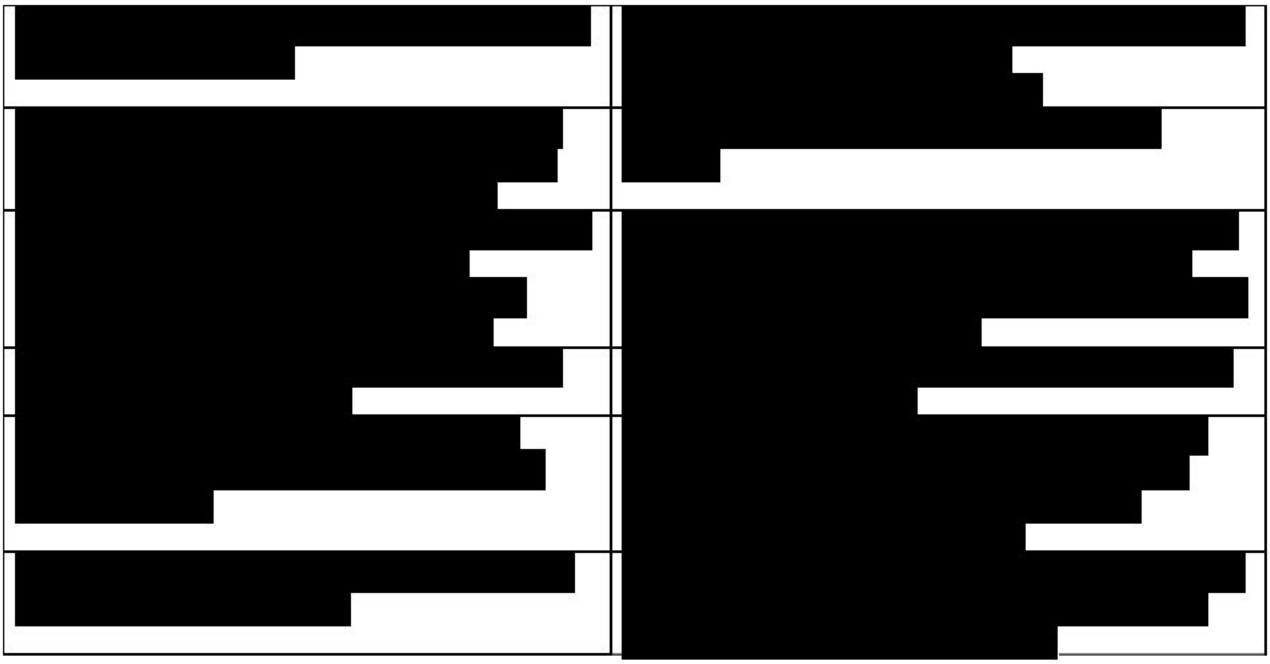
Protocol Full Title:	Phase 1 Trial of the Safety, Pharmacokinetics, Pharmacodynamics, and Preliminary Clinical Activity of RP-1664 in Participants with Advanced Solid Tumors
Sponsor Confidentiality Statement:	This document is confidential. It contains proprietary information of Repare Therapeutics (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this trial.
GCP Statement	This trial is to be performed in full compliance with International Council for Harmonization (ICH) of Technical Requirements for Pharmaceuticals for Human Use and all applicable local Good Clinical Practice (GCP) guidelines and regulations. All required trial documentation will be archived as required by regulatory authorities.
Protocol Number:	RP-1664-01
Version:	3.0
Amendment Number:	2
Compound Number(s):	RP-1664
Trial Phase:	Phase 1
Acronym:	LIONS (P**L**K4 Inh**i**bit**o**r i**n** Advanced **S**olid Tumors)
Short Title:	Phase 1 First-in-Human Trial of RP-1664 in Participants with Advanced Solid Tumors
Sponsor Name and Address:	Repare Therapeutics 7171 Frederick-Banting Building 2 St-Laurent, Quebec, H4S 1Z9 Canada
Regulatory Agency Identifier Number(s):	IND:165637, EU Trial Number: 2024-511259-16-00
Sponsor Approval Date:	24 March 2025

1 PROTOCOL SUMMARY

1.1 Protocol Synopsis

Objectives and Endpoints

Primary Objectives	Primary Endpoints
To assess the safety and tolerability of RP-1664 in participants with eligible, advanced solid tumors	Incidence and severity of treatment-emergent adverse events (TEAEs)
To define a dose and schedule of RP-1664 that is tolerated and has clinical activity	Dose and schedule based on safety, pharmacokinetic (PK), pharmacodynamic, and available efficacy data
[redacted]	[redacted]



Overall Design

Several key aspects of the trial design are summarized below.

Intervention Model:	N/A	**Population Type:**	Adolescent (*United States [US] only*) and adult participants
Control:	None	**Population Diagnosis or Condition:**	Advanced solid tumors
Active Comparator:	N/A	**Population Age:**	Minimum: 12 years (*US only*; ≥ 40 kg if less than 18 years except participants with neuroblastoma must weigh ≥ 30 kg); 18 years– Maximum: N/A
Trial Intervention Assignment Method:	N/A	**Site Distribution:**	Multi-site and multi-regional

Number of Arms: 1

Blinding: Not applicable (no blinding).

Number of Participants: Approximately 80 evaluable participants (planned)

Trial Duration: Approximately 36 months

This is a multicenter, open-label Phase 1 trial to investigate the safety, PK, pharmacodynamic, and preliminary efficacy of the Polo-Like Kinase 4 (PLK4) inhibitor RP-1664 in participants with molecularly selected advanced solid tumors. The trial is estimated to enroll approximately

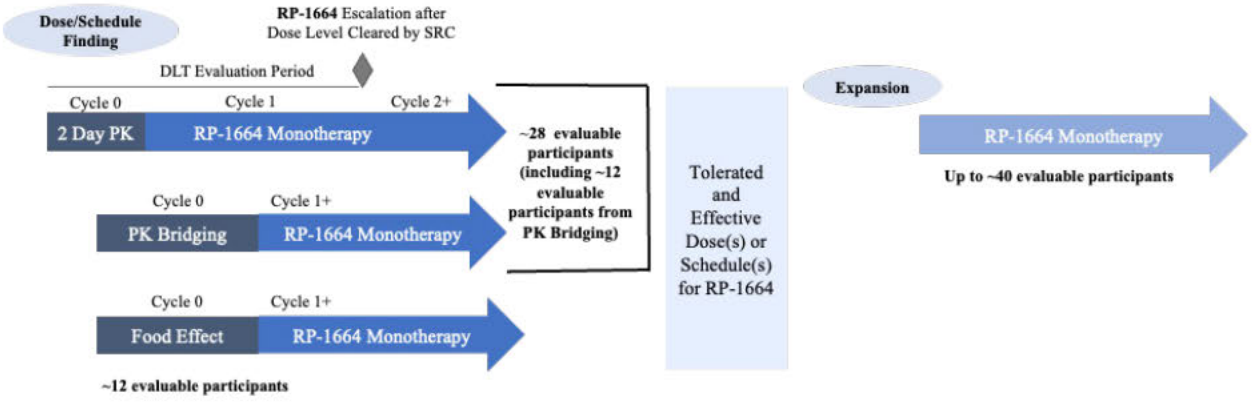
80 evaluable participants (definition of evaluable participants provided in Section 9.1) with solid tumors harboring any one of the following:

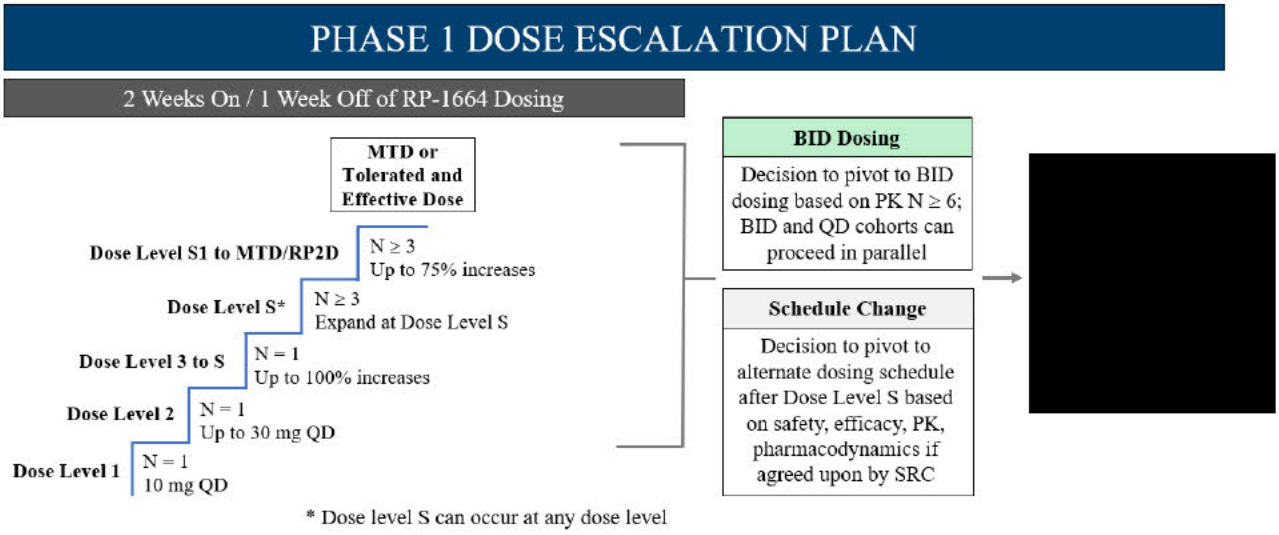
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

Phase 1 Dose Finding and Expansion Cohorts

[redacted]





BID = twice daily; MTD = maximum tolerated dose; PD = pharmacodynamic; PK = pharmacokinetic; QD = once daily; SRC = Safety Review Committee

The trial will follow a Bayesian Optimal Interval (BOIN) design to guide escalation and de-escalation decisions, establish a maximum tolerated dose (MTD), and to identify a dose and schedule of RP-1664 that is tolerable and has clinical activity. All participants will undergo a dedicated PK evaluation period starting at Cycle 0 Day 1 and will be assigned to receive either:

1) A single dose of RP-1664 given as an adolescent/adult whole capsule at the highest Safety Review Committee (SRC) approved dose level with PK collection over the subsequent 48 hours to characterize the $t_{1/2}$ of RP-1664 in the fasted state, or

2) Two doses of RP-1664 as pediatric sprinkle capsules, one in the fed-state (with a high-fat meal) and one in the fasted-state (RP-1664 sprinkled over soft food), to examine the effect of food on RP-1664 PK, or

3) Two doses of RP-1664, one as the adolescent/adult whole capsule and the other as a pediatric sprinkle capsule, to compare the PK of the two formulations.

After completion of Cycle 0, participants will begin C1D1 at the assigned, SRC-approved dose and schedule being tested.

The starting dose (Dose Level 1) is anticipated to be 10 mg once daily (QD), when calculated based on the principles outlined in the International Conference on Harmonization (ICH) S9 Nonclinical Evaluation of Anti-cancer Pharmaceuticals (Section 2.2.6). Since neutropenia has been observed in preclinical safety studies and is an anticipated toxicity in humans, RP-1664 will initially be given QD on a 2 weeks on/1 week off schedule to allow 1 week for bone marrow recovery. Since the projected efficacious dose of RP-1664 in humans is approximately 300 mg QD (based on preclinical models), 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, or
- >50% decrease in platelets or neutrophils from Cycle 0 Day 1, or
- >2 g/dL decrease in hemoglobin from Cycle 0 Day 1, or
- Any ≥ Grade 2 drug-related non-hematological toxicity lasting >5 days or requiring clinical intervention, except Grade 2 fatigue, nausea, vomiting, diarrhea, or constipation, or
- 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

[redacted]

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.

Dose modifications, including adjustments to treatment frequency (e.g., QD to BID or BID to QD dosing), schedule changes, or intra-participant dose escalations, will be allowed for participants to manage AEs and/or maximize RP-1664 exposure and clinical benefit. These changes in doses or schedules will be allowed only to previously SRC-approved levels or frequencies that have been cleared for DLT evaluation.

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 the PK profiles of 12 evaluable participants have been analyzed.

An additional subset of 12 participants from the Dose and Schedule Finding portion of the trial will be enrolled into the PK bridging portion of the trial at Cycle 0 to compare the systemic exposure of the RP-1664 adolescent/adult whole capsule versus a pediatric sprinkle capsule formulation.

For all participants, treatment with RP-1664 will continue until radiographic progression, intolerability to trial intervention, risk to participant as determined by the Investigator and/or Sponsor, consent withdrawal, start of a non-trial anticancer treatment, major protocol noncompliance that would jeopardize participant safety and/or data interpretation as determined by the Sponsor, pregnancy, or death. Participants are allowed to continue RP-1664 treatment after disease progression if the Investigator deems that it is in the participant's best interest. In such cases, the participant will be required to provide signed written consent agreeing to treatment after disease progression (see Section 4.1).

Eligibility Criteria

Inclusion Criteria:

To be eligible to participate in this trial, participants must meet all the following criteria:

1. Written informed consent and/or assent, according to local guidelines, signed and dated by the participant or legal guardian prior to the performance of any trial-

specific procedures, sampling, or analyses. Participants with impaired decision-making capacity must have a close caregiver or legally authorized representative (LAR) present.

2. Male or female participants ≥ 18 years of age at the time of signing the informed consent.

   US only: Male or female participants ≥ 12 years of age at the time of signing the informed consent and/or assent. Participants < 18 years of age must weigh at least 40 kg and be at a 6th grade reading level or higher, except for participants with neuroblastoma who must weigh at least 30 kg. The dose of RP-1664 will be adjusted for participants with neuroblastoma weighing 30 - < 40 kg based on the body surface area (BSA) table [redacted]

   Note: Participants 12 to 17 years of age will be enrolled only after at least 4 participants ≥ 18 years-of-age have completed 1 cycle of therapy.

3. Ability to comply with the protocol and trial procedures [redacted]

4. Ability to swallow and retain whole, intact oral medications.

5. Life expectancy ≥ 4 months after the start of the treatment according to the Investigator's judgment.

6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (refer to [redacted] for participants > 16 years of age or Lansky performance status ≥ 60% for participants ≤ 16 years of age [redacted]

7. Participant must have locally advanced or metastatic solid tumor that has progressed or was nonresponsive or intolerant to available therapies and for which no standard or available curative therapy exists, or in the opinion of the Investigator, is not a candidate for, or if the participant declines standard-of-care therapy. Documented counselling by center investigator on benefits/risks of standard-of-care therapy is required for enrolled participants who decline standard-of-care therapy.

8. Measurable disease per RECIST v1.1 [redacted] or measurable or evaluable disease per INRC [redacted]

Exception: Participants with prostate or ovarian cancer that have non-measurable disease, but elevated tumor markers may be eligible if agreed upon by the Sponsor and Investigator. In these cases, Prostate Cancer Working Group (PCWG3) criteria (radionuclide bone scan and prostate specific antigen [PSA], [redacted] Gynecological Cancer Intergroup (GCIG) criteria (cancer antigen 125 [CA-125], [redacted]) will be used respectively to assess anti-tumor activity.

For participants with neuroblastoma per INRC, measurable or evaluable disease includes at least one of the following: Measurable tumor by CT or MRI; or a positive

MIBG or PET; or positive bone marrow biopsy/aspirate in at least one site. If a patient has a history of bone marrow disease, bone marrow evaluations are required at baseline evaluation. If the results are negative, bone marrow aspirates or biopsies do not need to be repeated unless clinically indicated or for confirmation of complete remission (CR).

9. Provision of archival tumor tissue (if adequate archival tumor tissue is not available, tumor tissue should be acquired by a fresh biopsy prior to enrollment).

   Note: 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. US only: Participants 12 to 17 years of age are not required to provide a biopsy.

10. All participants' tumors must have evidence of at least one of the following reported from a Clinical Laboratory Improvement Amendments (CLIA)-certified or equivalent (ex-US) laboratory:

    - Gain or amplification of TRIM37, RAD51C, PPM1D, BRIP1, RNF43, or chromosome region 17q23
    - Overexpression of TRIM37
    - Genomically unaltered TP53
    - Other genomic profile with mechanistic rationale as agreed upon by the Investigator and Sponsor

    Note: For all participants, an anonymized/redacted Molecular Pathology report should be submitted to the Sponsor or designee during Pre-screening to confirm eligibility. For details, see the Molecular Eligibility Manual.

11. Acceptable organ function at Screening, as evidenced by the following laboratory data:

    a. Creatinine clearance ≥ 60 mL/min using Cockcroft-Gault equation or institution standard formula.

       - *US only:* For participants 12 to 17 years of age, adequate renal function is defined as: calculated creatinine clearance by Cockcroft- Gault or institutional standard, including institutional formula specific for this age group.

    b. Total bilirubin ≤ 1.5 × upper limit of normal (ULN) or < 3.0 × ULN if known Gilbert's disease.

    c. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 × ULN or ≤ 5.0 × ULN in the case of presence of liver metastases.

    d. Albumin > 2.0 g/dL

12. Acceptable hematologic function at Screening:

    a. No red blood cell (RBC) or platelet transfusions, and no myeloid, erythroid, or thrombopoietic growth factors within 7 days of the first dose of trial intervention

    b. Hemoglobin ≥ 9.5 g/dL except for participants with neuroblastoma with bone marrow involvement who are required to have hemoglobin ≥ 8.0 g/dL

    c. Absolute neutrophil count (ANC) ≥ 2000 cells/mm^3 except for participants with neuroblastoma with bone marrow involvement who are required to have ANC ≥ 1000 cells/mm^3. Participants with neuroblastoma with bone marrow involvement are required to have ANC ≥ 750/uL.

    d. Platelet count ≥ 100,000 cells/mm^3. Participants with neuroblastoma without bone marrow involvement are required to have platelet count ≥ 100,000 cells/mm^3 (transfusion independent, defined as not receiving platelet transfusions for at least 7 days prior to enrollment). Participants with neuroblastoma with bone marrow involvement are required to have platelet count ≥ 75,000 cells/mm^3 (transfusion independent, defined as not receiving platelet transfusions for at least 7 days prior to enrollment).

13. Negative pregnancy test (serum) for women of childbearing potential (WOCBP) at Screening.

    a. WOCBP is defined as fertile, following menarche and until becoming post-menopausal unless permanently sterile. WOCBP, who are sexually active, and their partners must agree to use a highly effective form of contraception [redacted] throughout their participation in the trial and for 6 months after the last dose of trial intervention. Female participants must refrain from donating eggs during their participation in the trial and for 6 months following last dose of trial intervention.

    b. Women are considered post-menopausal and not of childbearing potential if they have had no menses for 12 months without an alternative, potentially reversible medical cause or permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.

14. Male participants with female partners of childbearing potential must follow a contraception method at least as conservative as Clinical Trial Facilitation Group (CTFG) recommendations [redacted] during their participation in the trial for 6 months following last dose of trial intervention. Male participants must also refrain from donating sperm during their participation in the trial and for 6 months following last dose of trial intervention.

15. For participants in the food effect portion of the trial, ability to consume a high-fat meal and fast for 12 hours.

Exclusion Criteria:

An individual who meets any of the following criteria will be excluded from participation in this trial:

1. History or current condition (such as transfusion-dependent anemia, thrombocytopenia, or chronic neutropenia, except for participants with neuroblastoma with bone marrow involvement) or laboratory abnormality that in the opinion of the Investigator or Sponsor might pose a significant risk to participant safety, confound the trial results, or interfere with participation for the full duration of the trial treatment.

2. Life-threatening illness, medical condition, active uncontrolled infection, or organ system dysfunction (such as coagulopathy or encephalopathy), or other reasons which, in the Investigator's opinion, could compromise the participant's safety, or interfere with or compromise the integrity of the trial outcomes.

3. Uncontrolled, symptomatic brain metastases. Participants with previously treated brain metastases may participate provided the metastases are stable (without evidence of progression by imaging within 4 weeks prior to the first dose of trial intervention and any neurologic symptoms are controlled and stable), they have no evidence of new or enlarged brain metastases, and they are clinically stable and off steroids for at least 7 days prior to trial treatment.

4. Presence of other known second malignancy with the exception of any cancer that has been in complete remission for ≥ 2 years or completely resected squamous and basal cell carcinomas of the skin.

5. Active, uncontrolled bacterial, fungal, or viral infection, including hepatitis B virus, hepatitis C virus (HCV), known human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS)-related illness. In equivocal cases, participants whose viral load is negative may be eligible. Eligibility criteria for HIV positive participants currently on highly active antiretroviral therapy (HAART) should be evaluated and discussed with the Medical Monitor and will be based on current and past CD4 and T-cell counts, history (if any) of AIDS-defining conditions (e.g., opportunistic infections), and status of HIV treatment.

6. Clinically significant vascular (both arterial and venous) and non-vascular cardiac conditions, active or within 6 months prior to enrollment, including:

    a. Arterial disease such as cerebral vascular accident/stroke (including transient ischemic attack, myocardial infarction, and unstable angina)

    b. Venous diseases such as deep vein thrombosis and/or pulmonary embolism, central venous thrombosis

c. Non-vascular cardiac disease such as congestive heart failure (New York Heart Association Classification Class ≥ 2)

d. Conduction abnormality not controlled with pacemaker or medication

e. Significant ventricular or supraventricular arrhythmias, including history of Torsades de pointes (TdP) unless all risk factors that contributed to TdP have been corrected. Participants with chronic rate-controlled atrial fibrillation in the absence of other cardiac abnormalities are eligible.

f. Family history of sudden unexplained death or long electrocardiogram (ECG) interval measured from the onset of the QRS complex to the end of the T wave (QT syndrome)

7. Mean resting QT interval corrected for heart rate (QTc) interval using the Fridericia formula (QTcF) > 470 msec (as calculated per institutional standards) demonstrated by at least 2 ECGs ≥ 1 minute apart at trial entry.

8. Moderate or severe hepatic impairment (i.e., Child-Pugh class B or C).

9. Uncontrolled hypertension (systolic blood pressure [BP] ≥ 160 mmHg and/or diastolic BP ≥ 100 mmHg) despite adequate treatment prior to first dose of treatment.

10. Persistent Grade > 1 non-hematological toxicity from prior cancer therapy (except alopecia, anorexia or toxicity that is stable and poses no significant risk to the participant). Grade 2 peripheral neuropathy after documented treatment with taxanes and/or platinum-based therapy is allowed.

11. Chemotherapy, small molecule or biologic antineoplastic agent given within 21 days or < 5 half-lives, whichever is shorter, prior to first dose of trial intervention. For compounds for which 5 half-lives is ≤ 21 days, a minimum of 10 days between termination of the prior treatment and administration of trial intervention is required.

12. Other anticancer therapy (chemotherapy, immunotherapy, hormonal anticancer therapy, biological therapy, lanreotide/octreotide for neuroendocrine tumors (NETs)/neuroendocrine carcinomas (NECs), or other novel agent) while the participant is receiving trial intervention. For participants with breast or prostate cancer, continuation of long-term luteinizing hormone-releasing hormone (LHRH) or gonadotrophin releasing hormone (GnRH) are allowed if these medications were prescribed for at least 4 months before trial entry.

13. Previously prescribed receptor activator of nuclear factor kappa B ligand (RANKL) inhibitor initiated less than 4 months prior to trial entry. Bisphosphonates are allowed if initiated/administered at least 28 days prior to enrollment.

14. I-131 Meta-Iodo-Benzyl-Guanidine (MIGB) therapy within 6 weeks prior to initiation of trial treatment.

15. Prior treatment with a PLK4 inhibitor.

16. Use of radiotherapy (except for palliative reasons) within 14 days prior to trial treatment initiation.

17. Current treatment with medications that are known to prolong the QT interval [redacted].

18. Participants who are receiving strong P-glycoprotein (P-gp) inhibitors and/or breast cancer resistance protein (BCRP) inhibitors within 14 days prior to first dose of trial intervention [redacted]

    Note: RP-1664 is an in vitro inducer of CYP3A, CYP2B6, and CYP1A2. Investigators should consult with the Medical Monitor prior to enrollment of participants taking sensitive substrates of these enzymes, in particular CYP3A [redacted] *Participants must use additional methods of contraception if using estrogen/progestin-based agents.*

    Note: RP-1664 is a substrate of CYP1A1. Literature examples of CYP1A1 inhibitors are limited and the existence of clinically relevant CYP1A1 inhibitors are also limited. If investigators have questions with regards to particular concomitant medications, they should contact the Sponsor

19. Major surgical procedures ≤ 28 days prior to trial treatment initiation, Participants must have recovered from any of the effects of any major surgery. No waiting period is required following central venous access placement, biopsy collection or minor surgeries as long as Investigator assesses the impact on trial participation.

20. Gastrointestinal abnormalities, including inability to take whole, intact oral medication, requirement for intravenous alimentation, prior surgical procedures affecting absorption including total gastric resection or lap band, active inflammatory gastrointestinal disease, chronic diarrhea, symptomatic diverticular disease, treatment for active peptic ulcer disease in the past 6 months, and malabsorption syndromes.

21. Participants who are breastfeeding at screening or planning to become pregnant (self or partner) at any time during trial participation.

22. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol and/or follow-up procedures outlined in the protocol.

Trial Interventions

RP-1664 adolescent/adult whole capsules will be supplied as immediate-release solid dosage form for oral self-administration. The pediatric drug product for the Food Effect and PK Bridging portion of the trial will be supplied as sprinkle capsules.

Committees

Independent Committees: SRC.