; FISH = fluorescent in situ hybridization; ICF = informed consent form; INRC = International Neuroblastoma Response Criteria; MRI = magnetic resonance imaging; NGS = next-generation sequencing; OHC = hydroxycholesterol; PE = physical examination; PK = pharmacokinetic; PSA = prostate-specific antigen; QD = once daily; QTcF = Fridericia formula for correct QT interval; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SNP = single nucleotide polymorphism; US = United States

a. **Screening:** Screening Period extends from Day -28 to Day -1. Screening assessments may be used as Cycle 0 Day 1 assessments if performed within 96 hours of the first dose of RP-1664, except for the ctDNA blood draw, vital signs, and ECGs. ECOG or Lansky performance status and PE that are completed within 24 hours of first dose of RP-1664 may be used as Cycle 0 Day 1 assessments. Participants must continue to meet eligibility criteria prior to first dose of RP-1664 on Cycle 0 Day 1.
b. **Cycle 0:** The 2-day PK Cycle 0 is not required for participants in the food effect or PK bridging portion of the trial.
c. **EOT/ET:** A post-treatment/ET visit will be conducted following the last dose of trial intervention and within 7 days after the date of treatment discontinuation but prior to the start of the next anticancer therapy.
d. **Safety Follow-Up:** Required for all participants who discontinued from the trial for whatever reason.
e. **Survival Follow-Up:** Survival follow-up will be conducted approximately every 90 days (±14 days) after date of treatment discontinuation until the end of trial (for up to 6 months), participant withdrawal of consent to trial, or death. This follow-up may be conducted by telephone contact or standard method used by participating centers and agreed by the Sponsor.
f. **Procedures/Assessments:** Pre-screening for molecular eligibility can take place up to 180 days before first dose of RP-1664. Screening procedures and tumor assessment must be performed within 28 days before first dose of RP-1664.
g. **Day 10 of Cycle 2:** Labs and vital signs can be done locally at these timepoints as long as they are reviewed by the research team on the day of draw.
h. **CXD1:** The start of a new additional cycle should always coincide with the start of trial 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 CXD1 visit to enable flexibility with visit scheduling.
i. **Day 8 of Additional Cycles:** CBC and vital signs to be assessed only on C3D8 and not thereafter. Labs and vital signs can be done locally as long as they are reviewed by the research team on the day of draw. For Cycle 3, ctDNA should be collected on Day 8 and not on Day 1, however for Cycles 4 and up, ctDNA should be collected on Day 1. Blood samples for 4β-OHC and total cholesterol are only collected up to Cycle 3.
j. **Molecular Eligibility:** NGS, FISH, or SNP microarray reports will be emailed for central review to confirm molecular eligibility or determine if additional testing is required.
k. **Abbreviated PE:** Starting at Cycle 2, abbreviated PE to be performed every 2 cycles (unless full PE necessary by Investigator judgment).
l. **Height:** Pediatric participants will have their height measured every 3 cycles.
m. **Vital Signs:** Blood pressure, heart rate, and temperature to be measured after the participant has been sitting for 5 minutes.
n. **ECG:** 12-lead ECGs to be done in triplicate ≥ 1 minute apart per Table 4. The triplicate ECG measurements must occur within a 30 minute time period. Participants should be in supine position and resting for at least 10 minutes before trial-related ECGs. QTcF should be recorded (QTcB is not required). Participants in the food effect or PK bridging portion of the trial should have ECGs collected per Table 11 and Table 12, respectively.
o. **Pregnancy Test**: For women of childbearing potential, a serum pregnancy test is required at Screening. If pregnancy test was done within 96 hours of Cycle 0 Day 1, repeat testing is not required. A serum or urine pregnancy test must be performed on Day 1 of each cycle starting on Cycle 2, at EOT, and at Safety Follow-up visit. A pregnancy test can be performed more frequently if required per local regulations.

p. **Clinical Safety Laboratory Tests:** Clinical laboratory tests (including serum or plasma chemistry, hematology [including reticulocyte count], and urinalysis) will be performed at local laboratories according to the laboratory's normal procedures. See Section **Error! Reference source not found.** for a complete listing of laboratory tests to be performed.

q. [redacted].

r. **Baseline Tumor Biopsy:** If archival tissue does not meet trial requirements, a pre-treatment biopsy is mandatory prior to enrollment. If the participant is participating in the paired biopsy, a pre-treatment and an on-treatment biopsy are mandatory. Biopsy tissue must be shipped to the Sponsor-designated lab during Screening or by Cycle 1 Day 1 (+7 days). 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. *US only:* Participants 12 to 17 years of age are not required to provide a biopsy.

s. **On-treatment Tumor Biopsy**: This assessment applies only to participants providing a paired biopsy. Biopsy should be collected on Cycle 2 Day 17, 2 to 6 hours after dosing of RP-1664. If biopsy collection at this timepoint is not possible, please contact the Sponsor to schedule an appropriate time for on-treatment biopsy.

t. **Post-Progression Tumor Biopsy:** An optional tumor biopsy will be requested post-progression for participants with prior confirmed responses or stable disease ≥ 16 weeks.

u. [redacted].

[redacted]. **Mandatory Archival Tumor Tissue:** Archival tissue is to be submitted to the Sponsor-designated lab during Screening. Refer to Laboratory Manual for further details. If adequate archived tumor tissue is not available and/or a fresh biopsy cannot be safely performed, the participant may still be eligible with prior Sponsor approval. The Sponsor prefers archival material from the primary tumor if available.

w. **RP-1664 Administration:** Cycle 0 dosing should start Monday to Wednesday, if unable to accommodate weekend visits. A +5-day window is allowed prior to initiating the Cycle 0 Day 5 Fasted PK or PK bridging blood collection.

x. **Review of Dosing Diary:** Dosing diary will be reviewed at each participant visit and collected at each CXD1 visit and at EOT. Additional details are in the Pharmacy Manual.

y. [redacted]

bb. [redacted]

[redacted]. **Urine Collection:** Urine collection is only required for participants in the food effect portion of the trial. Urine samples will be collected (0 to 3, 3 to 6, and 6 to 12 hours) while participants are in the clinic on Cycle 0 Day 5.

dd. **Tumor Assessment:** Tumor assessments by disease-appropriate standard criteria (e.g., RECIST v1.1 or INRC) using CT/MRI of known sites of disease as clinically indicated. Tumor assessments must be performed at Screening and every 6 weeks (±7 days) from C1D1 for the first 3 assessments, or sooner if clinically indicated). Thereafter, assessments must be performed every 9 weeks (±7 days). Per RECIST v1.1, complete response or partial response 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 trial treatment or every 9 weeks thereafter). If a participant discontinues treatment for a reason other than radiographic disease progression, withdrawal of consent to trial, lost to follow-up, or death, scans should continue at the specified intervals until progression is confirmed or until start of subsequent anticancer treatment. All radiographic images/scans at the timepoints specified as well as any unscheduled images/scans should be archived by the trial sites for potential future evaluation.

ee. **Tumor Assessment at Screening**: Scans performed prior to signing of the ICF as part of routine clinical management are acceptable for use as baseline tumor imaging if they are of diagnostic quality and performed within 28 days prior to the first dose on Cycle 0 Day 1.

ff. **Serum Tumor Markers:** This assessment applies only to participants with cancers being monitored by circulating tumor markers (e.g., CA-125 or PSA). The baseline assessment should be performed within 96 hours of the first dose on Cycle 0 Day 1. If the assessment is done during Screening prior to this time, it should be repeated within the allotted time frame. It should then be collected on Day 1 of each subsequent cycle starting at Cycle 2, or per standard of care, through end of treatment.

gg. **Post-trial Therapy Data Collection:** All anticancer therapies with start and stop dates should be recorded for 6 months after treatment discontinuation

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Table 5: Schedule of Activities for Participants Enrolled on Daily Dosing (21-Day Cycles; if needed)

	Pre-screening	Screening[a]	Cycle 0										Cycle 1			Cycle 2			Additional Cycles		EOT/ ET[c]	Safety Follow-up Visit[d]	Survival Follow-up[e]
			PK Cycle for Food Effect or PK Bridging Cohorts								PK Cycle[b]												
			Fed (Food Effect) or Formulation 1 (PK Bridging)				Fasted (Food Effect) or Formulation 2 (PK Bridging)				Fasted												
Trial Days **Procedures/ Assessments[f]**	**-180 to -1**	**-28 to -1**	**1[a]**	**2**	**3**	**4**	**5 (+5)**	**6**	**7**	**8**	**1[a]**	**2**	**1**	**8 (+2)**	**15 (+2)**	**1 (+3)**	**8 (+2)**	**15 (+2)**	**1 (+3)[g]**	**8 (+2)[h]**	**Within +7 days of Disc of Trt date**	**30 days after last dose (+14 days)**	**Every 90 days (±14 days)**
Pre-screen informed consent	X																						
Screening/main informed consent		X																					
Inclusion/ exclusion criteria		X	X								X												
Molecular eligibility[i]	X																						
Demographics	X																						
Medical/cancer history		X																					
Physical examination		X	X								X										X		
Abbreviated PE[j]																X[j]			X[j]			X	
Height[k]		X																	X[k]				
Weight		X	X								X					X			X		X	X	

	Pre-screening	Screening[a]	Cycle 0										Cycle 1			Cycle 2			Additional Cycles		EOT/ ET[c]	Safety Follow-up Visit[d]	Survival Follow-up[e]
			PK Cycle for Food Effect or PK Bridging Cohorts								PK Cycle[b]												
			Fed (Food Effect) or Formulation 1 (PK Bridging)				Fasted (Food Effect) or Formulation 2 (PK Bridging)				Fasted												
Trial Days **Procedures/ Assessments[f]**	**-180 to -1**	**-28 to -1**	**1[a]**	**2**	**3**	**4**	**5 (+5)**	**6**	**7**	**8**	**1[a]**	**2**	**1**	**8 (+2)**	**15 (+2)**	**1 (+3)**	**8 (+2)**	**15 (+2)**	**1 (+3)[g]**	**8 (+2)[h]**	**Within +7 days of Disc of Trt date**	**30 days after last dose (+14 days)**	**Every 90 days (±14 days)**
Vital sign measurements[l]		X	X								X		X	X	X	X	X	X	X	X[h]	X	X	
ECOG or Lansky performance status		X									X					X			X		X	X	
12-lead ECG[m]		X	X				X				X			X		X			X				
Pregnancy test[n]		X	X								X					X			X		X	X	
Clinical safety lab tests[o]		X	X								X					X			X		X	X	
CBC with diff. (included in safety lab tests)														X	X		X	X		X[h]			
ctDNA whole blood[p]		X	X								X				X		X		X[h]	X[h]	X		
Tumor biopsy[q,r,s]		X[q]															X[r]				X[s]		
Central testing for molecular eligibility[t]	X																						

	Pre-screening	Screening[a]	Cycle 0										Cycle 1			Cycle 2			Additional Cycles		EOT/ ET[c]	Safety Follow-up Visit[d]	Survival Follow-up[e]
			PK Cycle for Food Effect or PK Bridging Cohorts								PK Cycle[b]												
			Fed (Food Effect) or Formulation 1 (PK Bridging)				Fasted (Food Effect) or Formulation 2 (PK Bridging)				Fasted												
Trial Days **Procedures/ Assessments[f]**	**-180 to -1**	**-28 to -1**	**1[a]**	**2**	**3**	**4**	**5 (+5)**	**6**	**7**	**8**	**1[a]**	**2**	**1**	**8 (+2)**	**15 (+2)**	**1 (+3)**	**8 (+2)**	**15 (+2)**	**1 (+3)[g]**	**8 (+2)[h]**	**Within +7 days of Disc of Trt date**	**30 days after last dose (+14 days)**	**Every 90 days (±14 days)**
Archival tumor tissue[u]	X[t]	X																					
RP-1664 dispensed/collected			*Dispensed and collected according to Pharmacy Manual*																				
RP-1664 administration[v]			X				X				X		*See Section **Error! Reference source not found.**, Dosing and Administration*										
Review of dosing diary[w]													X	X	X	X	X	X	X		X		
PK sample collection[x]			X	X[y]	X[y]	X[y]	X[y]	X[y]	X[y]	X[y]	X[z]	X[z]	X[z]	X[z]		X[z]	X[z]		X[z]				
Blood collection (4β-OHC/total cholesterol)[aa]		X	X												X		X			X			
Urine collection[bb]							X																
Tumor assessments: RECIST or INRC[cc]		X[dd]											*To be assessed every 6 weeks (±7 days) from Cycle 1 Day 1 for the first 3 tumor assessments. Thereafter, every 9 weeks (±7 days)*											

	Pre-screening	Screening[a]	Cycle 0										Cycle 1			Cycle 2			Additional Cycles		EOT/ ET[c]	Safety Follow-up Visit[d]	Survival Follow-up[e]
			PK Cycle for Food Effect or PK Bridging Cohorts								PK Cycle[b]												
			Fed (Food Effect) or Formulation 1 (PK Bridging)				Fasted (Food Effect) or Formulation 2 (PK Bridging)				Fasted												
Trial Days **Procedures/ Assessments[f]**	**-180 to -1**	**-28 to -1**	**1[a]**	**2**	**3**	**4**	**5 (+5)**	**6**	**7**	**8**	**1[a]**	**2**	**1**	**8 (+2)**	**15 (+2)**	**1 (+3)**	**8 (+2)**	**15 (+2)**	**1 (+3)[g]**	**8 (+2)[h]**	**Within +7 days of Disc of Trt date**	**30 days after last dose (+14 days)**	**Every 90 days (±14 days)**
Serum tumor markers[ee]		X	*To be assessed at least once per cycle from Cycle 0 Day 1 and at EOT (or as per standard of care schedule).*																				
AE assessment		*To be collected from the time of ICF signing; see Section* **Error! Reference source not found.**																					
Concomitant medications/ Procedures (transf. and growth factors included)		*To be collected from the time of Screening Visit through the Safety Follow-up visit*																					
Post-trial therapy data collection[ff]																							X
Survival status																							X

AE = adverse event; BID = twice daily; CA-125 = cancer antigen 125, CBC = complete blood count; CT = computed tomography; ctDNA = circulating tumor DNA; CXDX = Cycle X Day X, Disc of Trt = Discontinuation of treatment; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; ET = early termination; FISH = fluorescent in situ hybridization; ICF = informed consent form; INRC = International Neuroblastoma Response Criteria; MRI = magnetic resonance imaging; NGS = next-generation sequencing; OHC = hydroxycholesterol; PE = physical examination; PK = pharmacokinetic; PSA = prostate-specific antigen; QD = once daily; QTcF = Fridericia formula for correct QT interval; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SNP = single nucleotide polymorphism; US = United States

a. **Screening:** Screening Period extends from Day -28 to Day -1. Screening assessments may be used as Cycle 0 Day 1 assessments if performed within 96 hours of the first dose of RP-1664, except for the ctDNA blood draw, vital signs, and ECGs. ECOG or Lansky performance status and PE that are completed within 24 hours of first dose of RP-1664 may be used as Cycle 0 Day 1 assessments. Participants must continue to meet eligibility criteria prior to first dose of RP-1664 on Cycle 0 Day 1.
b. **Cycle 0:** The 2-day PK Cycle 0 is not required for participants in the food effect or PK bridging portion of the trial.
c. **EOT/ET:** A post-treatment/ET visit will be conducted following the last dose of trial intervention and within 7 days after the date of treatment discontinuation but prior to the start of the next anticancer therapy.
d. **Safety Follow-Up:** Required for all participants who discontinued from the trial for whatever reason.
e. **Survival Follow-Up:** Survival follow-up will be conducted approximately every 90 days (±14 days) after date of treatment discontinuation until the end of trial (for up to 6 months), participant withdrawal of consent to trial, or death. This follow-up may be conducted by telephone contact or standard method used by participating centers and agreed by the Sponsor.
f. **Procedures/Assessments:** Pre-screening for molecular eligibility can take place up to 180 days before first dose of RP-1664. Screening procedures and tumor assessment must be performed within 28 days before first dose of RP-1664.
g. **CXD1:** The start of a new additional cycle should always coincide with the start of trial 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 CXD1 visit to enable flexibility with visit scheduling.
h. **Day 8 of Additional Cycles:** CBC and vital signs to be assessed only on C2 and C3. Labs and vital signs can be done locally at these timepoints as long as they are reviewed by the research team on the day of draw. For Cycle 3, ctDNA should be collected on Day 8 and not on Day 1, however for Cycles 4 and up, ctDNA should be collected on Day 1. Blood samples for 4β-OHC and total cholesterol are only collected up to Cycle 3.
i. **Molecular Eligibility:** NGS, FISH, or SNP microarray reports will be emailed for central review to confirm molecular eligibility or determine if additional testing is required.
j. **Abbreviated PE:** Starting at Cycle 2, abbreviated PE to be performed every 2 cycles (unless full PE necessary by Investigator judgment).
k. **Height:** Pediatric participants will have their height measured every 3 cycles.
l. **Vital Signs:** Blood pressure, heart rate, and temperature to be measured after the participant has been sitting for 5 minutes.
m. **ECG:** 12-lead ECGs to be done in triplicate ≥ 1 minute apart per Table 6. The triplicate ECG measurements must occur within a 30 minute time period. Participants should be in supine position and resting for at least 10 minutes before trial-related ECGs. QTcF should be recorded (QTcB is not required). Participants in the food effect portion and PK bridging portionof the trial should have ECGs collected per Table 11 and Table 12, respectively.
n. **Pregnancy Test:** For women of childbearing potential, a serum pregnancy test is required at Screening. If pregnancy test was done within 96 hours of Cycle 0 Day 1, repeat testing is not required. A serum or urine pregnancy test must be performed on Day 1 of each cycle starting on Cycle 2, at EOT, and at the Safety Follow-up visit. A pregnancy test can be performed more frequently if required per local regulations.
o. **Clinical Safety Laboratory Tests:** Clinical laboratory tests (including serum or plasma chemistry, hematology [including reticulocyte count], and urinalysis) will be performed at local laboratories according to the laboratory's normal procedures. See Section **Error! Reference source not found.** for a complete listing of laboratory tests to be performed.
p. **ctDNA Whole Blood:** Blood can be collected either pre- or post-dose for all timepoints except for Cycle 0 Day 1 which must be collected predose. After Cycle 4, if CXD1 was delayed (eg due to an AE), ctDNA sample should be collected at actual cycle visit. For visits prior to Cycle 4, if CXDX is delayed, ctDNA should be collected both at planned and actual cycle visit. Please refer to Lab Manual for guidance on sample collection.

q. **Baseline Tumor Biopsy:** If archival tissue does not meet trial requirements, a pre-treatment biopsy during Screening is mandatory. If a biopsy cannot be safely performed, the participant may still be eligible with prior Sponsor approval. If the participant is providing paired biopsies, a pre-treatment and an on-treatment biopsy are mandatory. Biopsy tissue must be shipped to the Sponsor-designated lab during Screening or by Cycle 1 Day 1 (+7 days). 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. *US only:* Participants 12 to 17 years of age are not required to provide a biopsy.

r. **On-treatment Tumor Biopsy**: This assessment applies only to participants providing a paired biopsy. Biopsy should be collected on Cycle 2 Day 8 (+2), 2 to 6 hours after dosing of RP-1664. Participants must have taken a minimum of 7 consecutive days of RP-1664 prior to on-treatment biopsy collection. If biopsy collection at this timepoint is not possible, please contact the Sponsor to schedule an appropriate time for on-treatment biopsy.

s. **Post-Progression Tumor Biopsy:** An optional tumor biopsy will be requested post-progression for participants with prior confirmed responses or stable disease ≥ 16 weeks.

t. [redacted]

u. **Mandatory Archival Tumor Tissue:** Archival tissue is to be submitted to the Sponsor-designated lab during Screening. Refer to Laboratory Manual for further details. If adequate archived tumor tissue is not available and/or a fresh biopsy cannot be safely performed, the participant may still be eligible with prior Sponsor approval. The Sponsor prefers archival material from the primary tumor if available.

v. **RP-1664 Administration:** Cycle 0 dosing should start Monday to Wednesday, if unable to accommodate weekend visits. A +5-day window is allowed prior to initiating the Cycle 0 Day 5 Fasted PK or PK bridging blood collection.

w. **Review of Dosing Diary:** Dosing diary will be reviewed at each participant visit and collected at each CXD1 visit and at EOT. Additional details are in the Pharmacy Manual.

x. [redacted]

bb. **Urine Collection:** Urine collection is only required for participants in the food effect portion of the trial. Urine samples will be collected (0 to 3, 3 to 6, and 6 to 12 hours) while participants are in the clinic on Cycle 0 Day 5.

cc. **Tumor Assessment:** Tumor assessments by disease-appropriate standard criteria (e.g., RECIST v1.1 or INRC) using CT/MRI of known sites of disease as clinically indicated. Tumor assessments must be performed at Screening and every 6 weeks (±7 days) from C1D1 for the first 3 assessments, or sooner if clinically indicated). Thereafter, assessments must be performed every 9 weeks (±7 days). Per RECIST v1.1, complete response or partial response 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 trial treatment or every 9 weeks thereafter). If a participant discontinues treatment for a reason other than radiographic disease progression, withdrawal of consent to trial, lost to follow-up, or death, scans should continue at the specified intervals until progression is confirmed or until start of subsequent anticancer treatment. All radiographic images/scans at the timepoints specified as well as any unscheduled images/scans should be archived by the trial sites for potential future evaluation.

dd. **Tumor Assessment at Screening:** Scans performed prior to signing of the ICF as part of routine clinical management are acceptable for use as baseline tumor imaging if they are of diagnostic quality and performed within 28 days prior to the first dose on Cycle 0 Day 1.

ee. **Serum Tumor Markers:** This assessment applies only to participants with cancers being monitored by circulating tumor markers (e.g., CA-125 or PSA). The baseline assessment should be performed within 96 hours of the first dose on Cycle 0 Day 1. If the assessment is done during Screening prior to this time, it should be repeated within the allotted time frame. It should then be collected on Day 1 of each subsequent cycle starting at Cycle 2, or per standard of care, through EOT.

ff. **Post-trial Therapy Data Collection:** All anticancer therapies with start and stop dates should be recorded for 6 months after treatment discontinuation.

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Table 7: Schedule of Activities for Participants Enrolled on 1 Week On/1 Week Off Dosing (28-Day Cycles, if Needed)

	Pre-screening	Screening[a]	Cycle 0										Cycle 1				Cycle 2			Additional Cycles		EOT/ ET[c]	Safety Follow-up Visit[d]	Survival Follow-up[e]
			PK Cycle For Food Effect or PK Bridging Cohorts								PK Cycle[b]													
			Fed (Food Effect) or Formulation 1 (PK Bridging)				Fasted (Food Effect) or Formulation 2 (PK Bridging)				Fasted													
Trial Days **Procedures/ Assessments[f]**	**-180 to -1**	**-28 to -1**	**1[a]**	**2**	**3**	**4**	**5 (+5)**	**6**	**7**	**8**	**1[a]**	**2**	**1**	**7 (-1)**	**15 (+2)**	**22 (+2)**	**1 (+3)**	**7 (-1)**	**17 (+2)**	**1 (+3)[g]**	**15 (+2)[h]**	**Within +7 days of Disc of Trt date**	**30 days after last dose (+14 days)**	**Every 90 days (±14 days)**
Pre-screen informed consent	X																							
Screening/main informed consent		X																						
Inclusion/ exclusion criteria		X	X								X													
Molecular eligibility[i]	X																							
Demographics	X																							
Medical/cancer history		X																						

	Pre-screening	Screening[a]	Cycle 0										Cycle 1				Cycle 2			Additional Cycles		EOT/ ET[c]	Safety Follow-up Visit[d]	Survival Follow-up[e]
			PK Cycle For Food Effect or PK Bridging Cohorts								PK Cycle[b]													
			Fed (Food Effect) or Formulation 1 (PK Bridging)				Fasted (Food Effect) or Formulation 2 (PK Bridging)				Fasted													
Trial Days **Procedures/ Assessments[f]**	**-180 to -1**	**-28 to -1**	**1[a]**	**2**	**3**	**4**	**5 (+5)**	**6**	**7**	**8**	**1[a]**	**2**	**1**	**7 (-1)**	**15 (+2)**	**22 (+2)**	**1 (+3)**	**7 (-1)**	**17 (+2)**	**1 (+3)[g]**	**15 (+2)[h]**	**Within +7 days of Disc of Trt date**	**30 days after last dose (+14 days)**	**Every 90 days (±14 days)**
Physical examination		X	X								X											X		
Abbreviated PE[j]																	X			X[j]			X	
Height[k]		X																		X[k]				
Weight		X	X								X						X			X		X	X	
Vital sign measurements[l]		X	X								X		X	X	X	X	X	X	X	X	X[h]	X	X	
ECOG or Lansky performance status		X									X						X			X		X	X	
12-lead ECG[m]		X	X				X				X			X			X			X				
Pregnancy test[n]		X	X								X						X			X		X	X	
Clinical safety lab tests[o]		X	X								X						X			X		X	X	

	Pre-screening	Screening[a]	Cycle 0										Cycle 1				Cycle 2			Additional Cycles		EOT/ ET[c]	Safety Follow-up Visit[d]	Survival Follow-up[e]
			PK Cycle For Food Effect or PK Bridging Cohorts								PK Cycle[b]													
			Fed (Food Effect) or Formulation 1 (PK Bridging)				Fasted (Food Effect) or Formulation 2 (PK Bridging)				Fasted													
Trial Days **Procedures/ Assessments[f]**	**-180 to -1**	**-28 to -1**	**1[a]**	**2**	**3**	**4**	**5 (+5)**	**6**	**7**	**8**	**1[a]**	**2**	**1**	**7 (-1)**	**15 (+2)**	**22 (+2)**	**1 (+3)**	**7 (-1)**	**17 (+2)**	**1 (+3)[g]**	**15 (+2)[h]**	**Within +7 days of Disc of Trt date**	**30 days after last dose (+14 days)**	**Every 90 days (±14 days)**
CBC with diff. (included in safety lab tests)														X	X	X		X	X		X[h]			
ctDNA whole blood[p]		X	X								X				X			X		X[h]	X[h]	X		
Tumor biopsy[q,r,s]		X[q]																X[r]				X[s]		
Central testing for molecular eligibility[t]	X																							
Archival tumor tissue[u]	X[t]	X[t]																						
RP-1664 dispensed/collected			*Dispensed and collected according to Pharmacy Manual*																					
RP-1664 administration[v]			X				X				X		*See Section* ***Error! Reference source not found.****, Dosing and Administration*											

	Pre-screening	Screening[a]	Cycle 0										Cycle 1				Cycle 2			Additional Cycles		EOT/ ET[c]	Safety Follow-up Visit[d]	Survival Follow-up[e]
			PK Cycle For Food Effect or PK Bridging Cohorts								PK Cycle[b]													
			Fed (Food Effect) or Formulation 1 (PK Bridging)				Fasted (Food Effect) or Formulation 2 (PK Bridging)				Fasted													
Trial Days **Procedures/ Assessments[f]**	**-180 to -1**	**-28 to -1**	**1[a]**	**2**	**3**	**4**	**5 (+5)**	**6**	**7**	**8**	**1[a]**	**2**	**1**	**7 (-1)**	**15 (+2)**	**22 (+2)**	**1 (+3)**	**7 (-1)**	**17 (+2)**	**1 (+3)[g]**	**15 (+2)[h]**	**Within +7 days of Disc of Trt date**	**30 days after last dose (+14 days)**	**Every 90 days (±14 days)**
Review of dosing diary[w]													X	X	X		X	X	X	X		X		
PK sample collection[x]			X	X[y]	X[y]	X[y]	X[y]	X[y]	X[y]	X[y]	X[z]	X[z]	X[z]	X[z]			X[z]	X[z]		X[z]				
Blood collection (4β-OHC/total cholesterol)[aa]		X	X											X				X						
Urine collection[bb]							X																	
Tumor assessments: RECIST or INRC[cc]		X[dd]											*To be assessed every 6 weeks (±7 days) from Cycle 1 Day 1 for the first 3 tumor assessments. Thereafter, every 9 weeks (±7 days).*											
Serum tumor markers[ee]		X	*To be assessed at least once per cycle from Cycle 0 Day 1 and at EOT (or as per standard of care schedule).*																					
AE assessment		*To be collected from the time of ICF signing; see Section* **Error! Reference source not found.**																						

	Pre-screening	Screening[a]	Cycle 0										Cycle 1				Cycle 2			Additional Cycles		EOT/ ET[c]	Safety Follow-up Visit[d]	Survival Follow-up[e]
			PK Cycle For Food Effect or PK Bridging Cohorts								PK Cycle[b]													
			Fed (Food Effect) or Formulation 1 (PK Bridging)				Fasted (Food Effect) or Formulation 2 (PK Bridging)				Fasted													
Trial Days **Procedures/ Assessments[f]**	**-180 to -1**	**-28 to -1**	**1[a]**	**2**	**3**	**4**	**5 (+5)**	**6**	**7**	**8**	**1[a]**	**2**	**1**	**7 (-1)**	**15 (+2)**	**22 (+2)**	**1 (+3)**	**7 (-1)**	**17 (+2)**	**1 (+3)[g]**	**15 (+2)[h]**	**Within +7 days of Disc of Trt date**	**30 days after last dose (+14 days)**	**Every 90 days (±14 days)**
Concomitant medications/ procedures (transf. and growth factors included)		*To be collected from the time of Screening Visit through the Safety Follow-up visit*																						
Post-trial therapy data collection[ff]																								X
Survival status																								X

AE = adverse event; BID = twice daily; CA-125 = cancer antigen 125, CBC = complete blood count; CT = computed tomography; ctDNA = circulating tumor DNA; CXDX = Cycle X Day X, Disc of Trt = Discontinuation of treatment; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; ET = early termination; FISH = fluorescent in situ hybridization; ICF = informed consent form; INRC = International Neuroblastoma Response Criteria; MRI = magnetic resonance imaging; NGS = next-generation sequencing; OHC = hydroxycholesterol; PE = physical examination; PK = pharmacokinetic; PSA = prostate-specific antigen; QD = once daily; QTcF = Fridericia formula for correct QT interval; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SNP = single nucleotide polymorphism; US = United States

a. **Screening:** The Screening Period extends from Day -28 to Day -1. Screening assessments may be used as Cycle 0 Day 1 assessments if performed within 96 hours of the first dose of RP-1664, except for the ctDNA blood draw, vital signs, and ECGs. ECOG or Lansky performance status and PE that are completed within 24 hours of first dose of RP-1664 may be used as Cycle 0 Day 1 assessments. Participants must continue to meet eligibility criteria prior to first dose of RP-1664 on Cycle 0 Day 1.

b. **Cycle 0:** The 2-day PK Cycle 0 is not required for participants in the food effect or PK bridging portion of the trial.
c. **EOT/ET:** A post-treatment/ET visit will be conducted following the last dose of trial intervention and within 7 days after the date of treatment discontinuation but prior to the start of the next anticancer therapy.
d. **Safety Follow-Up:** Required for all participants who discontinued from the trial for whatever reason.
e. **Survival Follow-Up:** Survival follow-up will be conducted approximately every 90 days (±14 days) after date of treatment discontinuation until the end of trial (for up to 6 months), participant withdrawal of consent to trial, or death. This follow-up may be conducted by telephone contact or standard method used by participating centers and agreed by the Sponsor.
f. **Procedures/Assessments:** Pre-screening for molecular eligibility can take place up to 180 days before first dose of RP-1664. Screening procedures and tumor assessment must be performed within 28 days before first dose of RP-1664.
g. **CXD1:** The start of a new additional cycle should always coincide with the start of trial 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 CXD1 visit to enable flexibility with visit scheduling.
h. **Day 17 of Cycle 2 or Day 15 of Additional Cycles:** CBC and vital signs to be assessed only on C2 and C3. For Cycle 3, ctDNA should be collected on Day 15 and not on Day 1, however for Cycles 4 and up, ctDNA should be collected on Day 1.
i. **Molecular Eligibility:** NGS, FISH, or SNP microarray reports will be emailed for central review to confirm molecular eligibility or determine if additional testing is required.
j. **Abbreviated PE:** Starting at Cycle 2, abbreviated PE to be performed every 2 cycles (unless full PE necessary by Investigator judgment).
k. **Height:** Pediatric participants will have their height measured every 3 cycles.
l. **Vital Signs:** Blood pressure, heart rate, and temperature to be measured after the participant has been sitting for 5 minutes.
m. **ECG:** 12-lead ECGs to be done in triplicate ≥ 1 minute apart per Table 8. The triplicate ECG measurements must occur within a 30 minute time period. Participants should be in supine position and resting for at least 10 minutes before trial-related ECGs. QTcF should be recorded (QTcB is not required). Participants in the food effect or PK bridging portion of the trial should have ECGs collected per Table 11 and Table 12, respectively.
n. **Pregnancy Test:** For women of childbearing potential, a serum pregnancy test is required at Screening. If a pregnancy test was done within 96 hours of Cycle 0 Day 1, repeat testing is not required. A serum or urine pregnancy test must be performed on Day 1 of each cycle starting on Cycle 2, at EOT, and at Safety Follow-up visit. A pregnancy test can be performed more frequently if required per local regulations.
o. **Clinical Safety Laboratory Tests:** Clinical laboratory tests (including serum or plasma chemistry, hematology [including reticulocyte count], and urinalysis) will be performed at local laboratories according to the laboratory's normal procedures. See Section **Error! Reference source not found.** for a complete listing of laboratory tests to be performed.
p. **ctDNA Whole Blood:** Blood can be collected as 30 mL at Screening and 30 mL at C0D1, for a total of 60 mL. Blood can be collected either pre- or post- dose for all on-treatment timepoints. After Cycle 4, if CXD1 was delayed (eg, due to an AE), ctDNA sample should be collected at actual cycle visit. For visit prior to Cycle 4, if CXDX is delayed, ctDNA should be collected both at planned and actual cycle visit. Please refer to Lab Manual for guidance on sample collection.
q. **Baseline Tumor Biopsy:** If archival tissue does not meet trial requirements, a pre-treatment biopsy is mandatory prior to enrollment. If the participant is providing a paired biopsy, a pre-treatment and an on-treatment biopsy are mandatory. Biopsy tissue must be shipped to the Sponsor-designated lab during Screening or by Cycle 1 Day 1 (+7 days). 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. *US only:* Participants 12 to 17 years of age are not required to provide a biopsy.

r. **On-treatment Tumor Biopsy**: This assessment applies only to participants providing a paired biopsy. The biopsy should be collected on Cycle 2 Day 7 after 6 prior days of dosing with RP-1664. If biopsy collection at this timepoint is not possible, please contact the Sponsor to schedule an appropriate time for on-treatment biopsy.

s. **Post-Progression Tumor Biopsy:** An optional tumor biopsy will be requested post-progression for participants with prior confirmed responses or stable disease ≥ 16 weeks.

t. [redacted]

u. **Mandatory Archival Tumor Tissue:** Archival tissue is to be submitted to the Sponsor-designated lab during Screening. Refer to Laboratory Manual for further details. If adequate archived tumor tissue is not available and/or a fresh biopsy cannot be safely performed, the participant may still be eligible with prior Sponsor approval. The Sponsor prefers archival material from the primary tumor if available.

v. **RP-1664 Administration:** Cycle 0 dosing should start Monday to Wednesday, if unable to accommodate weekend visits. A +5-day window is allowed prior to initiating the Cycle 0 Day 5 Fasted PK or PK bridging blood collection.

w. [redacted]

bb. **Urine Collection:** Urine collection is only required for participants in the food effect portion of the trial. Urine samples will be collected (0 to 3, 3 to 6, and 6 to 12 hours) while participants are in the clinic on Cycle 0 Day 5.

cc. **Tumor Assessment:** Tumor assessments by disease-appropriate standard criteria (e.g., RECIST v1.1 or INRC) using CT/MRI of known sites of disease as clinically indicated. Tumor assessments must be performed at Screening and every 6 weeks (±7 days) from C1D1 for the first 3 assessments, or sooner if clinically indicated). Thereafter, assessments must be performed every 9 weeks (±7 days). Per RECIST v1.1, complete response or partial response 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 trial treatment or every 9 weeks thereafter). If a participant discontinues treatment for a reason other than radiographic disease progression, withdrawal of consent to trial, lost to follow-up, or death, scans

should continue at the specified intervals until progression is confirmed or until start of subsequent anticancer treatment. All radiographic images/scans at the timepoints specified as well as any unscheduled images/scans should be archived by the trial sites for potential future evaluation.

dd. **Tumor Assessment at Screening:** Scans performed prior to signing of the ICF as part of routine clinical management are acceptable for use as baseline tumor imaging if they are of diagnostic quality and performed within 28 days prior to the first dose on Cycle 0 Day 1.

ee. **Serum Tumor Markers:** This assessment applies only to participants with cancers being monitored by circulating tumor markers (e.g., CA-125 or PSA). The baseline assessment should be performed within 96 hours of the first dose on Cycle 0 Day 1. If the assessment is done during Screening prior to this time, it should be repeated within the allotted time frame. It should then be collected on Day 1 of each subsequent cycle starting at Cycle 2, or per standard of care, through end of treatment.

ff. **Post-trial Therapy Data Collection:** All anticancer therapies with start and stop dates should be recorded for 6 months after treatment discontinuation.

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Table 9 Schedule of Activities for Participants Enrolled on 2 Weeks On/2 Weeks Off Dosing (28-Day Cycles; if Needed)

	Pre-screening	Screening[a]	Cycle 0										Cycle 1				Cycle 2				Additional Cycles		EOT/ ET[c]	Safety Follow-up Visit[d]	Survival Follow-up[e]
			PK Cycle For Food Effect or PK Bridging Cohorts								PK Cycle[b]														
			Fed (Food Effect) or Formulation 1 (PK Bridging)				Fasted (Food Effect) or Formulation 2 (PK Bridging)				Fasted														
Trial Days	**-180 to -1**	**-28 to -1**	**1[a]**	**2**	**3**	**4**	**5 (+5)**	**6**	**7**	**8**	**1[a]**	**2**	**1**	**8 (+2)**	**15 (+2)**	**22 (+2)**	**1 (+3)**	**8 (+2)**	**15 (+2)**	**22 (+2)**	**1 (+3)[g]**	**15 (+2)[h]**	**Within +7 days of Disc of Trt date**	**30 days after last dose (±14 days)**	**Every 90 days (±14 days)**
Procedures/ Assessments[f]																									
Pre-screen informed consent	X																								
Screening/main informed consent		X																							
Inclusion/exclusion criteria		X	X								X														
Molecular eligibility[i]	X																								
Demographics	X																								
Medical/cancer history		X																							
Physical examination		X	X								X												X		

	Pre-screening	Screening[a]	Cycle 0										Cycle 1				Cycle 2				Additional Cycles		EOT/ ET[c]	Safety Follow-up Visit[d]	Survival Follow-up[e]
			PK Cycle For Food Effect or PK Bridging Cohorts								PK Cycle[b]														
			Fed (Food Effect) or Formulation 1 (PK Bridging)				Fasted (Food Effect) or Formulation 2 (PK Bridging)				Fasted														
Trial Days **Procedures/ Assessments[f]**	**-180 to -1**	**-28 to -1**	**1[a]**	**2**	**3**	**4**	**5 (+5)**	**6**	**7**	**8**	**1[a]**	**2**	**1**	**8 (+2)**	**15 (+2)**	**22 (+2)**	**1 (+3)**	**8 (+2)**	**15 (+2)**	**22 (+2)**	**1 (+3)[g]**	**15 (+2)[h]**	**Within +7 days of Disc of Trt date**	**30 days after last dose (±14 days)**	**Every 90 days (±14 days)**
Abbreviated PE[j]																	X				X[j]			X	
Height[k]		X																			X[k]				
Weight		X	X								X						X				X		X	X	
Vital sign measurements[l]		X	X								X		X	X	X	X	X	X	X		X	X[h]	X	X	
ECOG or Lansky performance status		X									X						X				X		X	X	
12-lead ECG[m]		X	X				X				X			X			X				X				
Pregnancy test[n]		X	X								X						X				X		X	X	
Clinical safety lab tests[o]		X	X								X						X				X		X	X	

	Pre-screening	Screening[a]	Cycle 0										Cycle 1				Cycle 2				Additional Cycles		EOT/ ET[c]	Safety Follow-up Visit[d]	Survival Follow-up[e]
			PK Cycle For Food Effect or PK Bridging Cohorts								PK Cycle[b]														
			Fed (Food Effect) or Formulation 1 (PK Bridging)				Fasted (Food Effect) or Formulation 2 (PK Bridging)				Fasted														
Trial Days **Procedures/ Assessments[f]**	**-180 to -1**	**-28 to -1**	**1[a]**	**2**	**3**	**4**	**5 (+5)**	**6**	**7**	**8**	**1[a]**	**2**	**1**	**8 (+2)**	**15 (+2)**	**22 (+2)**	**1 (+3)**	**8 (+2)**	**15 (+2)**	**22 (+2)**	**1 (+3)[g]**	**15 (+2)[h]**	**Within +7 days of Disc of Trt date**	**30 days after last dose (±14 days)**	**Every 90 days (±14 days)**
CBC with diff. (included in safety lab tests)														X	X	X		X	X			X[h]			
ctDNA whole blood[p]		X[p]	X								X			X				X			X[h]	X[h]	X		
Tumor biopsy[q,r,s]		X[q]																X[r]					X[s]		
Central testing for molecular eligibility[t]	X																								
Archival tumor tissue[u]	X[t]	X																							
RP-1664 dispensed/collected			*Dispensed and collected according to Pharmacy Manual*																						
RP-1664 administration[v]			X				X				X		*See Section* ***Error! Reference source not found.****, Dosing and Administration*												

	Pre-screening	Screening[a]	Cycle 0										Cycle 1				Cycle 2				Additional Cycles		EOT/ ET[c]	Safety Follow-up Visit[d]	Survival Follow-up[e]
			PK Cycle For Food Effect or PK Bridging Cohorts								PK Cycle[b]														
			Fed (Food Effect) or Formulation 1 (PK Bridging)				Fasted (Food Effect) or Formulation 2 (PK Bridging)				Fasted														
Trial Days **Procedures/ Assessments[f]**	**-180 to -1**	**-28 to -1**	**1[a]**	**2**	**3**	**4**	**5 (+5)**	**6**	**7**	**8**	**1[a]**	**2**	**1**	**8 (+2)**	**15 (+2)**	**22 (+2)**	**1 (+3)**	**8 (+2)**	**15 (+2)**	**22 (+2)**	**1 (+3) [g]**	**15 (+2) [h]**	**Within +7 days of Disc of Trt date**	**30 days after last dose (±14 days)**	**Every 90 days (±14 days)**
Review of dosing diary[w]													X	X	X		X	X	X		X		X		
PK sample collection[x]			X	X[y]	X[y]	X[y]	X[y]	X[y]	X[y]	X[y]	X[z]	X[z]	X[z]	X[z]			X[z]	X[z]			X[z]				
Blood collection (4β-OHC/total cholesterol)[aa]		X	X												X				X			X			
Urine collection[bb]							X																		
Tumor assessments: RECIST or INRC[cc]		X[dd]											*To be assessed every 6 weeks (±7 days) from Cycle 1 Day 1 for the first 3 tumor assessments. Thereafter, every 9 weeks (±7 days).*													
Serum tumor markers[ee]		X	*To be assessed at least once per cycle from Cycle 0 Day 1 and at EOT (or as per standard of care schedule).*																						
AE assessment		*To be collected from the time of ICF signing; see Section* **Error! Reference source not found.**																							

	Pre-screening	Screening[a]	Cycle 0										Cycle 1				Cycle 2				Additional Cycles		EOT/ ET[c]	Safety Follow-up Visit[d]	Survival Follow-up[e]
			PK Cycle For Food Effect or PK Bridging Cohorts								PK Cycle[b]														
			Fed (Food Effect) or Formulation 1 (PK Bridging)				Fasted (Food Effect) or Formulation 2 (PK Bridging)				Fasted														
Trial Days **Procedures/ Assessments[f]**	**-180 to -1**	**-28 to -1**	**1[a]**	**2**	**3**	**4**	**5 (+5)**	**6**	**7**	**8**	**1[a]**	**2**	**1**	**8 (+2)**	**15 (+2)**	**22 (+2)**	**1 (+3)**	**8 (+2)**	**15 (+2)**	**22 (+2)**	**1 (+3)[g]**	**15 (+2)[h]**	**Within +7 days of Disc of Trt date**	**30 days after last dose (±14 days)**	**Every 90 days (±14 days)**
Concomitant medications/ procedures (transf. and growth factors included)		*To be collected from the time of Screening Visit through the Safety Follow-up visit*																							
Post-trial therapy data collection[ff]																									X
Survival status																									X

AE = adverse event; BID = twice daily; CA-125 = cancer antigen 125, CBC = complete blood count; CT = computed tomography; ctDNA = circulating tumor DNA; CXDX = Cycle X Day X, Disc of Trt = Discontinuation of treatment; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; ET = early termination; FISH = fluorescent in situ hybridization; ICF = informed consent form; INRC = International Neuroblastoma Response Criteria; MRI = magnetic resonance imaging; NGS = next-generation sequencing; OHC = hydroxycholesterol; PE = physical examination; PK = pharmacokinetic; PSA = prostate-specific antigen; QD = once daily; QTcF = Fridericia formula for correct QT interval; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SNP = single nucleotide polymorphism; US = United States

a. **Screening:** Screening Period extends from Day -28 to Day -1. Screening assessments may be used as Cycle 0 Day 1 assessments if performed within 96 hours of the first dose of RP-1664, except for the ctDNA blood draw, vital signs, and ECGs. ECOG or Lansky performance status and PE that are completed within 24 hours of first dose of RP-1664 may be used as Cycle 0 Day 1 assessments. Participants must continue to meet eligibility criteria prior to first dose of RP-1664 on Cycle 0 Day 1.

b. **Cycle 0:** The 2-day PK Cycle 0 is not required for participants in the food effect or PK bridging portion of the trial.

c. **EOT/ET:** A post-treatment/ET visit will be conducted following the last dose of trial intervention and within 7 days after the date of treatment discontinuation but prior to the start of the next anticancer therapy.
d. **Safety Follow-Up:** Required for all participants who discontinued from the trial for whatever reason.
e. **Survival Follow-Up:** Survival follow-up will be conducted approximately every 90 days (±14 days) after date of treatment discontinuation until the end of trial (for up to 6 months), participant withdrawal of consent to trial, or death. This follow-up may be conducted by telephone contact or standard method used by participating centers and agreed by the Sponsor.
f. **Procedures/Assessments:** Pre-screening for molecular eligibility can take place up to 180 days before first dose of RP-1664. Screening procedures and tumor assessment must be performed within 28 days before first dose of RP-1664.
g. **CXD1:** The start of a new additional cycle should always coincide with the start of trial 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 CXD1 visit to enable flexibility with visit scheduling.
h. **Day 15 of Additional Cycles:** CBC and vital signs to be assessed only on C2 and C3. For Cycle 3, ctDNA should be collected on Day 15 and not on Day 1, however for Cycles 4 and up, ctDNA should be collected on Day 1. Blood samples for 4β-OHC and total cholesterol are only collected up to Cycle 3.
i. **Molecular Eligibility:** NGS, FISH, or SNP microarray reports will be emailed for central review to confirm molecular eligibility or determine if additional testing is required.
j. **Abbreviated PE:** Starting at Cycle 2, abbreviated PE to be performed every 2 cycles (unless full PE necessary by Investigator judgment).
k. **Height:** Pediatric participants will have their height measured every 3 cycles.
l. **Vital Signs:** Blood pressure, heart rate, and temperature to be measured after the participant has been sitting for 5 minutes.
m. **ECG:** 12-lead ECGs to be done in triplicate ≥ 1 minute apart per Table 10. The triplicate ECG measurements must occur within a 30 minute time period. Participants should be in supine position and resting for at least 10 minutes before trial-related ECGs. QTcF should be recorded (QTcB is not required). Participants in the food effect or PK bridging portion of the trial should have ECGs collected per Table 11 and Table 12, respectively.
n. **Pregnancy Test:** For women of childbearing potential, a serum pregnancy test is required at Screening. If a pregnancy test was done within 96 hours of Cycle 0 Day 1, repeat testing is not required. A serum or urine pregnancy test must be performed on Day 1 of each cycle starting on Cycle 2, at EOT, and at Safety Follow-up visit. A pregnancy test can be performed more frequently if required per local regulations.
o. **Clinical Safety Laboratory Tests:** Clinical laboratory tests (including serum or plasma chemistry, hematology [including reticulocyte count], and urinalysis) will be performed at local laboratories according to the laboratory's normal procedures. See Section **Error! Reference source not found.** for a complete listing of laboratory tests to be performed.
p. **ctDNA Whole Blood:** Blood can be collected as 30 mL at Screening and 30 mL at C0D1, for a total of 60 mL. Blood can be collected either pre- or post- dose for all on-treatment timepoints. After Cycle 4, if CXD1 was delayed (eg, due to an AE), ctDNA sample should be collected at actual cycle visit. For visit prior to Cycle 4, if CXDX is delayed, ctDNA should be collected both at planned and actual cycle visit. Please refer to Lab Manual for guidance on sample collection.
q. **Baseline Tumor Biopsy:** If archival tissue does not meet trial requirements, a pre-treatment biopsy is mandatory prior to enrollment. If the participant is providing a paired biopsy, a pre-treatment and an on-treatment biopsy are mandatory. Biopsy tissue must be shipped to the Sponsor-designated lab during Screening or by Cycle 1 Day 1 (+7 days). 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. *US only:* Participants 12 to 17 years of age are not required to provide a biopsy.

r. **On-treatment Tumor Biopsy**: This assessment applies only to participants providing a paired biopsy. Biopsy should be collected on Cycle 2 Day 8 (+2), 2 to 6 hours after dosing of RP-1664. Participants must have taken a minimum of 7 consecutive days of RP-1664 prior to on-treatment biopsy collection. If biopsy collection at this timepoint is not possible, please contact the Sponsor to schedule appropriate time for on-treatment biopsy.

s. **Post-Progression Tumor Biopsy:** An optional tumor biopsy will be requested post-progression for participants with prior confirmed responses or stable disease ≥ 16 weeks.

t. [redacted]

u. **Mandatory Archival Tumor Tissue:** Archival tissue is to be submitted to the Sponsor-designated lab during Screening. Refer to Laboratory Manual for further details. If adequate archived tumor tissue is not available and/or a fresh biopsy cannot be safely performed, the participant may still be eligible with prior Sponsor approval. The Sponsor prefers archival material from the primary tumor if available.

v. **RP-1664 Administration:** Cycle 0 dosing should start Monday to Wednesday, if unable to accommodate weekend visits. A +5-day window is allowed prior to initiating the Cycle 0 Day 5 Fasted PK or PK bridging blood collection, if unable to accommodate weekend visits.

w. **Review of Dosing Diary:** Dosing diary will be reviewed at each participant visit and collected at each CXD1 visit and at EOT. Additional details are in the Pharmacy Manual.

x. [redacted]

bb. **Urine Collection:** Urine collection is only required for participants in the food effect portion of the trial. Urine samples will be collected (0 to 3, 3 to 6, and 6 to 12 hours) while participants are in the clinic on Cycle 0 Day 5.

cc. **Tumor Assessment:** Tumor assessments by disease-appropriate standard criteria (e.g., RECIST v1.1 or INRC) using CT/MRI of known sites of disease as clinically indicated. Tumor assessments must be performed at Screening and every 6 weeks (±7 days) from C1D1 for the first 3 assessments, or sooner if clinically indicated). Thereafter, assessments must be performed every 9 weeks (±7 days). Per RECIST v1.1, complete response or partial response 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 trial treatment or every 9 weeks thereafter). If a participant discontinues treatment for a reason other than radiographic disease progression, withdrawal of consent to trial, lost to follow-up, or death, scans should continue at the specified intervals until progression is confirmed or until start of subsequent anticancer treatment. All radiographic images/scans at the timepoints specified as well as any unscheduled images/scans should be archived by the trial sites for potential future evaluation.

dd. **Tumor Assessment at Screening:** Scans performed prior to signing of the ICF as part of routine clinical management are acceptable for use as baseline tumor imaging if they are of diagnostic quality and performed within 28 days prior to the first dose on Cycle 0 Day 1.

ee. **Serum Tumor Markers:** This assessment applies only to participants with cancers being monitored by circulating tumor markers (e.g., CA-125 or PSA). The baseline assessment should be performed within 96 hours of the first dose on Cycle 0 Day 1. If the assessment is done during Screening prior to this time, it should be repeated within the allotted time frame. It should then be collected on Day 1 of each subsequent cycle starting at Cycle 2, or per standard of care, through end of treatment.

ff. **Post-trial Therapy Data Collection:** All anticancer therapies with start and stop dates should be recorded for 6 months after treatment discontinuation.

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14.1.6 Lansky Play-Performance Scale for Pediatric Participants

This scale may be used for children in this trial for ages 1 to 16 years who have any type of malignancy. It may be used for both inpatients and outpatients and for participants undergoing active treatment as well as long-term follow-up. It is rated by parents based on their child's activity over the past week.

An excerpt of the relevant directions for parents is as follows:

"Think about your child's play and activity over the past week. Think about both good days and bad days. Average out this period. Now read the descriptions and pick the one that best describes your child's play during the past week."

Rating	Description
100	fully active, normal
90	minor restrictions with strenuous physical activity
80	active, but gets tired more quickly
70	both greater restriction of, and less time spent in, active play
60	up and around, but minimal active play; keeps busy with quieter activities
50	lying around much of the day, but gets dressed; no active play; participates in all quiet play and activities
40	mostly in bed; participates in quiet activities
30	stuck in bed; needs help even for quiet play
20	often sleeping; play is entirely limited to very passive activities
10	does not play nor get out of bed
0	unresponsive

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15.REFERENCE

Eisenhauer EA, et al. (2009). New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer, 45(2), 228-47.