Protocol for

Official Title of Study

A PHASE 1B/2 STUDY OF REPOTRECTINIB IN COMBINATION WITH TRAMETINIB FOR THE TREATMENT OF SUBJECTS WITH KRASG12D-MUTANT ADVANCED SOLID TUMORS (TRIDENT-2)

NCT05071183

February 04, 2022

SUBPROTOCOL 1: REPOTRECTINIB + TRAMETINIB

A PHASE 1B/2 STUDY OF REPOTRECTINIB IN COMBINATION WITH TRAMETINIB FOR THE TREATMENT OF SUBJECTS WITH *KRAS*^{G12D}-MUTANT ADVANCED SOLID TUMORS (TRIDENT-2)

Investigational Product Number:	TPX-0005
Investigational Product Name:	Repotrectinib
Protocol Number:	TPX-0005-13
United States (US) Investigational New Drug (IND) Number:	153890
European Clinical Studies Database (EudraCT) Number:	TBD
Phase:	1b/2
Protocol Version:	3.0
Sponsor Name and Address:	Turning Point Therapeutics, Inc. [redacted]
Medical Monitor:	[redacted]

TURNING POINT THERAPEUTICS APPROVAL

Protocol Number: TPX-0005-13, Subprotocol 1

Version (Date): 3.0 (04 February 2022)

Subprotocol Title: A Phase 1b/2 Study of Repotrectinib in Combination with Trametinib for the Treatment of Subjects with *KRAS*^{G12D}-Mutant Advanced Solid Tumors (TRIDENT-2)

[redacted] Date: 04-Feb-2022 | 14:53 PST

[redacted]
Executive Director, Clinical Development
Turning Point Therapeutics, Inc.

PRINCIPAL INVESTIGATOR STATEMENT OF AGREEMENT

I, the undersigned Principal Investigator, have read and understood the following subprotocol, TPX-0005-13, Subprotocol 1, Version 3.0, 04 February 2022, and its appendices.

I promise to abide by the International Conference for Harmonisation (ICH) Guidelines for Good Clinical Practices (GCP), the Declaration of Helsinki, and all applicable laws and regulations, and agree that, in all cases, the most restrictive regulation related to a given aspect of research involving protection of human subjects will be followed. If I have a question regarding my obligations during the conduct of this protocol, I have ready access to these aforementioned regulations, as either my personal copy, or available on file from the Chairperson of the Institutional Review Board (IRB)/Ethics Committee (EC) or the Sponsor, via local authorities and, I am authorized to enter into this commitment to conduct the study outlined in this protocol, and my signature below signifies that I agree to conduct the study as outlined herein.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL SYNOPSIS

Name of Sponsor/Company:
Turning Point Therapeutics, Inc. (Sponsor)

Indication:
Treatment of patients with locally advanced or metastatic *KRAS*-mutant solid tumors

Name of Investigational Product(s):
Repotrectinib, trametinib (Mekinist® [trametinib] USPI 2020)

Title of Subprotocol:
A Phase 1b/2 Study of Repotrectinib in Combination with Trametinib for the Treatment of Subjects with *KRAS*^{G12D}-Mutant Advanced Solid Tumors (TRIDENT-2)

Phase of Development
Phase 1b/2

Objectives

Phase 1b Primary Objectives

- Evaluate the safety and tolerability of repotrectinib at increasing dose levels in combination with trametinib for the treatment of subjects with locally advanced or metastatic *KRAS*-mutant solid tumors.
- Determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of repotrectinib in combination with trametinib for the treatment of subjects with locally advanced or metastatic *KRAS*-mutant solid tumors.

Phase 1b Secondary Objectives

- Characterize the pharmacokinetic (PK) profile of repotrectinib in combination with trametinib.
- Describe the preliminary efficacy of repotrectinib in combination with trametinib.

Phase 2 Primary Objective

- Evaluate the efficacy of repotrectinib in combination with trametinib for the treatment of subjects with locally advanced or metastatic *KRAS*-mutant solid tumors as measured by objective response rate (ORR).

Phase 2 Secondary Objectives

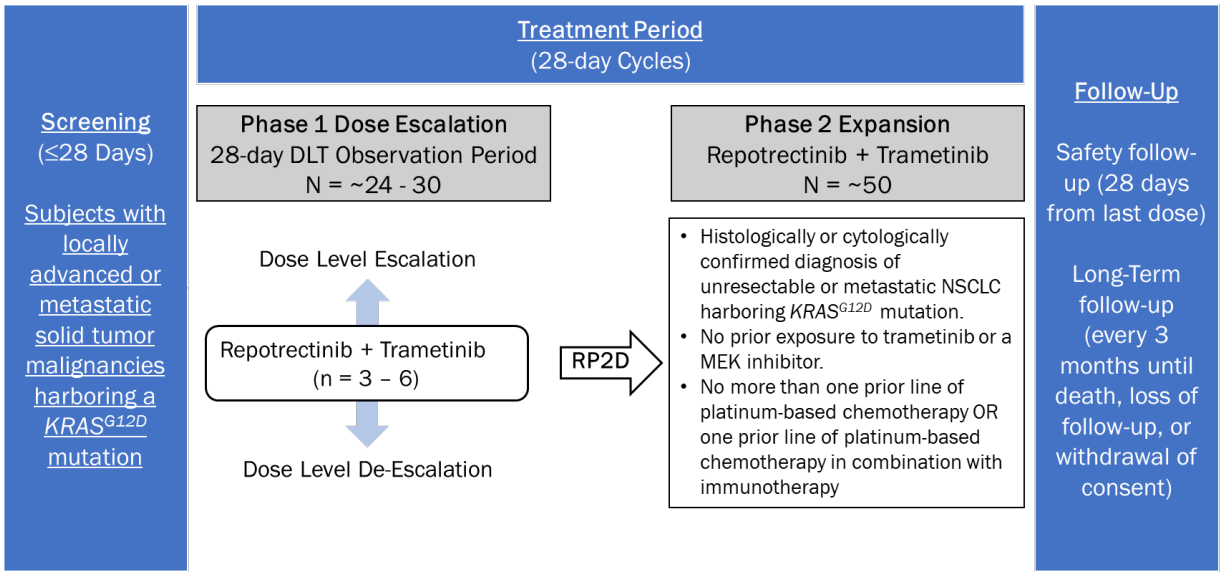
- Evaluate the efficacy of repotrectinib in combination with trametinib for the treatment of subjects with locally advanced or metastatic *KRAS*-mutant solid tumors as measured by clinical benefit rate (CBR), progression-free survival (PFS), duration of response (DOR), time to response (TTR), and overall survival (OS).
- Evaluate the safety and tolerability of repotrectinib in combination with trametinib.
- Characterize the PK profile of repotrectinib in combination with trametinib.

Exploratory Objectives (All Phases)

- Evaluate biomarkers potentially predictive of response in subjects treated with repotrectinib in combination with trametinib.
- Explore the potential prognostic utility of genomic alterations and characterize intrinsic or acquired resistance in subjects treated with repotrectinib in combination with trametinib using tissue-based or liquid-based biopsy samples.

Overall Study Design:

This subprotocol is a Phase 1b/2 multi-center, open-label study to evaluate the efficacy, safety, tolerability, and PK of repotrectinib in combination with trametinib, for the treatment of subjects with locally advanced or metastatic *KRAS*^{G12D}-mutant solid tumors. The study will consist of two portions: Phase 1b Dose Escalation and Phase 2 Expansion. The overall study design for this subprotocol is shown in the figure below.



Abbreviations: KRAS = Kirsten rat sarcoma viral oncogene homolog; MEK = mitogen-activated protein kinase; NSCLC = non-small cell lung cancer; RP2D = recommended Phase 2 dose.

Phase 1b Dose Escalation

Subjects with locally advanced or metastatic solid tumor malignancies harboring a *KRAS*^{G12D} mutation will be enrolled into the Phase 1b dose escalation portion of the study to determine the MTD/RP2D of repotrectinib in combination with trametinib. Dose escalation will follow a traditional 3+3 design.

Phase 2 Expansion

Once the MTD/RP2D of repotrectinib in combination with trametinib has been determined, subjects will be enrolled into a Phase 2 expansion portion. The Phase 2 portion is designed to explore the anti-tumor efficacy and safety of repotrectinib in combination with trametinib for the treatment of patients with locally advanced or metastatic NSCLC harboring a *KRAS*^{G12D} mutation.

Treatment Duration

Subjects may receive treatment with repotrectinib in combination with trametinib until disease progression or unacceptable toxicity. Subjects may continue treatment with single agent repotrectinib or trametinib if there is continuing clinical benefit per Investigator's judgment and in consultation with the Sponsor's Medical Monitor. After discontinuation of both study drugs, subjects will continue to be followed on study for overall survival.

Phase 1b Dose Escalation Study Design:

Subjects with locally advanced or metastatic solid tumor malignancies harboring a *KRAS*^{G12D} mutation will be enrolled into the Phase 1b dose escalation portion of the study to determine the MTD/RP2D of repotrectinib in combination with trametinib. Initially, approximately 24 – 30 subjects with locally advanced or metastatic solid tumor malignancies harboring a *KRAS*^{G12D} mutation will be enrolled.

Dose escalation will follow a traditional 3+3 design. Three to six DLT-evaluable subjects at each dose level will be administered daily (QD) doses of repotrectinib in combination with trametinib according to the table below (starting with Dose Level 1) and evaluated for dose-limiting toxicities (DLTs) during Cycle 1 (i.e., for 28 days). After the first 3 subjects have completed their first cycle of study treatment (Cycle 1), a safety evaluation will be conducted by a Safety Review Committee to determine if enrollment of subjects in the next dose level (Dose Level 2) may begin. If no subjects experience a DLT within the first 28 days of Dose Level 1 treatment, then dose escalation may proceed to the next dose level, according to the table below. If 1 of the 3 initial subjects at Dose Level 1 experiences a DLT, then the next 3 subjects will be enrolled prior to escalating to the next dose level. Enrollment into all subsequent dose levels will follow the same procedure. If ≥ 33% of subjects at any dose level experience a DLT within the first 28 days of treatment, the dose levels will be de-escalated to Dose Level -2 or -3 according to SRC recommendation and following approval by the Sponsor, as detailed in the table below. If Dose Level -2 is tolerable, testing of alternate escalating dose levels (-2a, -2b) may occur as outlined in the table below. If Dose Level -2 is not tolerable, subjects will be de-escalated to Dose Level -3. If Dose Level -3 is tolerable, testing of alternate escalating dose levels (-3a, -3b) may occur as outlined in the table below. Alternative regimens or additional dose levels or dose level increments may be explored based on emergent clinical safety, efficacy, and PK data. See Section 3.2 for further details of dose finding.

Dose-finding Dose Levels

Dose Level	Repotrectinib	Trametinib
3	160 mg QD/BID[a]	2 mg QD
2	160 mg QD	2 mg QD
1 (Starting Dose)	120 mg QD	2 mg QD
(-2b)	160 mg QD/BID[a]	1.0 mg QD
(-2a)	160 mg QD	1.0 mg QD
-2	120 mg QD	1.0 mg QD
(-3b)	160 mg QD/BID[a]	0.5 mg QD
(-3a)	160 mg QD	0.5 mg QD
-3	120 mg QD	0.5 mg QD

Abbreviations: BID = twice daily; QD = once daily; TRAE = treatment-related adverse event.
[a] 160 mg QD (once daily) for the first 14 days, after which the dose may be increased to 160 mg BID based on subject safety and tolerability and assuming specific criteria are met. Subjects must meet the following criteria while on 160 mg QD prior to dose increase to 160 mg BID: no evidence of grade ≥ 3 TRAE, unmanageable grade ≥ 2 dizziness, ataxia or paresthesia; or grade ≥ 3 clinically significant lab abnormalities.

A Safety Review Committee, including study Investigators and the Sponsor Medical Monitor, will provide recommendations for dose escalation, confirmation of DLTs, dose de-escalation, and determination of the RP2D. At least 6 subjects will be treated at the RP2D prior to proceeding into the Phase 2 portion of the study. Additional subjects may be added at a dose level to gather more safety, PK, and efficacy data.

Criteria for Defining Dose-limiting Toxicities

Subjects are eligible for Dose-limiting Toxicities (DLT) evaluation if they experience a DLT during the first cycle of treatment (i.e., 28 days), or do not experience a DLT during the first cycle of treatment while able to receive at least 75% of planned doses during the first cycle of treatment. Subjects who do not fulfill these requirements will be replaced for DLT evaluation but will remain in the overall safety and efficacy analyses.

A DLT is defined as an adverse event (AE) or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness, or concomitant medications that meets any of the following criteria:

Category[a]	**Criteria**
Toxicities resulting in an excessive number of missed doses	• Inability to deliver at least 75% of the planned doses of repotrectinib and trametinib during Cycle 1 treatment because of toxicity attributed to study drug (excluding toxicities clearly related to disease progression or intercurrent illness)
Hematologic toxicities	• Grade ≥ 4 neutropenia (ANC < 500/ mm^3) lasting > 7 days • Grade ≥ 4 platelet count decrease (platelets < 25,000/mm^3) or Grade ≥ 2 (< 75,000/mm^3) associated with clinically significant bleeding • Grade ≥ 4 anemia • Grade ≥ 3 febrile neutropenia (defined as ANC < 1,000/mm^3 with a single temperature of ≥ 38.3°C [≥ 101°F] or a sustained temperature of ≥ 38°C [≥ 100.4°F] for > 1 hour)
Renal	• Grade ≥ 3 creatinine increase (> 3 × upper limit of normal [ULN])
Hepatic	• Grade ≥ 3 total bilirubin elevation (> 3 × ULN) • Grade ≥ 2 total bilirubin elevation (> 1.5 × ULN) and grade ≥ 2 ALT or AST elevation (> 3 × ULN) • Grade 3 ALT elevation (> 5 × ULN) that does not resolve to grade ≤ 1 within 7 days or any grade ≥ 4 ALT elevation • Grade 3 AST elevation (> 5 × ULN) that does not resolve to grade ≤ 1 within 7 days or any grade ≥ 4 AST elevation • Grade 4 elevations in ALP
Pancreatic	• Grade ≥ 3 amylase or lipase elevation
Cardiac	• Grade ≥ 3
Other AEs	• Grade 3 electrolyte disturbances that require hospitalization • Grade 4 electrolytes abnormalities • Grade ≥ 3 AE, persisting after optimal treatment with standard medical therapy except for the exceptions noted below under "Exceptions to DLT criteria" • In view of the Investigators and Sponsor, any other unacceptable toxicity encountered
Exceptions to DLT criteria	• Grade 3 elevations in ALP

	• Grade 3 electrolytes abnormalities that are adequately managed by IV or PO supplementation as evidenced by an improvement to grade ≤ 1 within 3 days • Grade 3 fatigue which resolves to grade ≤ 1 in ≤ 7 days • Isolated grade 3 laboratory abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset • Grade 3 dizziness which resolves to grade ≤ 1 within ≤ 7 days

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; DLT = dose-limiting toxicity; IV = intravenous; PO = per os (by mouth); ULN = upper limit of normal.
Note: Adverse event grading based on CTCAE v5.0.
[a] Toxicities clearly related to disease progression or intercurrent illness will not be considered DLTs.

In addition, clinically important or persistent toxicities not included in the above criteria may be considered a DLT following review by the Sponsor and study Investigators. All DLTs should represent a clinically significant shift from baseline. These will be evaluated according to National Cancer Institute (NCI) CTCAE v5.0.

To fully characterize the safety of repotrectinib in combination with trametinib, subjects who are discontinued from treatment before completing the DLT evaluation period (28 days, Cycle 1) due to disease progression or other event unrelated to study drugs, or who did not adequately complete the PK evaluations within Cycle 1, may be replaced.

Determination of MTD

The MTD is defined as the highest dose level of repotrectinib given in combination with trametinib observed to cause a DLT in fewer than 33% of the treated subjects in the first treatment cycle (i.e., 28 days, Cycle 1).

Recommended Phase 2 Dose (RP2D) Definition

The RP2D is the dose chosen for further study in Phase 2 based on the Phase 1b results. RP2D dose selection will be based on the entirety of the safety, efficacy, and clinical pharmacology data using an integrated quantitative approach. The RP2D may be the MTD unless one or more of the following suggest an alternate dose below the MTD would be preferable:

a. clinically significant anti-tumor effect (complete response [CR], partial response [PR], or prolonged stable disease [SD]) occurs below the MTD, in which case a clinically active dose level may be selected as the RP2D;
b. the MTD is not achieved, in which case the highest dose level administered may become the RP2D; or
c. toxicities observed beyond the DLT evaluation period (Cycle 1) require selecting the RP2D below the MTD level.

Once the MTD of repotrectinib in combination with trametinib has been determined, the RP2D will be determined at or below the MTD.

Phase 2 Study Design:

Once the MTD/RP2D of repotrectinib in combination with trametinib has been determined, approximately 50 subjects will be enrolled into the Phase 2 expansion portion. The Phase 2 portion is designed to explore the anti-tumor efficacy and safety of repotrectinib in combination with trametinib for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC)

harboring a *KRAS*^{G12D} mutation. An interim futility analysis of the ORR will be performed after approximately 15 subjects are evaluable for tumor response. If ≤ 2 responders (confirmed CR or PR) are observed from 15 evaluable subjects, the expansion cohort will be stopped for futility. If ≥ 3 responders are observed, this cohort may continue depending on the overall benefit and risk assessment at the interim analysis. Tumor assessments will include all known or suspected disease sites. All radiographic efficacy endpoints will be assessed using RECIST v1.1. Intracranial responses will be assessed by modified RECIST v1.1. For all tumor assessments, the imaging modality used at baseline should be the same modality used throughout the study. Safety will be monitored *via* laboratory assessments, physical examinations, electrocardiograms (ECG), vital signs, and TEAEs according to CTCAE v5.0. PK data will also be collected. In addition, safety will be monitored by a Safety Review Committee comprised of at minimum the Sponsor Medical Monitor and study Investigators to review all relevant safety and other relevant clinical data.
Number of subjects (planned): Phase 1b Dose Escalation: approximately 24 – 30 subjects Phase 2 Expansion: approximately 50 subjects

Inclusion Criteria:

Phase 1 AND Phase 2

1. Subject must have a histologically or cytologically confirmed diagnosis of unresectable or metastatic solid tumor malignancy harboring a *KRAS*^{G12D} mutation.
    - Documented *KRAS*^{G12D} mutation as determined by a quantitative polymerase chain reaction (qPCR) or next-generation sequencing (NGS) test performed in a Clinical Laboratory Improvement Amendments (CLIA) laboratory or equivalently accredited diagnostic laboratory. Local tissue-based or liquid biopsy diagnostic testing will be permitted.
    - Adequate tumor tissue needs to be sent to the Sponsor designated central diagnostic laboratory for retrospective confirmation by a central diagnostic laboratory test selected by the Sponsor. See the Study Laboratory Manual for details.
2. Eastern Cooperative Oncology Group (ECOG) Performance Status 0–1.
3. Age ≥ 18 (or as required by local regulation).
4. Willing and able to provide written institutional review board (IRB)/ethics committee (EC)-approved Informed Consent.
5. At least 1 measurable target lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Subjects with central nervous system (CNS)-only measurable target lesion ≥ 5 mm as defined by RECIST v1.1 are eligible.
6. Required wash-out time that is related to prior therapies before starting repotrectinib combination treatment:
    - At least 14 days or 5 half-lives (whichever is shorter) must have elapsed after discontinuation of prior systemic therapy and all side effects from prior treatments must have resolved to grade ≤ 1 with the exception of alopecia.
    - At least 14 days must have elapsed after discontinuation of prior immunotherapy and all immune-related side effects from prior immunotherapy must have resolved to grade ≤ 1.
7. Subjects with asymptomatic CNS metastases (treated or untreated) and/or asymptomatic leptomeningeal carcinomatosis are eligible to enroll if they satisfy the following criteria:
    - Subjects requiring steroids at a stable or decreasing dose (≤ 12 mg/day dexamethasone or equivalent) for at least 14 days.
    - Subjects on stable doses of levetiracetam (same dose for 14 days).
    - A minimum of 14 days must have elapsed from the completion of whole brain radiation treatment (WBRT) before the start of treatment, and all side effects (with the exception of alopecia) from WBRT are resolved to grade ≤ 1.
    - A minimum of 7 days must have elapsed from the completion of stereotactic radiosurgery before the start of treatment and all side effects (with the exception of alopecia) from stereotactic radiosurgery are resolved to grade ≤ 1.
8. Baseline laboratory values fulfilling the following requirements:

Absolute Neutrophils Count	≥ 1,500/mm^3 (1.5 x 10^9/L)
Platelets	≥ 100,000/mm^3 (100 x 10^9/L) independent of platelets transfusion support for at least 7 days prior to dosing
Hemoglobin	≥ 9.0 g/dL independent of transfusion support for at least 7 days prior to dosing
Creatinine Clearance*	> 40 mL/min

Total Serum Bilirubin	< 1.5 x ULN (≤ 3.0 × ULN for patients with Gilbert's Syndrome or liver metastases)
Liver Transaminases (AST/ALT)	< 2.5 x ULN; < 5 x ULN if liver metastases are present
Alkaline Phosphatase	< 2.5 x ULN; < 5 x ULN if liver and/or bone metastasis are present.
Serum Calcium, Magnesium and Potassium	Normal or CTCAE grade ≤ 1 with or without supplementation.

Abbreviations: AST/ALT = aspartate aminotransferase/alanine aminotransferase, ULN = upper limit of normal.
* calculated by Cockcroft and Gault's formula: (140 - age [yr.]) x body weight [kg] x 1.23 x (0.85 if female) /serum creatinine [µmol/L].

9. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test during screening and be neither breastfeeding nor intending to become pregnant during study participation. Female patients will be considered to be of childbearing potential unless they have undergone permanent sterilization or are postmenopausal. Postmenopausal is defined as at least 12 months without menses with no other medical reasons (e.g., chemical menopause due to anticancer treatment). For WOCBP and for men, agreement to use a highly effective contraceptive method from the time of screening throughout the study until 4 months (WOCBP) or 6 months (men) after administration of the last dose of any study drug. Highly effective contraceptive methods consist of prior sterilization, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), injectable or implantable contraceptives. All male study subjects must agree to use condoms throughout the study and 6 months after administration of the last dose. Male partners of WOCBP subjects must agree to condom use throughout the study and for 4 months following the last dose of study drug. True abstinence is acceptable if evaluated as consistent with the preferred and the usual lifestyle of the subject. Periodic abstinence is not an acceptable method of contraception.
10. Ability to swallow capsules and tablets intact (without chewing, crushing, or opening).
11. Life expectancy ≥ 3 months.
12. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

Additional Inclusion Criteria for Phase 1 only:

13. Subject must have received prior standard therapy appropriate for their tumor type and stage of disease, or in the opinion of the Investigator, would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy.
    - Subject must have received no more than 3 prior systemic regimens.
    - Maintenance therapy will not be counted as a separate regimen.
    - Adjuvant chemotherapy or chemotherapy administered as part of concurrent chemotherapy and radiation therapy will not count as a prior regimen of systemic therapy as long as recurrence occurred more than 6 months after the last day of chemotherapy.

Additional Inclusion Criteria for Phase 2 only:

14. Histologically or cytologically confirmed diagnosis of advanced or metastatic NSCLC harboring a $KRAS^{G12D}$ mutation.
    - Subject must have a documented $KRAS^{G12D}$ mutation as determined by a qPCR or NGS test performed in a CLIA laboratory or equivalently accredited diagnostic laboratory. Local tissue-based or liquid biopsy diagnostic testing will be permitted.

- Adequate tumor tissue needs to be sent to the Sponsor designated central diagnostic laboratory for retrospective confirmation by a central diagnostic laboratory test selected by the Sponsor. See the Study Laboratory Manual for details.

15. Subjects must have received no more than one prior line of platinum-based chemotherapy **OR** one prior line of platinum-based chemotherapy in combination with immunotherapy OR both platinum-based chemotherapy and single agent anti-PD1/PDL1 therapy in two separate lines of therapy.
    - Adjuvant chemotherapy or chemotherapy administered as part of concurrent chemotherapy and radiation therapy for the treatment of lung cancer will not count as a prior regimen of systemic therapy as long as recurrence of patient's lung cancer occurred more than 12 months after the last day of chemotherapy.

Exclusion Criteria:

1. Concurrent participation in another therapeutic clinical trial.
2. Symptomatic brain metastases or leptomeningeal involvement.
3. History of previous cancer requiring therapy within the previous 2 years, except for squamous cell or basal-cell carcinoma of the skin, or any *in situ* carcinoma that has been completely resected.
4. Major surgery within 4 weeks of start of treatment. Radiation therapy (except palliative to relieve bone pain) within 2 weeks of start of treatment. Palliative radiation (≤ 10 fractions) must have been completed at least 48 hours prior to start of treatment.
5. Clinically significant cardiovascular disease (either active or within 6 months prior to start of treatment): myocardial infarction, unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (New York Heart Association Classification Class ≥ II), cerebrovascular accident or transient ischemic attack, symptomatic bradycardia, requirement for anti-arrhythmic medication. Ongoing cardiac dysrhythmias of CTCAE grade ≥ 2.
6. Any of the following cardiac criteria:
    - Mean resting corrected QT interval (electrocardiogram [ECG] interval measured from the onset of the QRS complex to the end of the T wave) for heart rate (QTc) > 470 msec obtained from 3 ECGs, using the screening clinic ECG machine-derived QTc value
    - Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG (e.g., complete left bundle branch block, third degree heart block, second degree heart block, PR interval > 250 msec)
    - Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalemia, congenital long QT syndrome, family history of long QT syndrome, or any concomitant medication known to prolong the QT interval
7. Known clinically significant active infections not controlled with systemic treatment (bacterial, fungal, viral including human immunodeficiency virus [HIV] positivity, hepatitis B [HBV], and hepatitis C [HCV], and acquired immunodeficiency syndrome [AIDS]-related illness).
8. Gastrointestinal disease (e.g., Crohn's disease, ulcerative colitis, or short gut syndrome) or other malabsorption syndromes that would impact drug absorption.
9. Peripheral neuropathy, paresthesia, dizziness, dysgeusia, muscle weakness, ataxia grade ≥ 2.

10. Currently have or had a history of ILD, radiation pneumonitis that required steroid treatment, or drug-related pneumonitis.
11. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or that may interfere with the interpretation of study results and, in the judgment of the Investigator and/or Turning Point Therapeutics, would make the subject inappropriate for entry into this study, or could compromise protocol objectives in the opinion of the Investigator and/or Turning Point Therapeutics.
12. Current or anticipated use of drugs that are known to be strong CYP3A inhibitors or inducers as well as use of drugs that are sensitive CYP3A substrates as listed in Appendix 1.
13. Prior exposure to repotrectinib.
14. Prior exposure to a direct and specific inhibitor of KRAS
15. Prior exposure to trametinib or another mitogen-activated protein kinase (MEK) inhibitor.
16. Subjects have a history or current evidence of retinal vein occlusion (RVO) or central serous retinopathy (CSR) determined by an ophthalmology exam.
17. Current or anticipated use of drugs that are sensitive substrate with narrow therapeutic index for UGT1A1.
18. Current or anticipated use of drugs that are sensitive substrate with narrow therapeutic index for OATP1B1, OAT3, MATE1, and MATE2-K.
19. Current or anticipated use of drugs that are strong inhibitors of P-glycoprotein.

Investigational Products/Dosage Formulations:
Repotrectinib will be supplied as 40 mg capsules.
Trametinib will be supplied as commercially available in 0.5 mg or 2 mg tablets.

Dose Regimen and Route of Administration:
Repotrectinib and trametinib will be administered orally as a combination treatment. For the Phase 1b dose escalation portion of the study, subjects will be assigned to a repotrectinib and trametinib dose according to the currently open dose level for 28 consecutive days in repeated four-week cycles.
For the Phase 2 expansion portion of the study, subjects will be allocated to receive repotrectinib and trametinib at the RP2D combination determined during the Phase 1b dose escalation portion for 28 consecutive days in repeated four-week cycles.

Criteria for Evaluation
Primary Endpoint for Phase 1:
- Incidence of first cycle (28 days) DLTs to determine MTD and/or RP2D.

Secondary Endpoints for Phase 1:
- ORR assessed by the Investigator using RECIST v1.1
- Pharmacokinetic parameters of repotrectinib
- Pharmacokinetic parameters of trametinib

Phase 2 Primary Endpoint:
- ORR assessed by Investigator per RECIST v1.1.

Phase 2 Secondary Endpoints:

- DOR, TTR, and CBR by the Investigator
- PFS and OS
- Intracranial objective response rate (IC-ORR) assessed according to modified RECIST v1.1 in subjects with brain metastases.
- Type, incidence, severity, timing, seriousness, and relatedness (to each study drug) of AEs and laboratory abnormalities
- Pharmacokinetic parameters of repotrectinib
- Pharmacokinetic parameters of trametinib

Exploratory Endpoints (All Phases):

- ORR and PFS by modulation of circulating tumor levels and genomic alterations observed pre- and post-dosing.

Sample Size Determinations:

Phase 1b Dose Escalation

For dose escalation, 3 to 6 DLT-evaluable subjects will be enrolled per dose level. Therefore, it is expected that approximately 24 – 30 subjects will be enrolled to determine the RP2D of repotrectinib in combination with trametinib.

Phase 2 Expansion

For the Phase 2 expansion, 50 subjects will be enrolled. In addition, up to 6 locally advanced or metastatic *KRAS*-mutant NSCLC subjects treated at the RP2D in Phase 1b will be pooled for the efficacy analysis. If 21 subjects out of 56 subjects have a confirmed objective response (ORR = 38%; 95% confidence interval [CI]: 25 – 51) where the lower limit of the 95% CI is > 23%, repotrectinib in combination with trametinib will be considered superior than the currently approved chemotherapy in the second-line setting for NSCLC in this expansion cohort, including the combination of docetaxel + ramucirumab (Cyramza® USPI, 2020) which has demonstrated a best ORR of 23% (95% CI: 20 – 26) in the second-line setting.

An interim futility analysis of the ORR will be performed after approximately 15 subjects are evaluable for tumor response. If ≤ 2 responders (confirmed CR or PR) are observed from 15 evaluable subjects, the expansion cohort will be stopped for futility. If ≥ 3 responders are observed, this cohort may continue depending on the overall benefit and risk assessment at the interim analysis. If ≥ 3 responders are observed, this cohort may continue depending on the overall benefit and risk assessment at the interim analysis. If the true ORR in this cohort is as targeted at 38%, the probability of observing ≤ 2 responders is 3.8%. If the true ORR is significantly lower than the target ORR (i.e., 10% instead of 38%), the probability is 81.6%.

SCHEDULE OF ACTIVITIES

Table 1: Schedule of Activities: Repotrectinib + Trametinib

	Screening (≤ 28 Days)	Cycle 1 (28 days)				Cycle 2 (28 days)		Cycle 3 (28 days)	Cycle 4 and Beyond	End of Treatment	Safety Follow-up	Long-Term Follow-up
Study Visit		Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	Day 1			
Visit Window[1]	**NA**		±1	±1	±1	±2	±2	±2	±2	+7	+7	
Informed Consent[2]	X											
Tumor Molecular Alteration[3]	X											
Tumor Treatment History[4]	X											
Medical History	X											
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	
Height	X											
Weight	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs[5]	X	X	X	X	X	X	X	X	X	X	X	
Ophthalmologic exam[6]	X											
Study Drug Administration at Clinic												
Repotrectinib		X	X	X	X	X		X	X[7]			
Trametinib		X	X	X	X	X		X	X[7]			
Dispense Repotrectinib and Trametinib		X		X[8]		X		X	X			
Diary Review: Repotrectinib and/or Trametinib Compliance[9]		X	X	X	X	X	X	X	X	X		

	Screening (≤ 28 Days)	Cycle 1 (28 days)				Cycle 2 (28 days)		Cycle 3 (28 days)	Cycle 4 and Beyond	End of Treatment	Safety Follow-up	Long-Term Follow-up
Study Visit		**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 15**	**Day 1**	**Day 1**			
Visit Window[1]	**NA**		**±1**	**±1**	**±1**	**±2**	**±2**	**±2**	**±2**	+7	+7	
Laboratory												
Complete Blood Count with Differential[10]	X	X	X	X	X	X	X	X	X	X	X	
Complete Chemistry Panel[11]	X	X	X	X	X	X	X	X	X	X	X	
Coagulation[12]	X	X	X	X	X	X		X	X	X	X	
Pregnancy Test (serum)[13]	X	X				X		X	X	X	X	
Urine Analysis[14]	X	X	X	X	X	X		X	X	X	X	
Blood Specimens for ccfDNA Enrichment[15]	X							X		X		
Cardiac Safety Monitoring												
Triplicate 12-lead ECG[16]	X	X	X	X	X	X		X	X	X		
Echocardiogram/ MUGA for LVEF Assessment[17]	X					X			X		X	
Pharmacokinetics												
Pharmacokinetic Blood Sampling Trametinib[18]		X	X	X	X	X		X	X	X		
Pharmacokinetic Blood Sampling Repotrectinib[18]		X	X	X	X	X		X	X	X		
Tumor Assessment												
CT or MRI (chest/abdomen/pelvis)[19]	X							X		X		
CT or MRI of Brain[20]	X							X		X		
Bone Scan[21]	X											

	Screening (≤ 28 Days)	Cycle 1 (28 days)				Cycle 2 (28 days)		Cycle 3 (28 days)	Cycle 4 and Beyond	End of Treatment	Safety Follow-up	Long-Term Follow-up
Study Visit		Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	Day 1			
Visit Window[1]	**NA**		±1	±1	±1	±2	±2	±2	±2	+7	+7	
Other Clinical Assessments												
Adverse Events[22]	X[22]	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications and Non-Drug Supportive Interventions[23]	X	X	X	X	X	X	X	X	X	X	X	
Survival Follow-Up[24]												X

Abbreviations: CT = Computerized tomography; ccfDNA = Circulating cell-free DNA; CSR = central serous retinopathy; DCT = data collection tool; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; LVEF = Left ventricular ejection fraction; mIU = Milli international unit; MRI = Magnetic resonance imaging; MUGA = multigated acquisition; NA = not applicable; RVO = retinal vein occlusion.

1. **Visit Window**: The 28-day screening period starts on the day informed consent is signed by the subject. The safety follow-up visit should be within 28 days from the last dose of both study drugs.
2. **Informed Consent:** Must be obtained before undergoing any protocol-specific procedures.
3. **Tumor Molecular Alteration:** Confirmation of $KRAS^{G12D}$ mutation (submit molecular pathology report-source document) and submit archival tumor tissue.
4. **Tumor Treatment History:** Record all prior therapies, including prior chemotherapy regimens and duration and best response of each chemotherapy regimen, prior immunotherapy regimens and duration and best response of each immunotherapy regimen (if applicable), prior radiation to the brain (if brain metastases are present, and methods of radiation: whole brain radiation, stereotactic radiosurgery).
5. **Vital Signs:** Body temperature, blood pressure, heart rate, and respiratory rate.
6. **Ophthalmologic Exam:** A standard ophthalmologic exam will be performed at Screening. The exam will include direct and indirect fundoscopic exams, visual acuity (corrected), visual field examination, and tonometry, with special attention to any retinal abnormalities that are predisposing factors for RVO or CSR. After Screening, additional ophthalmologic exams will be performed only as symptomatically warranted.
7. **Study Drug Administration in Clinic**: Study drug administration will be conducted in the clinic on days where a pre-dose PK sample is required. After Cycle 6 Day 1, subjects will not be required to take the study drug dose in the clinic on Day 1 of each subsequent cycle.
8. **Dispense Repotrectinib (C1D15):** For subjects assigned to repotrectinib BID dosing regimens (Dose Level 3, -2b, or -3b), repotrectinib will be dispensed on Day 15 following Investigator assessment of safety to confirm escalation from QD to BID dosing.
9. **Dosing Diary**: On Day 1 of each cycle, a new dosing diary will be provided to the subject. All subjects are required to complete dosing diary daily in conjunction with administration of repotrectinib and trametinib. At C1D1 all subjects should be trained by the site personnel how to complete the diary and inform them that all efforts should be made to record the dosing information as accurate as possible. The diary needs to be returned to the clinic together with the remaining study drug at each study visit. Study drug compliance and accountability needs to be reviewed at each study visit by the site personnel.
10. **Complete Blood Count with Differential:** White blood cell count, hemoglobin, platelets, absolute neutrophils, absolute lymphocytes, absolute monocytes, absolute eosinophils, and absolute basophils. On on-site dosing days, assessments will be performed **before** the dose of study drug is given. Complete Blood Count with Differential is *optional* on C1D1 if performed within the past 7 days.

11. **Complete Chemistry Panel:** ALT, AST, ALP, sodium, potassium, magnesium, chloride, total calcium, total bilirubin, BUN or urea, creatinine, uric acid, glucose (nonfasted), lipid panel (total cholesterol, LDL, HDL, triglycerides), albumin, phosphorus or phosphate, bicarbonate, total protein, lactate dehydrogenase, amylase, lipase. On on-site dosing days, assessments will be performed **before** the dose of study drug is given. Complete Chemistry Panel is *optional* on C1D1 if performed within the past 7 days.
12. **Coagulation:** Prothrombin time/international normalized ratio, partial thromboplastin time. On on-site dosing days, assessments will be performed **before** the dose of study drug is given. *Optional* on C1D1 if performed within the past 7 days.
13. **Serum Pregnancy Test:** For female subjects of childbearing potential, a serum pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed during Screening, Cycle 1 Day 1 (*optional* if performed within the past 7 days.), Cycle 2 Day 1 and Day 1 of each subsequent cycle, EOT, and Safety Follow-up visit. Only subjects with negative serum pregnancy tests can enroll. If the results of the serum pregnancy test are not available during the clinic visits (e.g., C2D1, C3D1, C4D1, etc.), a urine pregnancy test may be performed.
14. **Urine Analysis:** Urinalysis includes the analysis of protein, glucose, ketones, blood, and specific gravity. A microscopic (white blood cells/high-power field [HPF], red blood cells/HPF, and any additional findings) exam need be performed only if the urinalysis result is abnormal. Urinalysis is *optional* on C1D1 if performed within the past 7 days.
15. **Blood Specimens for ccfDNA Enrichment (20 mL blood specimen):** In all subjects, blood samples will be collected during Screening, at Cycle 3 Day 1 (in conjunction with tumor assessment evaluation; may be collected at next study visit if unable to obtain at the Cycle 3 Day 1 visit), and either at the time of radiographic disease progression or at the EOT (whichever occurs earlier; may also be collected at Safety Follow-up visit if unable to obtain at the EOT visit) for exploratory ccfDNA molecular profiling analyses. Blood will be collected across two 10 mL Streck Cell-Free DNA Blood Collection Tubes (for ccfDNA analysis). Circulating cell-free DNA (ccfDNA) will be isolated from blood. Details for handling of these specimens including processing, storage, and shipment will be provided in the Study Manual.
16. **Triplicate 12-lead ECGs:** At each timepoint, three consecutive 12-lead ECGs will be performed approximately two minutes apart to determine the mean QTc interval. Triplicate ECGs will be collected as follows:
    a) At Screening
    b) Day 1: at pre-dose (0 hour), at 1, 2, 4, 6, 8, and 24 hours post-dose
    c) Cycle 1 Day 8: at pre-dose (0 hour), and 2 hours post-dose
    d) Cycle 1 Day 15: at pre-dose (0 hour)
    e) Cycle 1 Day 22: at pre-dose (0 hour), at 1, 2, 4, 6, 8, and 24 hours post-dose
    f) Cycles 2-6, Day 1: at pre-dose (0 hour), and 2 hours post-dose
    g) At End of Treatment

    When coinciding with blood sample draws for PK, the ECG assessment should be performed prior to blood sample collection such that the blood sample is collected at the nominal time. ECGs performed within 10% of the nominal time (e.g., within 6 minutes of the 60-minute assessment) from dosing are acceptable. In addition to these timepoints, ECGs should be repeated as clinically indicated. Additional ECG timepoints may be included based on the emerging data. Interpretation of the tracing will be made by a central ECG laboratory. Each ECG tracing should be labeled with the study number, subject initials, subject number, and date, and kept in the source documents at the study site. Only clinically significant abnormalities will be recorded in the AE CRF page. Clinically significant abnormalities at Screening/baseline should be recorded on the relevant medical history/current medical conditions CRF page. Clinically significant findings must be discussed with the Sponsor's Medical Monitor before enrolling the subject in the study.
17. **Echocardiography or MUGA for LVEF Assessments:** Echocardiography to be performed at Screening, on Cycle 2 Day 1 (± 7 days), and after every three cycles of treatment (± 7 days) (Cycles 4, 7, 10, 13, and so on), and at the Safety Follow-Up visit (± 7 days).
18. **Pharmacokinetic Blood Sampling:** All measurement times are relative to combination dose of repotrectinib and trametinib unless otherwise specified. Samples obtained within 10% of the nominal time (e.g., within 6 minutes of the 60-minute sample) from dosing will not be considered as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (e.g., CRF/DCT). Blood samples will be collected on the following days:
    a) Day 1: at pre-dose (0 hour), at 1, 2, 4, 6, 8, and 24 hours post-dose
    b) Cycle 1 Day 8: at pre-dose (0 hour), and 2 hours post-dose
    c) Cycle 1 Day 15: at pre-dose (0 hour)
    d) Cycle 1 Day 22: at pre-dose (0 hour), at 1, 2, 4, 6, 8, and 24 hours post-dose
    e) Cycles 2-6, Day 1: at pre-dose (0 hour), and 2 hours post-dose
    f) At End of Treatment

19. **CT or MRI Chest/Abdomen/Pelvis Tumor Assessment**: Tumor assessments will include all known or suspected disease sites. For all tumor assessments, the imaging modality that was used at baseline should be the same modality used throughout the study. CT or MRI scans are to be performed at Screening (≤ 28 Days from C1D1), C3D1 (± 7 days), every 2 cycles (± 7 days) up to Cycle 19, then every 3 cycles (± 7 days) up to Cycle 37, and then every 4 cycles (± 7 days) thereafter until documented progression of disease regardless of treatment delays resulting from toxicity, and at the EOT if more than 4 weeks have passed since the last imaging assessment. Subject responses will be confirmed ≥ 4 weeks later (ideally, the confirmation scan should be scheduled at end of the next cycle, i.e., 28 days) after the initial documentation of response by the Investigator. Subjects may continue treatment with repotrectinib and maintain the study schedule after disease progression if there is continuing clinical benefit per Investigator's judgment and in consultation with the Sponsor's Medical Monitor. For subjects discontinuing the study treatment before documented radiographic progression, tumor assessments should continue on schedule approximately every two cycles or at the current scan interval at the time of treatment discontinuation until radiographic evidence of disease progression, the start of a subsequent anticancer therapy, withdrawal of consent, whichever is first. Every effort should be made to maintain the assessment scheduling relative to Cycle 1 Day 1, especially if there are dosing cycle interruptions due to toxicities. For all subjects, scans should be assessed locally by the Principal Investigator as per RECIST v1.1.
20. **CT or MRI of the Brain:** At Screening, a CT/MRI of the brain should be obtained to rule out newly diagnosed, untreated brain metastases or to document stability of previously treated brain metastases. CT/MRI brain scans should be performed at every on-study tumor assessment for chest/abdomen/pelvis for subjects with brain metastases.
21. **Bone Scans**: Bone scans (or bone MRI if preferred by Investigator) will be performed at baseline (28 days prior to Cycle 1 Day 1) if bone metastases are suspected. In addition, bone scans can be performed if clinically indicated per Investigator's discretion. These scans are only repeated for subjects having a baseline scan, to confirm the absence of bone metastases in case of a Complete Response (CR). Subject responses will be confirmed ≥ 4 weeks later after the initial documentation of response by the Investigator.
22. **Adverse Events**: All AEs, whether reported by the subject or noted by study personnel, will be recorded in the subject's medical record and on the Adverse Event CRF at each subject contact. After informed consent for the clinical trial has been obtained but prior to initiation of study drug, only SAEs related to protocol-mandated assessments should be reported. After initiation of study drug, all AEs, regardless of relationship to study drug, will be reported until at least 28 days after the last dose of study treatment. Any SAEs occurring any time after the reporting period must be promptly reported if a causal relationship to the study drug is suspected.
23. **Concomitant Medications and Non-Drug Supportive Interventions:** All concomitant medications and non-drug supportive interventions should be recorded in the CRF.
24. **Survival Follow-Up**: For subjects discontinuing the study treatment due to documented radiographic progression, obtain survival status via phone call or medical chart review, including information about subsequent anticancer therapies (including best response) every 3 months until death, loss of follow-up, or withdrawal of consent, whichever comes first. For subjects discontinuing the study treatment prior to documented radiographic progression, tumor assessments should continue on the schedule approximately every 2 months or at the current scan interval at the time of treatment discontinuation until radiographic evidence of disease progression, the start of a subsequent anticancer therapy, or decision to no longer treat (e.g., supportive care only), whichever is first.

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ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
AE	adverse event
AIDS	acquired immunodeficiency syndrome
AKT	protein kinase B
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the plasma concentration-time curve
AUC_{inf}	area under the plasma concentration versus time curve to infinity
AUC_{last}	AUC from time zero to the last quantifiable concentration point (t_{last})
BCRP	breast cancer resistance protein
BICR	Blinded Independent Central Review
BID	twice a day
CBR	Clinical Benefit Rate
ccfDNA	circulating cell-free DNA
CHO	Chinese hamster ovary
CI	confidence interval
CL/F	oral clearance
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum observed plasma drug concentration
CNS	central nervous system
CR	complete response
CRC	colorectal cancer
CRF	Case Report Form
CSR	central serous retinopathy
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events

Term	Definition
CYP	cytochrome P450
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic CRF
EDC	electronic data capture
EE	Efficacy Evaluable
EGFR	epidermal growth factor receptor
EMT	epithelial-mesenchymal transition
EOT	End of Treatment
ERK	extracellular signal-regulated kinase
FAK	focal adhesion kinase
FAS	Full Analysis Set
FDA	Food and Drug Administration
GAPs	GTPase activating proteins
GCP	Good Clinical Practice
GDP	guanosine diphosphate
GEFs	guanine exchange factors
GEMM	genetically engineered mouse model
GLP	Good Laboratory Practice
GTP	Guanosine-5'-triphosphate
HBV	hepatitis B
HCV	hepatitis C
HEK	human embryonic kidney
hERG	human ether-a-go-go-related gene
HIV	human immunodeficiency virus
HPF	high-power field
IB	Investigator’s Brochure
IC_{50}	half maximal inhibitory concentration

Term	Definition
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IC-ORR	intracranial objective response rate
INR	international normalized ratio
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
JAK	janus kinase
KRAS	Kirsten rat sarcoma viral oncogene homolog
LFT	liver function test
LVEF	left ventricular ejection fraction
MAF	major allele frequency
MAPK	RAF-MEK-ERK transduction pathway
MATE	multidrug and toxin extrusion protein
MedDRA	Medical Dictionary for Regulatory Affairs
MEK	mitogen-activated extracellular signal-regulated kinase
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition
NA	not applicable
NCI	National Cancer Institute
ND	not determined
NE	not evaluable
NGS	next-generation sequencing
NN	non-CR/non-PD
NOAEL	no observable adverse effect level
NSCLC	non-small-cell lung cancer
NTRK-1	neurotrophin receptor kinase 1
NTRK-2	neurotrophin receptor kinase 2
NTRK-3	neurotrophin receptor kinase 3

Term	Definition
OATP	organic anion-transporting polypeptide
ORR	objective response rate
OS	overall survival
pAKT	phospho-AKT
PARP	poly (ADP-ribose) polymerase
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PI3K	phosphoinositide 3-kinase
P-gp	p-glycoprotein
PK	pharmacokinetics
PO	per os (by mouth)
PR	partial response
PS	Performance Status
PT	prothrombin time
PTT	partial thromboplastin time
QD	once a day
qPCR	quantitative polymerase chain reaction
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
R_{acc}	accumulation ratio
RECIST	Response Evaluation Criteria in Solid Tumors
ROS1	receptor tyrosine kinase encoded by the *ROS1* gene
RP2D	Recommended Phase 2 dose
RVO	retinal vein occlusion
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SLP	solute carrier
SRC	tyrosine kinase first identified in avian sarcoma virus
STAT	signal transducer and activator of transcription

Term	Definition
SOP	standard operating procedure
$t_{1/2}$	elimination half-life
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
T_{max}	time to reach maximum (peak) plasma drug concentration
TRAE	treatment-related adverse event
TTR	time to response
UGT	uridine 5'-diphospho-glucuronosyltransferase
ULN	upper limit of normal
V_z/F	apparent volume of distribution
WBRT	whole brain radiation treatment
WT	wild-type

1. INTRODUCTION

1.1. Repotrectinib Mechanism of Action and Indication

Repotrectinib is an oral, adenosine triphosphate (ATP)-competitive potent kinase inhibitor with activity against janus kinase (JAK2), tyrosine kinase first identified in avian sarcoma virus (SRC), and focal adhesion kinase (FAK) at clinically relevant concentrations, providing a unique polypharmacology profile for combatting multiple resistance mechanisms simultaneously, including bypass signaling, epithelial-mesenchymal transition (EMT), cancer cell stemness, and metastasis.

In this subprotocol, repotrectinib will be given in combination with trametinib for the treatment of subjects with locally advanced or metastatic *KRAS*^{G12D}-mutant solid tumors.

1.2. Background

1.2.1. KRAS as a Driver of Cancer

Kirsten rat sarcoma viral oncogene homolog (KRAS) is a small transductor GTPase protein that relays external growth signals and regulates a complex signaling network with multiple downstream pathways that are involved in tumor cell growth, survival, and proliferation (Jancík 2010). Under normal physiological conditions, KRAS acts as a molecular regulator with guanine exchange factors (GEFs) facilitating its activation by exchanging guanosine diphosphate (GDP) with guanosine-5'-triphosphate (GTP). After activated KRAS mediates transduction of growth signals, its intrinsic GTPase activity hydrolyses the bound GTP to GDP to become deactivated, often facilitated by GTPase activating proteins (GAPs). When mutated, impaired GAP stimulation favors the formation of persistently GTP-bound KRAS leading to the enhanced activation of KRAS, promoting binding of effectors to trigger signal transduction pathways including the RAF–MEK–ERK (MAPK) pathway, the aberrant activation of which has been found to drive many human cancer types (Cox 2014; Cully 2008; Keeton 2017; Vetter 2001).

Somatic mutations in KRAS are the most common activating lesions found in human cancer, with mutations at codons 12, 13, or 61 of KRAS occurring *de novo* in approximately one third of all human cancers and are especially prevalent in pancreatic adenocarcinomas, colorectal carcinomas, and non-small-cell lung cancer (NSCLC) (Keeton 2017; NCCN 2020). The *KRAS* oncogene is considered a prognostic biomarker, the presence of which is predictive of poor survival and lack of efficacy to therapy in the clinic (Lièvre 2006; NCCN 2020; Pao 2005; Slebos 1990).

Since the first detection of activated *KRAS* in human cancers in 1982, multiple approaches to develop drugs to treat malignancies arising from *KRAS* mutations have been investigated, including interfering with maturation, trafficking, and localization to the plasma membrane, or inhibiting downstream signaling (Keeton 2017). While many of these approaches have shown promising preclinical activity, the majority have shown limited efficacy in clinical trials (Cox 2014; Keeton 2017). KRAS has often been considered an undruggable target for direct inhibition, in part due to the relative cellular abundance and the high affinity of KRAS for binding GTP as well as the lack of a suitable binding location in critical regions on the smooth surface of the KRAS oncoprotein (Lindsay 2018; Ostrem 2013; Ni 2019). Only recently has

clinical activity been observed with selective allosteric KRAS^{G12C} inhibitors, with responses being noted especially in patients with NSCLC (Canon 2019; Hallin 2019; Ostrem 2013).

Over the years, research involving *KRAS*-mutant cancers have mainly focused on downstream mediators in part due to clinically-approved inhibitors of MAPK pathway proteins (e.g., inhibitors of MEK and BRAF), with notable successes such as combinations of MEK inhibitors (e.g., trametinib) with other targeted therapeutics in the case of malignant melanoma (Cox 2014). However, the majority of these efforts have been limited by adaptive feedback to reactivate MAPK signaling or compensatory upregulation of phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) signaling (Kitai 2017; Manchado 2016; Yaeger 2019; Tsubaki 2019).

1.2.2. *KRAS*-Mutant NSCLC and Treatment Approaches

Lung cancer remains the leading cause of cancer-related death globally, with an estimated 1.76 million people having died of lung cancer in 2018 (Bray 2018). NSCLC is the most common subtype of lung cancer, representing 80–90% of lung cancer cases (Planchard 2019). NSCLC is associated with a poor prognosis in the advanced or metastatic setting where the 5-year survival rate is estimated to be approximately 7% (Howlader 2019; ACS 2020). *KRAS* mutations occur in 20–40% of lung adenocarcinomas, with the most frequent mutations occurring in codons 12 and 13, and the most common subtypes including *G12C*, *G12V*, and *G12D* (Cox 2014; Ricciuti 2016). The presence of *KRAS* mutations is prognostic of poor survival for patients with NSCLC when compared to the absence of *KRAS*, independent of therapy (NCCN 2020). *KRAS* mutations are also predictive of lack of therapeutic efficacy with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs).

Although there are clinically-approved inhibitors of several MAPK pathway proteins (e.g., inhibitors of MEK, BRAF and EGFR) for a subset of NSCLC patients, to date there have been no approved targeted therapies for treatment of *KRAS*-mutant NSCLC (NCCN 2020).

Recently, development of selective allosteric KRAS^{G12C} inhibitors such as AMG510 and MRTX849 have demonstrated encouraging clinical activity in patients with *KRAS*^{G12C}-mutant NSCLC, with overall response rates (ORRs) as high as 54% (N = 13) observed with AMG510 (Amgen 2019; Canon 2019; Hallin 2019). However, *KRAS*^{G12C} mutations are only present in a small subset of NSCLC patients (approximately 13% of lung adenocarcinoma harbor *KRAS*^{G12C} mutations) and KRAS^{G12C} inhibitors rely on the mutant cysteine for binding and therefore do not affect the wild-type KRAS protein or other KRAS subtypes. In addition, resistance to direct targeting of KRAS can occur and may be due to genetic alterations in downstream pathways, thus combination therapies are likely needed to provide greater benefit than direct targeting of KRAS alone (Burns 2020).

Taken together, there is an urgent, unmet medical need for development of novel targeted therapeutics and novel therapeutic strategies for the treatment of patients with locally advanced or metastatic *KRAS*-mutant NSCLC.

1.3. Repotrectinib Combination Approaches and Rationales

1.3.1. Rationale for Repotrectinib in Combination with Trametinib

Trametinib (Mekinist® [trametinib] USPI 2020) is a reversible inhibitor of mitogen-activated extracellular signal-regulated kinase 1 (MEK1) and MEK2. MEK proteins are upstream regulators of the MAPK pathway, which promotes cellular proliferation. Trametinib is indicated, in combination with dabrafenib, for the treatment of patients with metastatic NSCLC with BRAF V600E mutation. Preclinical studies demonstrated sensitivity of cell lines harboring *KRAS* mutations to MEK inhibitors, supporting clinical evaluations of MEK inhibitors for patients with *KRAS*-mutant cancers (Sebolt-Leopold 1999; Davies 2007; Okumura 2014). However, clinical efficacy of MEK inhibitors such as trametinib in *KRAS*-mutant cancers has been limited, attributed to adaptive feedback mechanisms that reactivate MAPK signaling (Kitai 2017; Manchado 2016; Yaeger 2019; Tsubaki 2019). Preclinical data has demonstrated that MEK inhibition in *KRAS*-mutant cancer models caused autocrine activation of signal transducer and activator of transcription (STAT3) (Lee 2014). *KRAS*-mutant cancer cells cultured under long-term trametinib exposure exhibit upregulated FAK and AKT activation along with elevated S6 protein phosphorylation and became resistant to trametinib (internal data, unpublished).

In vitro studies have demonstrated that trametinib-mediated AKT activation is better suppressed in combination with repotrectinib, compared to combinations with individual SRC, FAK or JAK inhibitors (Murray 2020). Combination with repotrectinib represses S6, AKT and STAT3 activation and resensitizes these cancer cells to trametinib. Repotrectinib in combination with trametinib has demonstrated enhanced potency in *in vitro* $KRAS^{G12D}$ NSCLC cell models as well as in *ex vivo* patient-derived $KRAS^{G12D}$ NSCLC organoid models (Section 1.4.1.1). Repotrectinib and trametinib combination also demonstrated greater tumor growth inhibition than either single agent alone in an *in vivo* syngeneic genetically engineered mouse model (GEMM) $KRAS^{G12D}$ model as well as in a patient-derived $KRAS^{G12D}$ mutant lung xenograft model (Section 1.4.1.1).

Repotrectinib's ability to simultaneously inhibit SRC/FAK/JAK2 is expected to suppress MAPK reactivation and compensatory bypass signaling mediated by single agent trametinib therapy, with potential to yield improved efficacy in the clinic. Repotrectinib given in combination with trametinib may provide a promising treatment option for patients with advanced NSCLC harboring a $KRAS^{G12D}$ mutation.

1.4. Summary of Nonclinical Experience

Detailed overview of nonclinical pharmacology, pharmacokinetics, and safety assessment has been presented in the Investigator's Brochure (IB).

1.4.1. Nonclinical Pharmacology of Repotrectinib

Kinase selectivity of repotrectinib toward 456 human kinases (wild type [WT] and mutant) was evaluated in kinase binding assay using the KINOMEscan® profiling platform with potent hits further tested for IC_{50} values in enzymatic kinase inhibition assays. Overall, there were ten kinases with less than 10-fold selectivity over anaplastic lymphoma kinase (ALK) (IC_{50} 1.04 nM), including JAK2, FYN, LYN, YES, FGR, TXK, ARK5, SRC, DDR1, and FAK with IC_{50} values of 1.04, 1.05, 1.66, 2.15, 3.05, 3.17, 4.46, 5.29, 5.73 and 6.96 nM, respectively. It is known that tyrosine kinases are responsible for only a small fraction of phosphorylation events in

living cells (< 1%) (Hunter 1980; Sharma 2014). However, a subset of these tyrosine kinases, including JAK2, SRC and FAK, contribute to cancer malignancy, stemness, EMT and metastasis (Lee 2014; Mohrherr 2019; Sen 2009; Zhou 2017).

In H2228 cells, repotrectinib suppressed the phosphorylation of SRC, FAK and paxillin with IC_{50} values in a range of 80-100 nM and downregulated the expression of EGFR, CD44, and vimentin with IC_{50} values around 100 nM. In addition, repotrectinib inhibited the phosphorylation of the oncogenic transcription/ translation factor YB-1 with an IC_{50} value around 100 nM in H2228 cells. YB-1 regulates aspects of gene expression that lead to tumor cell growth and drug resistance (Lasham 2013; Kuwano 2019), including modulation of EGFR upregulation (Stratford 2007; Kuwano 2019), EMT (Castellana 2015; Kosnopfel 2018), and cancer cell stemness (Kang 2013; Yang 2017). Repotrectinib demonstrated an *in vitro* anti-metastatic activity by inhibiting cell migration in both H2228 cells and HT1080 human fibrosarcoma cells. Aberrant upregulation of JAK2/STAT pathways has been implicated in multiple human pathological diseases, including cancer (Bousoik 2018). Repotrectinib inhibited JAK2 signaling (pSTAT5 IC_{50} 139 nM) and cell proliferation (IC_{50} 169 nM) of SET2 cells harboring oncogenic JAK2 V617F mutation. Overall, repotrectinib demonstrated inhibition of JAK2/SRC/FAK in cellular assays and has the potential to overcome resistance from bypass signaling, EMT, cancer cell stemness and metastasis.

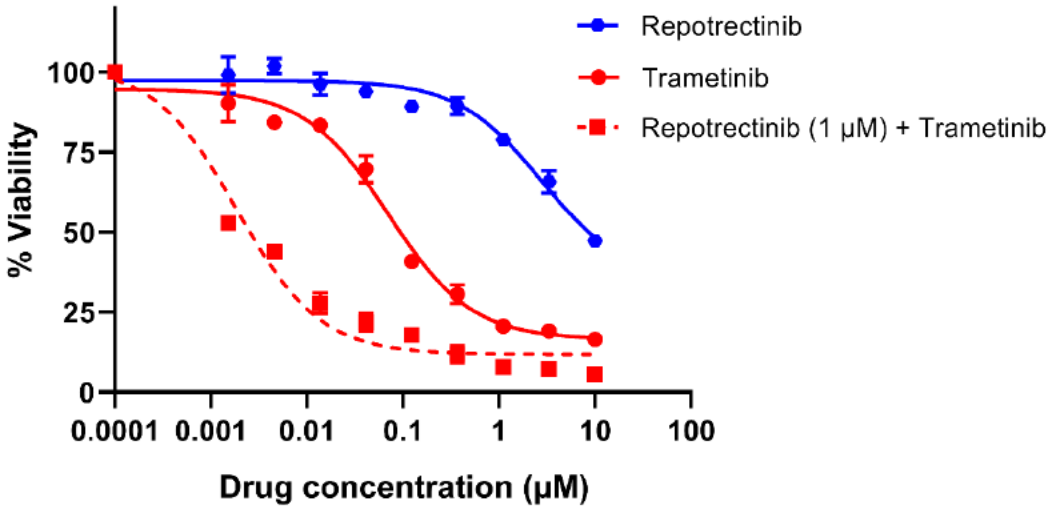
The secondary pharmacodynamics studies in a 44 safety-related targets screen indicated that repotrectinib only weakly inhibited three targets, including A_{2A} (IC_{50} 6300 nM), human L-type Ca^{2+} channel (IC_{50} 3500 nM), and LCK (IC_{50} 110 nM). Repotrectinib had minimal effects on human ion channels, including human ether-a-go-go-related gene (hERG) (IC_{50} 18 µM, Chinese hamster ovary [CHO] cells), hNaV1.5 (IC_{50} > 30 µM, human embryonic kidney [HEK]293 cells), and human L-type CaV1.2 (IC_{50} > 30 µM, HEK293 cells).

1.4.1.1. Nonclinical Pharmacology of Repotrectinib Given in Combination with Trametinib

The combination of repotrectinib with trametinib was evaluated for inhibition of cell viability across panels of NSCLC, colorectal cancer (CRC) and pancreatic cancer cell lines that harbor a spectrum of *KRAS* mutations. Addition of repotrectinib (1 µM) to trametinib treatment resulted in a >10 fold increase in trametinib anti-cell viability efficacy in 9 out of 15 $KRAS^{G12D}$ mutant cancer models screened (Murray 2020).

The effect on cell viability by repotrectinib in combination with various MAPK pathway inhibitors including trametinib, selumetinib, VS-6766, TNO199 and LY31214996 was assessed in NSCLC patient-derived organoid models harboring $KRAS^{G12D}$ mutations. The combination of repotrectinib with trametinib exhibited the greatest enhanced inhibition of cancer cell viability compared to other MAPK pathway inhibitor combinations in $KRAS^{G12D}$ mutant NSCLC cancers (Figure 1). Similar repotrectinib and trametinib combination benefit was demonstrated in-patient derived pancreatic *ex vivo* spheroid models harboring $KRAS^{G12D}$ mutations.

Figure 1: Patient Derived *KRAS*^{G12D} Lung Spheroid Model LU5178



To better assess the degree of synergy achieved by the combination, a more comprehensive combination dose matrix with serial titration of both trametinib and repotrectinib was evaluated in select KRAS-mutant cancer models and analyzed with Bliss additivity analysis software (Ianevski 2017). Repotrectinib enhances inhibition of cell viability by trametinib in a dose-dependent manner (Figure 2). Bliss analysis revealed that repotrectinib synergized with trametinib at clinically relevant drug concentrations showing Bliss scores > 10 (Figure 3).

Figure 2: Cell Viability Assay with Repotrectinib and Trametinib Combination in A427 *KRAS*^{G12D} Lung Cancer Model

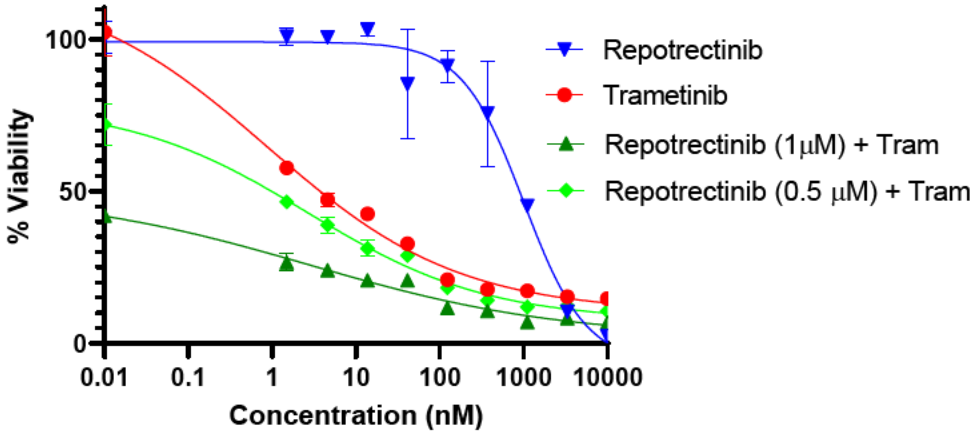
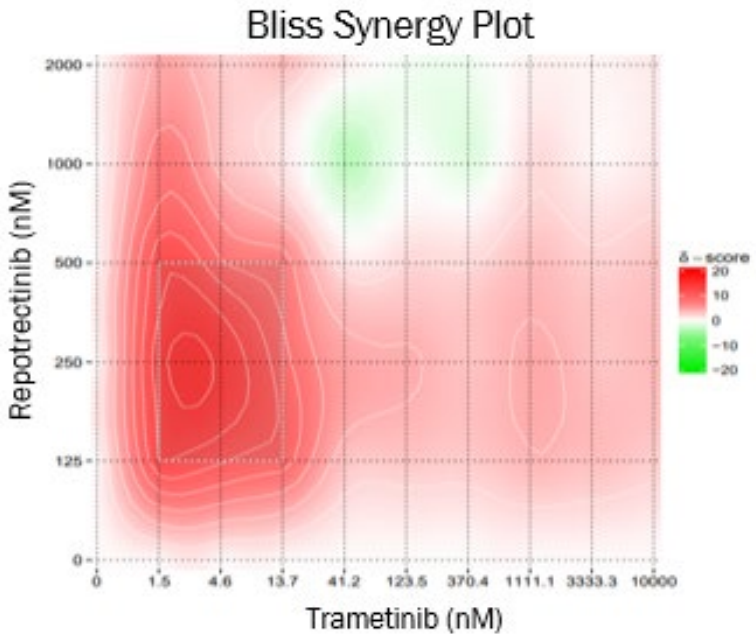


Figure 3: Bliss Synergy Analysis for Repotrectinib and Trametinib Combination in A427 *KRAS*^{G12D} Lung Cancer Model



Trametinib	Repotrectinib	BLISS Synergy Score
1.5 nM	250 nM	13.7
4.6 nM	250 nM	13.5
1.5 nM	125 nM	12.5
1.5 nM	500 nM	11.6

To understand the underlying mechanisms that resulted in greater efficacy, Western immunoblot analyses were performed with A427 cells (NSCLC *KRAS*^{G12D}) treated with single agent repotrectinib or trametinib vs the combination of repotrectinib and trametinib. Evaluation of downstream signal modulation by repotrectinib in combination with trametinib in A427 cells demonstrated greater inhibition of SRC, STAT3 and FAK phosphorylations, which coincided with increased inhibition of AKT and S6 phosphorylation compared to single agent treatments (Figure 4). The combination of repotrectinib and trametinib increased cell cycle inhibitor proteins such as p27 and p21 and inhibited RB1 phosphorylation more robustly than single agent treatments (Figure 5A). Furthermore, the repotrectinib and trametinib combination enhanced induction of apoptosis in comparison to single agent treatments as indicated by elevated cleavage of poly(ADP-ribose) polymerase (PARP) and caspase 3 (Figure 5B).

Figure 4: Repotrectinib and Trametinib Combination Suppresses Downstream Oncogenic Signaling in A427 *KRAS*^{G12D} Lung Cancer Model

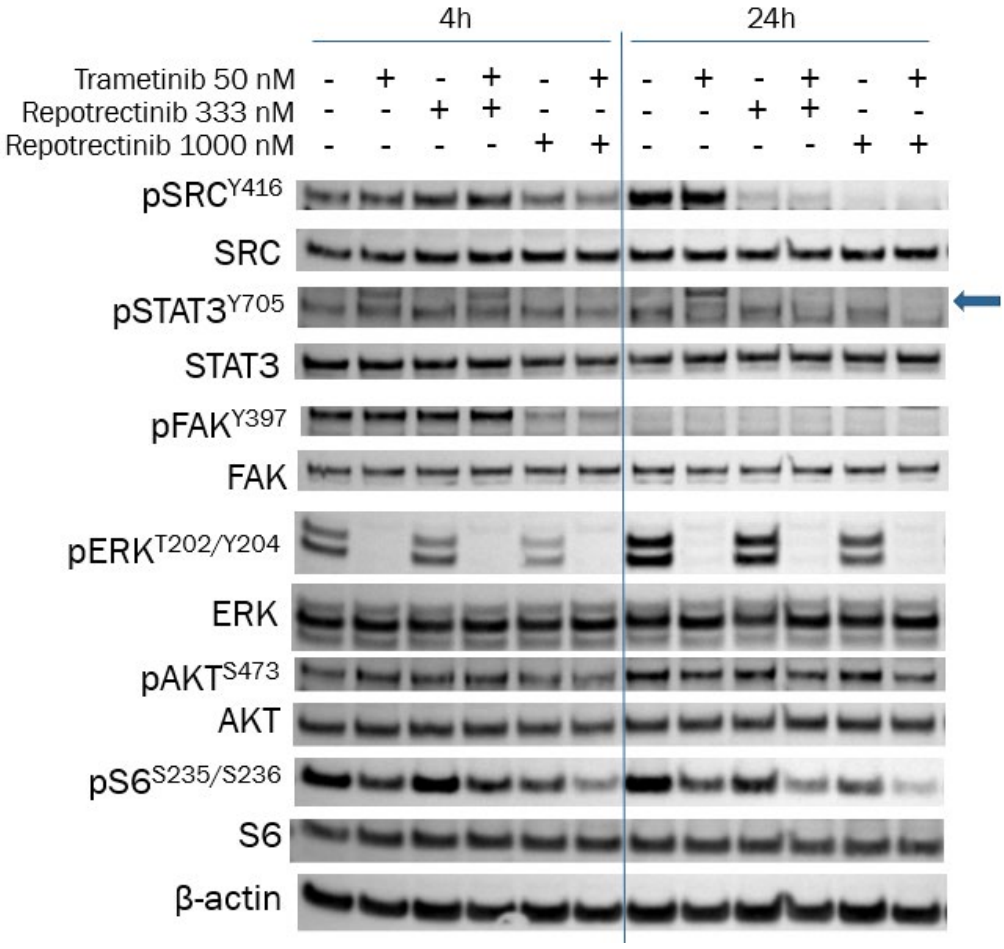
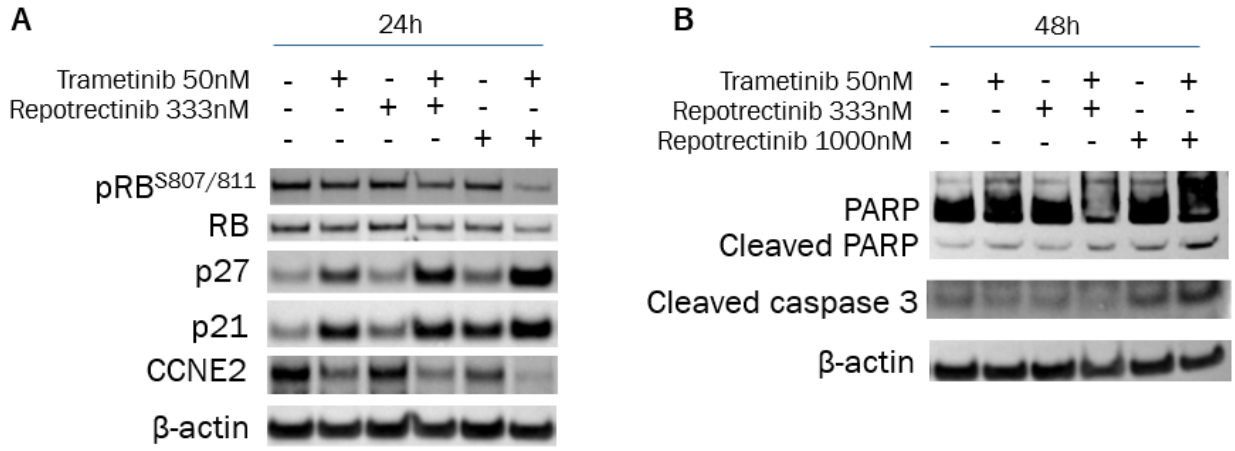


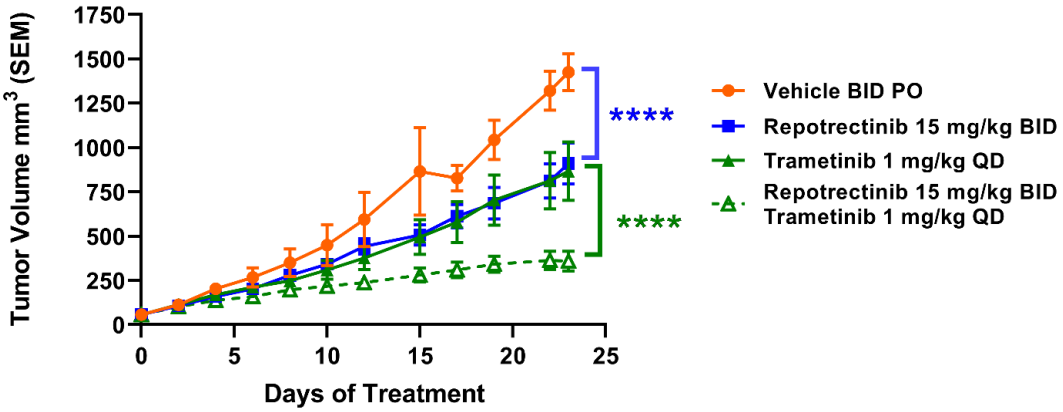
Figure 5: Repotrectinib and Trametinib Combination Increases Cell Cycle Arrest and Induction of Apoptosis



Trametinib induced a rebound in phospho-AKT (pAKT) levels in a subset of *KRAS*-mutant cells which was substantially suppressed by the combination with repotrectinib. In contrast, suppression of the trametinib-induced pAKT rebound was not achieved by combinations of trametinib with dasatinib (SRCi), ruxolitinib (JAK1/2i), or defactinib (FAKi), suggesting that concomitant SRC/FAK/JAK2 inhibition may be necessary (Murray 2020).

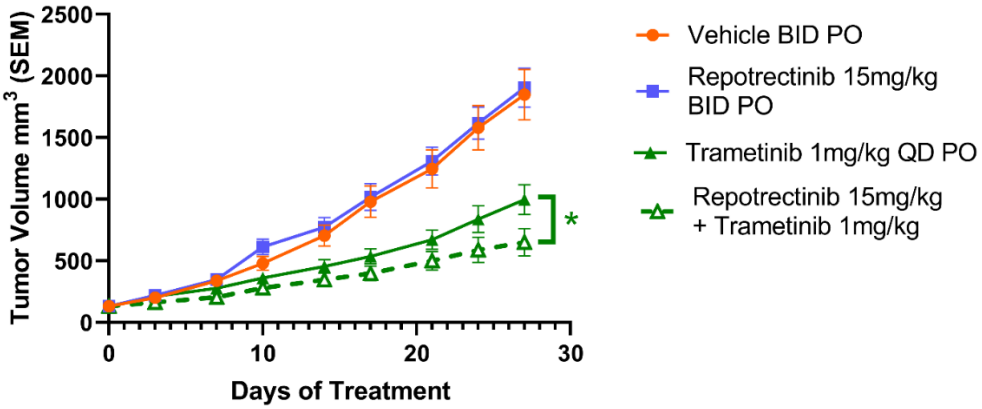
The combination efficacy of repotrectinib and trametinib was tested in two $KRAS^{G12D}$ *in vivo* lung models. In the syngeneic GEMM $KRAS^{G12D}$ lung model mLU6045, the combination of repotrectinib with trametinib demonstrated a 78% tumor growth inhibition vs 38% and 41% by repotrectinib or trametinib as single agents, respectively (p-value ≤ 0.0001) (Figure 6). In a patient-derived $KRAS^{G12D}$ lung xenograft model LU0876, the combination of repotrectinib and trametinib demonstrated a 70% tumor growth inhibition vs 50% by trametinib alone (p-value = 0.0483); repotrectinib single agent response was similar to vehicle treatment (Figure 7).

Figure 6: *In Vivo* GEMM $KRAS^{G12D}$ mLU6045 Syngeneic Murine Lung Model TGI Study



Abbreviations: BID = twice a day; GEMM = genetically engineered mouse model; PO = per os (by mouth); QD = once a day; SEM = standard error of the mean.
**** p-value ≤ 0.0001

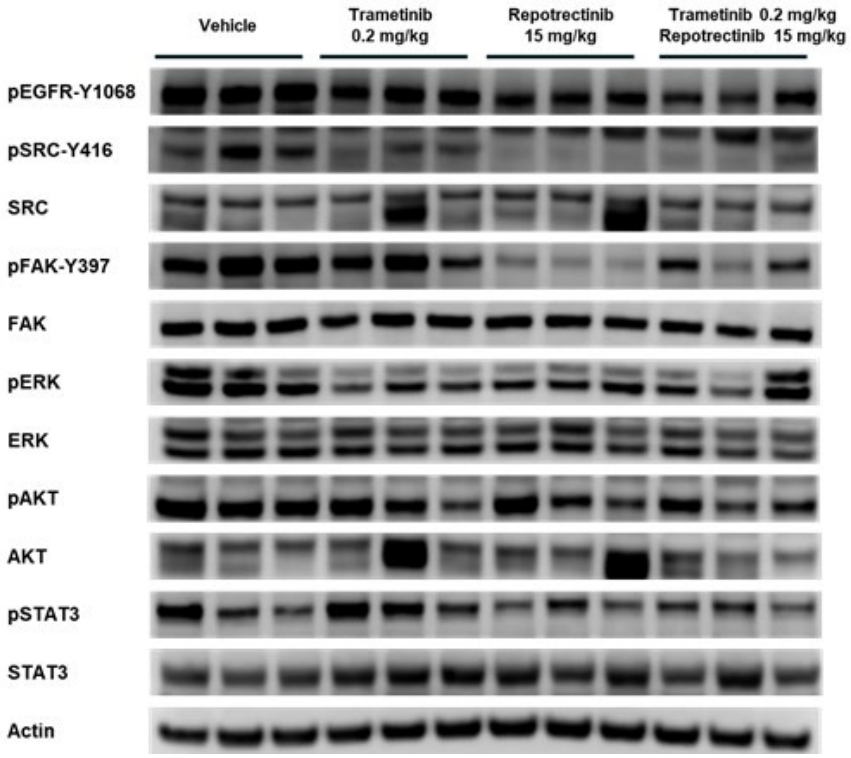
Figure 7: *In Vivo* Patient Derived $KRAS^{G12D}$ LU0876 Xenograft Lung Model TGI Study



Abbreviations: BID = twice a day; PO = per os (by mouth); QD = once a day; SEM = standard error of the mean.
* p-value = 0.0483

The combination of trametinib and repotrectinib in a Calu-6 (NSCLC *KRAS*^{Q61K}) murine xenograft study demonstrated *in vivo* that repotrectinib suppresses of SRC/FAK/STAT3 activation (Figure 8).

Figure 8: *In Vivo* Pharmacodynamic Evaluation of Signal Modulation by Repotrectinib and Trametinib treatment in *KRAS*^{Q61K} Calu6 Lung Model



1.4.2. Nonclinical Pharmacokinetics

Repotrectinib was highly bound (> 95%) to human serum albumin. The primary route of elimination of repotrectinib was CYP (cytochrome P450) 3A4-mediated metabolism, followed by glucuronidation of the oxidative metabolites, which were subsequently excreted into bile and urine. Repotrectinib weakly inhibited CYP enzymes with insignificant time-dependent inhibition. The only UGT (uridine 5'-diphospho-glucuronosyltransferase) inhibited by repotrectinib was UGT1A1. Human hepatocyte culture studies suggested that repotrectinib may induce CYP2B6 and CYP3A4(/5) enzymes. Repotrectinib was transported by P-glycoprotein (P-gp), and likely by breast cancer resistance protein (BCRP) and multidrug and toxin extrusion protein (MATE) 2-K. However, repotrectinib was not a substrate for any other human solute carrier (SLC) transporters evaluated. Repotrectinib inhibited P-gp, BCRP, organic anion-transporting polypeptide (OATP) 1B1, OAT3, MATE1 and MATE2-K.

1.4.3. Nonclinical Toxicology

In accordance with the ICH S9 Guideline "Nonclinical Evaluation for Anticancer Pharmaceuticals" (March 2010), the Sponsor has completed a comprehensive nonclinical safety program encompassing *in vitro* hERG assay, ECG assessment in monkeys, single- and repeat-dose exploratory toxicology studies, and definitive 28-day and 91-day toxicology studies with

28-day recovery periods conducted in rat and monkey, as well as genotoxicity and phototoxicity studies.

The nonclinical profile was well-characterized with adequate exposure margins to support the intended use of repotrectinib for patients with advanced solid tumors.

1.5. Clinical Experience

Repotrectinib is currently under evaluation in a Phase 1/2 clinical trial as a monotherapy in subjects with advanced or metastatic solid tumors harboring *ROS1*, *NTRK1-3*, or *ALK* rearrangements (TPX-0005-01 or TRIDENT-1). Repotrectinib is also being evaluated as a monotherapy in a clinical study of pediatric subjects and young adults with advanced or metastatic solid tumors harboring *ROS1*, *NTRK1-3*, or *ALK* alterations (TPX-0005-07).

Based on the safety, preliminary efficacy, and PK data obtained in Phase 1 of TRIDENT-1 (data cutoff of March 2019), the recommended Phase 2 dose (RP2D) was determined to be:

- 160 mg once daily (QD) for the first 14 days and may increase to 160 mg twice a day (BID) based on subject safety and tolerability. Subjects must meet the following criteria while on 160 mg QD prior to dose increase to 160 mg BID: no evidence of grade ≥ 3 treatment-related adverse event (TRAE), unmanageable grade ≥ 2 dizziness, ataxia or paresthesia; or grade ≥ 3 clinically significant lab abnormalities.

Repotrectinib absorption was relatively fast under fasting conditions, with a median time to reach maximum (peak) plasma drug concentration (T_{max}) of 2 hours. Mean C_{max} and AUC_{inf} increased after a single dose with increasing doses from 40 mg QD to 240 mg QD. Apparent volume of distribution (V_z/F) was medium with geometric mean values ranging from 229 to 506 L. Geometric mean oral clearance (CL/F) was low compared to human liver blood flow, ranging from 8.9 to 16.1 L/h. Mean terminal half-life was long after a single dose, ranging from 14.6 to 25.9 hours. The accumulation ratio (R_{acc}) values of C_{max} and AUC were lower than expected based on the single-dose terminal half-lives. The CL/F at steady state was higher than observed after a single dose at the same administered dose, suggesting a possible auto-induction of metabolic enzyme(s).

Overall, at the time of the most recent safety data cutoff (30 October 2020), 185 subjects have received at least one dose of repotrectinib in doses ranging from 40 mg QD to 200 mg BID in the TRIDENT-1 study. In the Phase 1 portion, the MTD was not reached. There were 4 dose-limiting toxicities (DLTs): 1 DLT of dizziness at 240 mg QD and 3 DLTs at 160 mg BID (2 DLTs of dizziness; 1 DLT of dyspnea and hypoxia).

Of the 185 subjects enrolled in the TRIDENT-1 study as of the 30 October 2020 safety data cutoff date, 180 (97.3%) subjects experienced at least one treatment-emergent adverse event (TEAE), with approximately half of the TEAEs reported with a maximum severity of grade 1 and 2 and the majority managed without dose modifications.

The most common TEAEs occurring in ≥ 20% of subjects regardless of relationship to study drug included dizziness (58.4%); dysgeusia (43.2%); constipation (32.4%); dyspnea (31.4%); fatigue (27.0%); paresthesia (25.4%); anemia (22.2%); and nausea (20.0%). TEAEs (grade ≥ 3) were experienced by 93 (50.3%) of 185 subjects. Dizziness (grade ≥ 3) occurred in 4 subjects (2.2%).

Dizziness (9 [5%] subjects) was the most common reason for dose interruption. The majority (80%) of dizziness events have been grade 1, and no subjects discontinued treatment due to dizziness.

In summary, safety data from the Phase 1 and Phase 2 patient populations of TRIDENT-1 demonstrate a favorable tolerability profile for repotrectinib.

1.5.1. Study TPX-0005-09: Mass Balance, Pharmacokinetics, and Metabolism of Repotrectinib in Healthy Male Subjects

TPX-0005-09 was conducted as a 2-part, 2-treatment, fixed-sequence study in 7 healthy male volunteers to investigate the mass balance, PK, and metabolism of a single oral dose and PK of an intravenous tracer of [^{14}C]repotrectinib in healthy male subjects. The treatments were administered after an overnight fast of at least 10 hours. Below is a summary of key findings. Refer to the Investigator's Brochure for further details.

Following concomitant administration of a single oral dose of 160-mg repotrectinib capsule formulation and intravenous administration of tracer [^{14}C]repotrectinib in study TPX-0005-09 (Period 1), the geometric mean absolute bioavailability of repotrectinib based on $AUC_{0-\infty}$ was approximately 45.7%. The geometric means $t_{1/2}$ of the IV formulation and the oral capsule dose were 32.5 and 36.2 hours, respectively.

Following oral administration of a 160 mg of [^{14}C]repotrectinib (100 μCi) dose (TPX-0005-09, Period 2), the mean total recovery of radioactivity in excreta was 93.7% with radioactivity recoveries in feces and urine of 88.8% and 4.84%, respectively. No metabolite exceeded 10% of total circulating drug-related radioactivity. All detected metabolites had been previously detected in rat and/or cynomolgus monkey following oral administration; therefore, there were no unique human metabolites.

1.6. Proposed Clinical Starting Dose

1.6.1. Repotrectinib in Combination with Trametinib

Repotrectinib is an oral, adenosine triphosphate (ATP)-competitive potent kinase inhibitor with activity against JAK2, SRC, and FAK. Among 185 subjects treated in the Phase 1 and Phase 2 portions of the TRIDENT-1 study, the most common toxicities observed were dizziness (58.4%), dysgeusia (43.2%), constipation (32.4%), dyspnea (31.4%), fatigue (27.0%), paresthesia (25.4%), anemia (22.2%), and nausea (20.0%). The majority of dizziness events were grade 1 or grade 2 and generally occurred within the first 14 days of treatment. A titration approach was implemented to minimize early onset of TEAEs, including dizziness, thus the RP2D of repotrectinib is 160 mg QD for the first 14 days, after which the dose may be increased to 160 mg BID based on subject safety and tolerability.

Trametinib is a MEK inhibitor indicated as monotherapy for the treatment of patients with metastatic melanoma with BRAF V600E or V600K mutations and in combination with dabrafenib for the treatment of patients with metastatic NSCLC harboring a BRAF V600E mutation. The most common adverse events (≥ 20%) seen with trametinib as a single agent include rash, diarrhea, and lymphedema (Mekinist® [trametinib] USPI 2020).

Based on the known toxicity profiles of both repotrectinib and trametinib described above, overlapping toxicities are not anticipated. However, in clinical trials, development of combination therapies of targeted agents can prove to be challenging because of toxicities observed with combined treatments, even if individual agents do not have overlapping toxicities. Therefore, the starting dose of repotrectinib in combination with trametinib for the Phase 1b dose escalation portion of the study will be 120 mg daily (QD), and the starting dose of trametinib will be 2 mg QD.

Further doses will be explored during the dose escalation, and the RP2D for repotrectinib given in combination with trametinib will be chosen based on the results from the Phase 1b portion of the study.

2. STUDY OBJECTIVES

2.1. Phase 1b Objectives

2.1.1. Primary Objectives

- Evaluate the safety and tolerability of repotrectinib at increasing dose levels in combination with trametinib for the treatment of subjects with locally advanced or metastatic *KRAS*-mutant solid tumors.
- Determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of repotrectinib in combination with trametinib for the treatment of subjects with locally advanced or metastatic *KRAS*-mutant solid tumors.

2.1.2. Secondary Objectives

- Characterize the pharmacokinetic (PK) profile of repotrectinib in combination with trametinib.
- Describe the preliminary efficacy of repotrectinib in combination with trametinib.

2.2. Phase 2 Objectives

2.2.1. Primary Objective

- Evaluate the efficacy of repotrectinib in combination with trametinib for the treatment of subjects with locally advanced or metastatic *KRAS*-mutant solid tumors as measured by objective response rate (ORR).

2.2.2. Secondary Objective

- Evaluate the efficacy of repotrectinib in combination with trametinib for the treatment of subjects with locally advanced or metastatic *KRAS*-mutant solid tumors as measured by clinical benefit rate (CBR), progression-free survival (PFS), duration of response (DOR), time to response (TTR), and overall survival (OS).
- Evaluate the safety and tolerability of repotrectinib in combination with trametinib.
- Characterize the PK profile of repotrectinib in combination with trametinib.

2.3. Exploratory Objectives (All Phases)

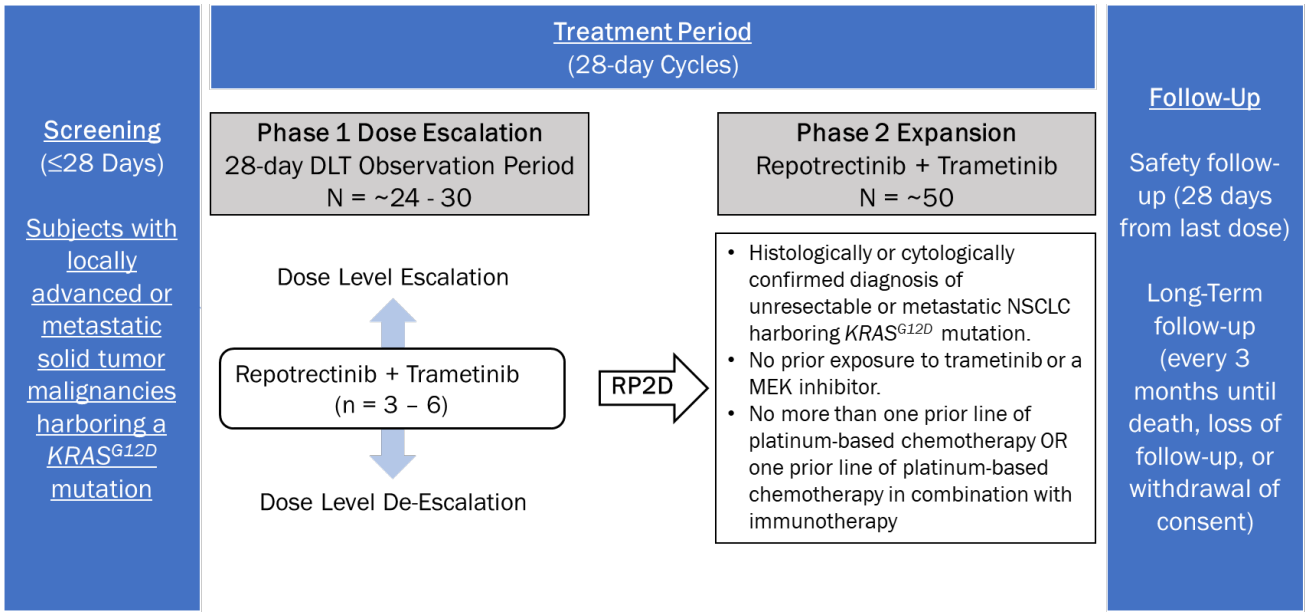
- Evaluate biomarkers potentially predictive of response in subjects treated with repotrectinib in combination with trametinib.
- Explore the potential prognostic utility of genomic alterations and characterize intrinsic or acquired resistance in subjects treated with repotrectinib in combination with trametinib using tissue-based or liquid-based biopsy samples.

3. STUDY DESIGN

3.1. Overall Study Design

This subprotocol is a Phase 1b/2 multi-center, open-label study to evaluate the efficacy, safety, tolerability, and PK of repotrectinib in combination with trametinib, for the treatment of subjects with locally advanced or metastatic *KRAS*^{G12D}-mutant solid tumors. The study will consist of two portions: Phase 1b Dose Escalation and Phase 2 Expansion (Figure 9).

Figure 9: Subprotocol 1 Study Design



Abbreviations: KRAS = Kirsten rat sarcoma viral oncogene homolog; MEK = mitogen-activated extracellular signal-regulated kinase; NSCLC = non-small cell lung cancer; RP2D = recommended Phase 2 dose.

3.2. Phase 1b Dose Escalation Study Design

The Phase 1b dose escalation portion of the study will follow a traditional 3+3 design, where three to six DLT-evaluable subjects with locally advanced or metastatic *KRAS*^{G12D} -mutant solid tumors will be enrolled at each dose level to determine the MTD/RP2D of repotrectinib in combination with trametinib through assessment of DLTs.

Initially, approximately 24 – 30 subjects with locally advanced or metastatic solid tumor malignancies harboring a *KRAS*^{G12D} mutation will be enrolled into the Phase 1b dose escalation portion. Three to six DLT-evaluable subjects at each dose level will be administered daily (QD) doses of repotrectinib in combination with trametinib according to Table 2 (starting with Dose Level 1) and evaluated for DLTs during Cycle 1 (i.e., for 28 days). After the first 3 subjects have completed their first cycle of study treatment (Cycle 1), a safety evaluation will be conducted by a Safety Review Committee to determine if enrollment of subjects in the next dose level (Dose Level 2) may begin. If no subjects experience a DLT within the first 28 days of Dose Level 1 treatment, then dose escalation may proceed to the next dose level, according to Table 2. If 1 of the 3 initial subjects at Dose Level 1 experiences a DLT, then the next 3 subjects will be enrolled prior to escalating to the next dose level. Enrollment into all subsequent dose levels will follow

the same procedure. If ≥ 33% of subjects at any dose level experience a DLT within the first 28 days of treatment, the dose levels will be de-escalated to Dose Level -2 or -3 according to SRC recommendation and following approval by the Sponsor, as detailed in Table 2. If Dose Level -2 is tolerable, testing of alternate escalating dose levels (-2a, -2b) may occur as outlined in Table 2. If Dose Level -2 is not tolerable, subjects will be de-escalated to Dose Level -3. If Dose Level -3 is tolerable, testing of alternate escalating dose levels (-3a, -3b) may occur as outlined in Table 2. Alternative regimens or additional dose levels or dose level increments may be explored based on emergent clinical safety, efficacy, and PK data. See Section 3.2.1.1 for criteria for determining DLTs. The decision to escalate to the next dose level will be based on the incidence of DLTs and the totality of clinical data including overall PK, safety, and preliminary efficacy observed within each dose level.

Table 2: Dose-finding Dose Levels

Dose Level	**Repotrectinib**	**Trametinib**
3	160 mg QD/BID[a]	2 mg QD
2	160 mg QD	2 mg QD
1 (Starting Dose)	120 mg QD	2 mg QD
(-2b)	160 mg QD/BID[a]	1.0 mg QD
(-2a)	160 mg QD	1.0 mg QD
-2	120 mg QD	1.0 mg QD
(-3b)	160 mg QD/BID[a]	0.5 mg QD
(-3a)	160 mg QD	0.5 mg QD
-3	120 mg QD	0.5 mg QD

Abbreviations: BID = twice daily; QD = once daily.
[a] 160 mg QD (once daily) for the first 14 days, after which the dose may be increased to 160 mg BID based on subject safety and tolerability and assuming specific criteria are met. Subjects must meet the following criteria while on 160 mg QD prior to dose increase to 160 mg BID: no evidence of grade ≥ 3 TRAE, unmanageable grade ≥ 2 dizziness, ataxia or paresthesia; or grade ≥ 3 clinically significant lab abnormalities.

A Safety Review Committee, including study Investigators and the Sponsor Medical Monitor, will provide recommendations for dose escalation, confirmation of DLTs, dose de-escalation, and determination of the RP2D (Section 3.2.1.3). At least 6 subjects will be treated at the RP2D prior to proceeding into the Phase 2 portion of the study. Additional subjects may be added at a dose level to gather more safety, PK, and efficacy data (Section 3.2.1.3).

To fully characterize the safety of the combination of repotrectinib and trametinib, subjects who are discontinued from treatment before completing the DLT evaluation period (28 days, Cycle 1) due to disease progression or other event unrelated to repotrectinib or trametinib, or who did not adequately complete the PK evaluations within Cycle 1, may be replaced.

Tumor assessments will include all known or suspected disease sites. All radiographic efficacy endpoints will be assessed using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Intracranial responses will be assessed by modified RECIST v1.1. For all tumor assessments, the imaging modality used at baseline should be the same modality used throughout the study.

Safety will be monitored *via* laboratory assessments, physical examinations, ECGs, vital signs, and TEAEs according to CTCAE v5.0. PK data will also be collected.

An end of treatment (EOT) visit will be conducted within 7 days of the last dose of both study drugs. A safety follow-up visit will be conducted within 28 days of last dose of both study drugs. Additionally, to assess overall survival status, each subject will be contacted via phone call (or medical chart review), including information about subsequent anticancer therapies (including best response), every three months after discontinuation of study drugs until death, loss to follow-up, or withdrawal of consent, whichever occurs first.

3.2.1.1. Dose-Limiting Toxicities

Subjects are eligible for DLT evaluation if they experience a DLT during the first cycle of treatment (i.e., 28 days) or do not experience a DLT during the first cycle of treatment while able to receive at least 75% of planned doses during the first cycle of treatment. Subjects who do not fulfill these requirements will be replaced for DLT evaluation but will remain in the overall safety and efficacy analyses.

A DLT is defined as an AE or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness, or concomitant medications that meets any of the criteria in Table 3.

Table 3: CTCAE Dose-Limiting Toxicities

Category[a]	Criteria
Toxicities resulting in an excessive number of missed doses	• Inability to deliver at least 75% of the planned doses of repotrectinib and trametinib during Cycle 1 treatment because of toxicity attributed to study drug (excluding toxicities clearly related to disease progression or intercurrent illness)
Hematologic toxicities	• Grade ≥ 4 neutropenia (ANC < 500/ mm^3) lasting > 7 days • Grade ≥ 4 platelet count decrease (platelets < 25,000/mm^3) or Grade ≥ 2 (< 75,000/mm^3) associated with clinically significant bleeding • Grade ≥ 4 anemia • Grade ≥ 3 febrile neutropenia (defined as ANC < 1,000/mm^3 with a single temperature of ≥ 38.3°C [≥ 101°F] or a sustained temperature of ≥ 38°C [≥ 100.4°F] for > 1 hour)
Renal	• Grade ≥ 3 creatinine increase (> 3 × upper limit of normal [ULN])
Hepatic	• Grade ≥ 3 total bilirubin elevation (> 3 × ULN) • Grade ≥ 2 total bilirubin elevation (> 1.5 × ULN) and grade ≥ 2 ALT or AST elevation (> 3 × ULN) • Grade 3 ALT elevation (> 5 × ULN) that does not resolve to grade ≤ 1 within 7 days or any grade ≥ 4 ALT elevation • Grade 3 AST elevation (> 5 × ULN) that does not resolve to grade ≤ 1 within 7 days or any grade ≥ 4 AST elevation • Grade 4 elevations in ALP
Pancreatic	• Grade ≥ 3 amylase or lipase elevation
Cardiac	• Grade ≥ 3
Other AEs	• Grade 3 electrolyte disturbances that require hospitalization • Grade 4 electrolytes abnormalities • Grade ≥ 3 AE, persisting after optimal treatment with standard medical therapy except for the exceptions noted below under "Exceptions to DLT criteria" • In view of the Investigators and Sponsor, any other unacceptable toxicity encountered
Exceptions to DLT criteria	• Grade 3 elevations in ALP • Grade 3 electrolytes abnormalities that are adequately managed by IV or PO supplementation as evidenced by an improvement to grade ≤ 1 within 3 days • Grade 3 fatigue which resolves to grade ≤ 1 in ≤ 7 days • Isolated grade 3 laboratory abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset • Grade 3 dizziness which resolves to grade ≤ 1 within ≤ 7 days

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events, v5.0; DLT = dose-limiting toxicity; IV = intravenous; PO = per os (by mouth); ULN = upper limit of normal.

Toxicities clearly related to disease progression or intercurrent illness will not be considered DLTs.

In addition, clinically important or persistent toxicities not included in the above criteria may be considered a DLT following review by the Sponsor and study Investigators. All DLTs should represent a clinically significant shift from baseline. These will be evaluated according to National Cancer Institute CTCAE v5.0.

To fully characterize the safety of repotrectinib in combination with trametinib, subjects who are discontinued from treatment before completing the DLT evaluation period (28 days, Cycle 1) due to disease progression or other event unrelated to study drugs, or who did not adequately complete the PK evaluations within Cycle 1, may be replaced.

Dose re-escalation for subjects with DLTs is not allowed in the Phase 1b portion of the study. Subjects experiencing a DLT may resume dosing at the next lower dose level (if applicable) once adequate recovery is achieved.

3.2.1.2. Determination of MTD

The MTD is defined as the highest dose level of repotrectinib given in combination with trametinib observed to cause a DLT in fewer than 33% of the treated subjects in the first treatment cycle (i.e., 28 days, Cycle 1).

3.2.1.3. Recommended Phase 2 Dose (RP2D) Definition

The RP2D is the dose chosen for further study in Phase 2 based on the Phase 1b results. RP2D dose selection will be based on the entirety of the safety, efficacy, and clinical pharmacology data using an integrated quantitative approach. The RP2D may be the MTD unless one or more of the following suggest an alternate dose below the MTD would be preferable:

a. clinically significant anti-tumor effect (complete response [CR], partial response [PR], or prolonged stable disease [SD]) occurs below the MTD, in which case a clinically active dose level may be selected as the RP2D;
b. the MTD is not achieved, in which case the highest dose level administered may become the RP2D; or
c. toxicities observed beyond the DLT evaluation period (Cycle 1) require selecting the RP2D below the MTD level.

Once the MTD of repotrectinib in combination with trametinib has been determined, the RP2D will be determined at or below the MTD. At least 6 subjects will be treated at the RP2D prior to proceeding into the Phase 2 portion of the study. Additional subjects may be added at a dose level to gather more safety, PK, and efficacy data.

3.2.1.4. Follow-Up After a Dose-Limiting Toxicity

When treatment is interrupted due to a DLT, the subject must be followed at least once a week for 4 weeks, and subsequently at a maximum interval of 4 weeks, until resolution or stabilization of the event, whichever comes first.

3.2.1.5. Safety Review Committee

For the Phase 1b portion of the study, a Safety Review Committee comprised of at minimum the Sponsor Medical Monitor and study Investigators will review all relevant safety and other relevant clinical data and will provide recommendations on the following:

- Confirmation of DLTs
- Dose escalation decisions within the dose escalation portion
- Selection of RP2D

3.3. Phase 2 Expansion Study Design

Once the MTD/RP2D of repotrectinib in combination with trametinib has been determined, approximately 50 subjects will be enrolled into the Phase 2 expansion portion. The Phase 2

portion is designed to explore the anti-tumor efficacy and safety of repotrectinib in combination with trametinib for the treatment of patients with locally advanced or metastatic NSCLC harboring a *KRAS*^{G12D} mutation.

An interim futility analysis of the ORR will be performed after approximately 15 subjects are evaluable for tumor response. If ≤ 2 responders (confirmed CR or PR) are observed from 15 evaluable subjects, the expansion cohort will be stopped for futility. If ≥ 3 responders are observed, this cohort may continue depending on the overall benefit and risk assessment at the interim analysis.

Tumor assessments will include all known or suspected disease sites. All radiographic efficacy endpoints will be assessed using RECIST v1.1. Intracranial responses will be assessed by modified RECIST v1.1. For all tumor assessments, the imaging modality used at baseline should be the same modality used throughout the study.

Safety will be monitored *via* laboratory assessments, physical examinations, electrocardiograms (ECG), vital signs, and TEAEs according to CTCAE v5.0. PK data will also be collected. In addition, safety will be monitored by a Safety Review Committee comprised of at minimum the Sponsor Medical Monitor and study Investigators to review all relevant safety and other relevant clinical data. The following study stopping rules will apply for the Phase 2 portion of the study:

- Any death (other than disease progression) that is at least possibly related to the study agent.
- Occurrence of two or more Grade 4 events that are at least possibly related to the study agent.

3.4. Study Duration

Subjects will remain on study treatment until confirmed radiographic disease progression, development of unacceptable toxicity, or withdrawal of consent. There is no limit to the number of cycles of treatment with repotrectinib or trametinib.

For subjects discontinuing the study treatment due to documented radiographic progression, obtain survival status via phone call or medical chart review, including information about subsequent anticancer therapies (including best response) every 3 months until death, loss of follow-up, or withdrawal of consent, whichever comes first. For subjects discontinuing the study treatment prior to documented radiographic progression, tumor assessments should continue on the schedule approximately every 2 months or at the current scan interval at the time of treatment discontinuation until radiographic evidence of disease progression, the start of a subsequent anticancer therapy, or decision to no longer treat (e.g., supportive care only), whichever is first.

3.5. Dose Modifications

For subjects who experience a DLT, dose adjustments are permitted if it is considered in the best interest of the subject to continue therapy after discussing with the Sponsor's Medical Monitor. Dose modification guidelines for repotrectinib are described in the Dose Modification Guidelines for Adverse Events table (Table 4). Dose reductions for repotrectinib will follow the dose levels provided in Table 2. The guidelines provided in the label for trametinib should be referenced and

followed to manage toxicities associated with trametinib (i.e., see Table 2 in Mekinist® [trametinib] USPI 2020).

If toxicity is clearly attributed to one drug based on the known toxicity profile then one drug may be modified while the other is continued at the current dose. If the toxicity cannot clearly be attributed to one drug, then a dose modification for both drugs will be implemented according to the Dose Modification Guidelines for Adverse Events table for repotrectinib (Table 4) and per label for trametinib (see Table 2 in Mekinist® [trametinib] USPI 2020).

Subjects who cannot be re-treated with study drug should have weekly follow-ups that include a physical examination, vital signs including weight, Eastern Cooperative Oncology Group (ECOG) performance status (PS), ECGs, and assessment of AEs and concomitant medication. Following a DLT or toxicity, hematology, renal, and liver function tests (LFTs) should be performed as appropriate.

If a subject requires a dose delay of > 28 days from the intended day of the next scheduled dose of study drugs, then the subject must be discontinued from the study. If a subject requires more than two dose reductions for a either agent, then the subject must be discontinued from the study.

Subjects who discontinue from the study for a study drug-related AE or a grade 3 or higher abnormal laboratory value must be followed as described in Section 7.3.

3.5.1. Dose Interruptions and Delays

Dose interruptions may occur in the event of a treatment-related toxicity or a non-treatment-related issue (e.g., elective surgery). If toxicity is clearly attributed to one drug based on the known toxicity profile then one drug may be interrupted while the other is continued. If the toxicity cannot clearly be attributed to one drug, then dose interruption for both drugs will be implemented.

Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the Investigator. Criteria required before treatment can resume for repotrectinib are described in the dose modification guidelines for adverse events table (Table 4). The guidelines provided in Table 4 are general guidelines for dose modifications due to toxicities that may arise from repotrectinib. The guidelines provided in the label for trametinib should be referenced and followed to manage toxicities (i.e., see Table 2 in Mekinist® [trametinib] USPI 2020).

Doses may be held as needed until toxicity resolution. Depending on when the AE is resolved, a treatment interruption may lead to the subject missing all subsequent planned doses within that same cycle or even to delay the initiation of the subsequent cycle.

If a treatment delay results from worsening of hematologic or biochemical parameters, the frequency of relevant laboratory assessments may be increased as clinically indicated.

If the AE that led to the treatment interruption recovers within the same cycle, then re-dosing in that cycle is allowed. Doses omitted for toxicity are not replaced within the same cycle. The need for a dose reduction at the time of treatment resumption should be based on the criteria defined in Table 4 unless otherwise agreed to following discussion between the Investigator and the Medical Monitor.

In the event of a treatment interruption for reasons other than treatment-related toxicity (e.g., elective surgery) lasting ≥ 14 days, treatment resumption must be discussed with the Medical Monitor.

All study visits (visit date calculations) are based off the Cycle 1 Day 1 visit date, regardless of dose interruptions, and evaluations are to be performed according to the Schedule of Activities (Table 1). Every effort should be made to maintain the tumor assessments scheduling as described in the Schedule of Activities.

Table 4: Repotrectinib Dose Modification Guidelines for Adverse Events (CTCAE v5.0)

Toxicity	CTCAE Grade 1*	CTCAE Grade 2*	CTCAE Grade 3	CTCAE Grade 4
Hematologic	Continue at same dose level.	Continue at same dose level.	Withhold dose until toxicity is grade ≤ 2, or has returned to baseline, then resume treatment at the same dose level or reduce by one dose level[1,2] as per the Investigator's discretion. Grade 3 lymphopenia without other dose-limiting events (e.g., opportunistic infection) may continue study treatment without interruption.	Withhold dose until toxicity is grade ≤ 2, or has returned to baseline, reduce the dose by one dose level[1,2] and resume treatment. Grade 4 lymphopenia without other dose-limiting events (e.g., opportunistic infection) may continue study treatment without interruption.
Non-Hematologic excluding dizziness, ataxia, and paresthesia	Continue at same dose level.	Continue at same dose level. For prolonged or intolerable CNS toxicity, withhold dose until toxicity is grade ≤ 1 or has returned to baseline, then reduce by one dose level[1,2] and resume treatment.	Withhold dose until toxicity is grade ≤ 1 or has returned to baseline.	Withhold dose until toxicity is grade ≤ 1 or has returned to baseline, then reduce by one dose level[1,2] and resume treatment; or discontinue treatment as per the Investigator's discretion.
ILD/Pneumonitis (occurred in the absence of disease progression, pulmonary embolism, positive cultures or radiation effect)	Asymptomatic, radiographic findings only: No need for dose adjustment. Initiate appropriate monitoring. Symptomatic: Withhold current dose until toxicity has returned to baseline. Rule out infection and consider initiating treatment with corticosteroids. Then resume treatment at the same dose. Discontinue permanently if pneumonitis recurs or if failure to recover after 28 days	Withhold current dose until toxicity has returned to baseline. Rule out infection and consider initiating treatment with corticosteroids. Then resume treatment at one dose level lower. Discontinue permanently if pneumonitis recurs or if failure to recover after 28 days of study treatment hold and steroid treatment.	Discontinue treatment permanently.	Discontinue treatment permanently.

Toxicity	CTCAE Grade 1*	CTCAE Grade 2*	CTCAE Grade 3	CTCAE Grade 4
	of study treatment hold and steroid treatment.			
AST or ALT elevation	Continue at same dose level.	Continue at same dose level. Withhold current dose if concurrent CTCAE grade ≥ 2 total bilirubin elevation (> 1.5 x ULN).	Withhold current dose until resolves to Grade ≤ 1.	Discontinue treatment permanently.
Prolonged QTc	Assess electrolytes and concomitant medications. Correct any electrolyte abnormalities, or hypoxia. Continue at the same dose level.	Assess electrolytes and concomitant medications. Correct any electrolyte abnormalities, or hypoxia. Continue at the same dose level.	Withhold dose Assess electrolytes and concomitant medications. Correct any electrolyte abnormalities, or hypoxia. Upon recovery to grade ≤ 1: if no other cause for QTc prolongation is found or is considered drug-related resume treatment at 1 dose level lower.	Discontinue treatment.
Dizziness, ataxia, or muscular weakness	Continue at same dose level.	Withhold current dose until toxicity is grade ≤ 1 or has returned to baseline OR reduce by 1 dose level immediately[1,2]	Withhold dose until toxicity is grade ≤ 1 or has returned to baseline, then reduce by 1 dose level[1,2] and resume treatment	Withhold dose until toxicity is grade ≤ 1 or has returned to baseline, then reduce by 1 dose level[1,2] and resume treatment; or discontinue treatment as per the Investigator's discretion after discussion with Medical Monitor.

Toxicity	CTCAE Grade 1*	CTCAE Grade 2*	CTCAE Grade 3	CTCAE Grade 4
Weight gain	Continue at same dose level. Implement effective weight management strategy (dietary advice from a nutritionist and food intake counseling).	Dose interrupt or dose reduce[1,2], if required.	Dose interrupt or dose reduce[1,2], if required.	Not applicable.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CNS = central nervous system; CTCAE = Common Terminology Criteria for Adverse Events, v5.0; ILD = interstitial lung disease; QTc = QT interval corrected for heart rate; ULN = upper limit of normal.
*Cycle will not be extended to cover for the missing doses. In cases where no specific dose adjustments for CTCAE Grade 1 or Grade 2 treatment-related toxicity are provided, Investigators should always manage their subjects according to their medical judgment, which may include dose reduction or interruption based on the particular clinical circumstances.
[1] If subjects are assigned to the Dose Level -3 dose level, further dose reductions will not be implemented. Subjects will be discontinued if a dose reduction is required.
[2] Dose reductions for repotrectinib will follow the dose levels provided in Table 2.

4. SUBJECT ELIGIBILITY CRITERIA

Each subject must meet all of the following inclusion criteria and none of the exclusion criteria to be enrolled in the study.

4.1. Subject Inclusion Criteria

Phase 1 AND Phase 2:

1. Subject must have a histologically or cytologically confirmed diagnosis of unresectable or metastatic solid tumor malignancy harboring a *KRAS* mutation.
   - Documented *KRAS*^{G12D} mutation as determined by a quantitative polymerase chain reaction (qPCR) or next-generation sequencing (NGS) test performed in a Clinical Laboratory Improvement Amendments (CLIA) laboratory or equivalently accredited diagnostic laboratory. Local tissue-based or liquid biopsy diagnostic testing will be permitted.
   - Adequate tumor tissue needs to be sent to the Sponsor designated central diagnostic laboratory for retrospective confirmation by a central diagnostic laboratory test selected by the Sponsor. See the Study Laboratory Manual for details.
2. Eastern Cooperative Oncology Group (ECOG) Performance Status 0–1
3. Age ≥ 18 (or as required by local regulation).
4. Willing and able to provide written institutional review board (IRB)/ethics committee (EC)-approved Informed Consent.
5. At least 1 measurable target lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Subjects with central nervous system (CNS)-only measurable target lesion ≥ 5 mm as defined by RECIST v1.1 are eligible.
6. Required wash-out time that is related to prior therapies before starting repotrectinib combination treatment:
   - At least 14 days or 5 half-lives (whichever is shorter) must have elapsed after discontinuation of prior systemic therapy and all side effects from prior treatments must have resolved to grade ≤ 1 with the exception of alopecia.
   - At least 14 days must have elapsed after discontinuation of prior immunotherapy and all immune-related side effects from prior immunotherapy must have resolved to grade ≤ 1.
7. Subjects with asymptomatic CNS metastases (treated or untreated) and/or asymptomatic leptomeningeal carcinomatosis are eligible to enroll if they satisfy the following criteria:
   - Subjects requiring steroids at a stable or decreasing dose (≤ 12 mg/day dexamethasone or equivalent) for at least 14 days.
   - Subjects on stable doses of levetiracetam (same dose for 14 days).
   - A minimum of 14 days must have elapsed from the completion of whole brain radiation treatment (WBRT) before the start of treatment, and all side effects (with the exception of alopecia) from WBRT are resolved to grade ≤ 1.
   - A minimum of 7 days must have elapsed from the completion of stereotactic radiosurgery before the start of treatment and all side effects (with the exception of alopecia) from stereotactic radiosurgery are resolved to grade ≤ 1.

8. Baseline laboratory values fulfilling the following requirements:

Absolute Neutrophils Count	≥ 1,500/mm^3 (1.5 x 10^9/L)
Platelets	≥ 100,000/mm^3 (100 x 10^9/L) independent of platelets transfusion support for at least 7 days prior to dosing
Hemoglobin	≥ 9.0 g/dL independent of transfusion support for at least 7 days prior to dosing
Creatinine Clearance*	> 40 mL/min
Total Serum Bilirubin	< 1.5 x ULN (≤ 3.0 × ULN for patients with Gilbert's Syndrome or liver metastases)
Liver Transaminases (AST/ALT)	< 2.5 x ULN; < 5 x ULN if liver metastases are present
Alkaline Phosphatase	< 2.5 x ULN; < 5 x ULN if liver and/or bone metastasis are present.
Serum Calcium, Magnesium and Potassium	Normal or CTCAE grade ≤ 1 with or without supplementation.

Abbreviations: AST/ALT = aspartate aminotransferase/alanine aminotransferase, ULN = upper limit of normal.
* calculated by Cockcroft and Gault's formula: (140 - age [yr.]) x body weight [kg] x 1.23 x (0.85 if female) /serum creatinine [µmol/L].

9. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test during screening and be neither breastfeeding nor intending to become pregnant during study participation. Female patients will be considered to be of childbearing potential unless they have undergone permanent sterilization or are postmenopausal. Postmenopausal is defined as at least 12 months without menses with no other medical reasons (e.g., chemical menopause due to anticancer treatment). For WOCBP and for men, agreement to use a highly effective contraceptive method from the time of screening throughout the study until 4 months (WOCBP) or 6 months (men) after administration of the last dose of any study drug. Highly effective contraceptive methods consist of prior sterilization, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), injectable or implantable contraceptives. All male study subjects must agree to use condoms throughout the study and 6 months after administration of the last dose. Male partners of WOCBP subjects must agree to condom use throughout the study and for 4 months following the last dose of study drug. True abstinence is acceptable if evaluated as consistent with the preferred and the usual lifestyle of the subject. Periodic abstinence is not an acceptable method of contraception.
10. Ability to swallow capsules and tablets intact (without chewing, crushing, or opening).
11. Life expectancy ≥ 3 months.
12. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

Additional Inclusion Criteria for Phase 1 Only:

13. Subject must have received prior standard therapy appropriate for their tumor type and stage of disease, or in the opinion of the Investigator, would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy.
    - Subject must have received no more than 3 prior systemic regimens.
    - Maintenance therapy will not be counted as a separate regimen.
    - Adjuvant chemotherapy or chemotherapy administered as part of concurrent chemotherapy and radiation therapy will not count as a prior regimen of systemic

therapy as long as recurrence occurred more than 6 months after the last day of chemotherapy.

Additional Inclusion Criteria for Phase 2 Only:

14. Histologically or cytologically confirmed diagnosis of advanced or metastatic NSCLC harboring a *KRAS*^{G12D} mutation.
    - Subject must have a documented *KRAS*^{G12D} mutation as determined by a qPCR or NGS test performed in a CLIA laboratory or equivalently accredited diagnostic laboratory. Local tissue-based or liquid biopsy diagnostic testing will be permitted.
    - Adequate tumor tissue needs to be sent to the Sponsor designated central diagnostic laboratory for retrospective confirmation by a central diagnostic laboratory test selected by the Sponsor. See the Study Laboratory Manual for details.
15. Subjects must have received no more than one prior line of platinum-based chemotherapy **OR** one prior line of platinum-based chemotherapy in combination with immunotherapy **OR** both platinum-based chemotherapy and single agent anti-PD1/PDL1 therapy in two separate lines of therapy.
    - Adjuvant chemotherapy or chemotherapy administered as part of concurrent chemotherapy and radiation therapy for the treatment of lung cancer will not count as a prior regimen of systemic therapy as long as recurrence of patient's lung cancer occurred more than 12 months after the last day of chemotherapy.

4.2. Subject Exclusion Criteria

1. Concurrent participation in another therapeutic clinical trial.
2. Symptomatic brain metastases or leptomeningeal involvement.
3. History of previous cancer requiring therapy within the previous 2 years, except for squamous cell or basal-cell carcinoma of the skin, or any in situ carcinoma that has been completely resected.
4. Major surgery within 4 weeks of start of treatment. Radiation therapy (except palliative to relieve bone pain) within 2 weeks of start of treatment. Palliative radiation (≤ 10 fractions) must have been completed at least 48 hours prior to start of treatment.
5. Clinically significant cardiovascular disease (either active or within 6 months prior to start of treatment): myocardial infarction, unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (New York Heart Association Classification Class ≥ II), cerebrovascular accident or transient ischemic attack, symptomatic bradycardia, requirement for anti-arrhythmic medication. Ongoing cardiac dysrhythmias of CTCAE grade ≥ 2.
6. Any of the following cardiac criteria:
    - Mean resting corrected QT interval (ECG interval measured from the onset of the QRS complex to the end of the T wave) for heart rate (QTc) > 470 msec obtained from 3 ECGs, using the screening clinic ECG machine-derived QTc value
    - Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG (e.g., complete left bundle branch block, third degree heart block, second degree heart block, PR interval > 250 msec)

- Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalemia, congenital long QT syndrome, family history of long QT syndrome, or any concomitant medication known to prolong the QT interval

7. Known clinically significant active infections not controlled with systemic treatment (bacterial, fungal, viral including human immunodeficiency virus [HIV] positivity, hepatitis B [HBV], and hepatitis C [HCV], and acquired immunodeficiency syndrome [AIDS]-related illness).
8. Gastrointestinal disease (e.g., Crohn's disease, ulcerative colitis, or short gut syndrome) or other malabsorption syndromes that would impact drug absorption.
9. Peripheral neuropathy, paresthesia, dizziness, dysgeusia, muscle weakness, ataxia grade ≥ 2.
10. Currently have or had a history of ILD, radiation pneumonitis that required steroid treatment, or drug-related pneumonitis.
11. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or that may interfere with the interpretation of study results and, in the judgment of the Investigator and/or Turning Point Therapeutics, would make the subject inappropriate for entry into this study, or could compromise protocol objectives in the opinion of the Investigator and/or Turning Point Therapeutics.
12. Current or anticipated use of drugs that are known to be strong CYP3A inhibitors or inducers as well as use of drugs that are sensitive CYP3A substrates as listed in Appendix 1.
13. Prior exposure to repotrectinib.
14. Prior exposure to a direct and specific inhibitor of KRAS.
15. Prior exposure to trametinib or another MEK inhibitor.
16. Subjects have a history or current evidence of retinal vein occlusion (RVO) or central serous retinopathy (CSR) determined by an ophthalmology exam.
17. Current or anticipated use of drugs that are sensitive substrate with narrow therapeutic index for UGT1A1.
18. Current or anticipated use of drugs that are sensitive substrate with narrow therapeutic index for OATP1B1, OAT3, MATE1, and MATE2-K.
19. Current or anticipated use of drugs that are strong inhibitors of P-glycoprotein.

5. STUDY TREATMENT

5.1. Allocation to Treatment

All subjects will be allocated to receive repotrectinib in combination with trametinib. For the Phase 1b dose escalation portion of the study, subjects will be assigned according to the currently open dose level. For the Phase 2 portion of the study, all subjects will receive repotrectinib in combination with trametinib at the RP2D schedule determined in the Phase 1b portion in 28-day cycles.

5.1.1. Repotrectinib + Trametinib

Repotrectinib and trametinib will be administered orally as a combination treatment. For the Phase 1b dose escalation portion of the study, subjects will be assigned to a repotrectinib and trametinib dose according to the currently open dose level for 28 consecutive days in repeated four-week cycles. For the Phase 2 expansion portion of the study, subjects will be allocated to receive repotrectinib and trametinib at the RP2D combination determined during the Phase 1b dose-finding portion for 28 consecutive days in repeated four-week cycles.

5.2. Investigational Product Supplies

5.2.1. Dosage Form(s) and Packaging

5.2.1.1. Repotrectinib

Repotrectinib (TPX-0005) will be supplied for oral administration as 40 mg capsules. Study drug will be supplied by the Sponsor.

The investigational repotrectinib drug product is currently supplied as size 0 hard gelatin capsules of 40 mg dosage strength to deliver the active pharmaceutical ingredient, repotrectinib (TPX-0005) and has been manufactured for use in the proposed clinical study (Table 5).

Repotrectinib capsules are contained in round high-density polyethylene (HDPE) bottles with an induction seal and child resistant cap closure. The bottle does not contain a desiccant or a pharmaceutical coil.

Table 5: Investigational Product: Repotrectinib Product and Dosage Information

	Investigational Product
Product Name:	Repotrectinib
Dosage Form:	Capsules
Unit Dose:	Capsules (40 mg)
Route of Administration:	Oral
Physical Description:	Size 0 hard gelatin capsules

5.2.1.2. Trametinib

As per label (Mekinist® [trametinib] USPI 2020), trametinib will be supplied as commercially available in 0.5 mg or 2 mg tablets. Study drug will be supplied by the Sponsor.

Trametinib 0.5 mg tablets are yellow, modified oval, biconvex, film-coated tablets with 'GS' debossed on one face and 'TFC' on the opposing face and are available in bottles of 30 (NDC 0078-0666-15). Trametinib 2 mg tablets are pink, round, biconvex, film-coated tablets with 'GS' debossed on one face and 'HMJ' on the opposing face and are available in bottles of 30 (NDC 0078-0668-15).

Table 6: Investigational Product: Trametinib Product and Dosage Information

	Investigational Product
Product Name:	Trametinib
Dosage Form:	Tablet
Unit Dose:	Tablets (0.5 mg and 2 mg)
Route of Administration:	Oral
Physical Description (0.5 mg):	Yellow, modified oval, biconvex, film-coated tablets with 'GS' debossed on one face and 'TFC' on the opposing face
Physical Description (2 mg):	Pink, round, biconvex, film-coated tablets with 'GS' debossed on one face and 'HMJ' on the opposing face

5.2.2. Investigational Product Storage and Accountability

5.2.2.1. Repotrectinib

Repotrectinib is currently stored at controlled ambient room temperature between 15°C to 30°C. Subjects should be instructed to keep their medication in its original container and stored at 15°C to 30°C (59°F to 86°F). Returned medication should be stored separately from medication that is yet to be dispensed. The repotrectinib capsule bottle must be stored as indicated. Deviations from the storage requirements, including any actions taken, must be documented, and reported to the Sponsor.

5.2.2.2. Trametinib

The trametinib bottles are stored at controlled refrigerated temperature at 2°C to 8°C (36°F to 46°F) (Mekinist® [trametinib] USPI 2020). Trametinib is dispensed in the original bottle; do not remove desiccant. Protect from moisture and light. Do not place study drug in pill boxes. Returned medication should be stored separately from medication that is yet to be dispensed. The trametinib bottles must be stored as indicated. Deviations from the storage requirements, including any actions taken, must be documented and reported to the Sponsor.

5.2.3. Destruction of Investigational Product Supplies

At each cycle visit, and at the end of the treatment study, all unused or partially used bottles must be returned by subjects to the Investigator and the Sponsor will provide instructions for disposition of any unused repotrectinib or trametinib. If the Sponsor authorizes destruction at the study site, the Investigator must ensure that the materials are destroyed in compliance with

applicable environmental regulations, institutional policy, and any special instructions provided by the Sponsor. Destruction must be adequately documented.

5.3. Dose Regimen and Route of Administration

5.3.1. Repotrectinib + Trametinib

Repotrectinib and trametinib will be administered orally as a combination treatment.

For the Phase 1b dose escalation portion of the study, subjects will be assigned to a repotrectinib and trametinib dose level according to the currently open dose level (i.e., Dose Level 1, Dose Level 2, etc.) for 28 consecutive days in repeated four-week cycles.

For the Phase 2 expansion portion of the study, subjects will be allocated to receive repotrectinib and trametinib at the RP2D determined during the Phase 1b dose escalation portion for 28 consecutive days in repeated four-week cycles.

Repotrectinib and trametinib should be taken with at least 8 oz (240 mL) of water, either 1 hour before or at least 2 hours after a meal. Each dose should be taken at the same time each day. If the study drug is given BID, then the study drug should be taken in the morning, and again in the evening approximately 12 hours later.

For subjects taking repotrectinib and trametinib QD: if the subject is more than 12 hours late taking the study drug, the dose should be skipped, and the subject should continue taking repotrectinib and trametinib the next day as scheduled.

For subjects taking repotrectinib and trametinib BID: if the subject is more than 6 hours late taking the study drug, the dose should be skipped, and the subject should continue with the next scheduled dose.

5.4. Concomitant Treatments

Any concomitant medications, blood products, as well as non-drug supportive interventions (e.g., paracentesis) received by subjects from the date of signed informed consent until the EOT visit should be recorded on the appropriate electronic Case Report Form (eCRF). The Investigator should be alerted if the subject is taking any agent known to affect or with the potential for drug interactions.

Note on COVID-19 Vaccination: The use of vaccines is not a restriction for this study. Currently enrolled and potential adult clinical trial subjects are allowed to receive the COVID-19 vaccine with no impact on their eligibility or ability to remain on study treatment. This guidance will also apply to pediatric and adolescent patients once vaccine approval is available for these populations. In addition, there is not a required wash-out period for the vaccine. The risk-benefit for COVID-19 vaccination while on study should be determined by the treating physician. Administration of the COVID-19 vaccine will be recorded in the medical history or the concomitant medications CRF, as applicable, as well as any adverse events related to the vaccine.

5.4.1. Prohibited Concomitant Medications

The concomitant use of known strong CYP3A4 inhibitors is prohibited including their administration at least within 2 weeks prior to the first study drug dose and throughout the study.

Subjects should avoid grapefruit juice or grapefruit/grapefruit-related citrus fruits (Seville oranges, pomelos). Coadministration of study drug in combination with strong CYP3A4 inducers is prohibited including their administration at least within 2 weeks prior to the first study drug dose and throughout the study. See Appendix 1 for a list of known CYP3A4 inhibitors and inducers.

Current or anticipated use of drugs that are sensitive CYP3A4 substrates should be avoided including their administration at least within 2 weeks prior to the first study drug dose and throughout the study. Concomitant medication suspected of being a sensitive CYP3A4 substrate must be approved by the Sponsor.

Current or anticipated use of drugs that are sensitive substrate with narrow therapeutic index for UGT1A1 should be avoided, including their administration within at least 2 weeks prior to the first study drug dose and throughout the study. Concomitant medication suspected of being a sensitive UGT1A1 substrate with narrow therapeutic index must be approved by the Sponsor.

Concomitant use of drugs that are known to be sensitive substrates with narrow therapeutic index for OATP1B1, OAT3, MATE1, and MATE2-K should be avoided including their administration at least within 2 weeks prior to the first study drug dose and throughout the study. Concomitant medication suspected of being a sensitive OATP1B1, OAT3, MATE1 and MATE2-K substrate with narrow therapeutic index must be approved by the Sponsor.

Current or anticipated use of drugs that are strong inhibitors of P-gp should be avoided, including their administration within at least 2 weeks prior to the first study drug dose and throughout the study. Concomitant medication with suspected strong P-gp inhibitory effect must be approved by the Sponsor.

If there is a question about a particular concomitant medication, discuss with the Medical Monitor.

5.4.1.1. Other Anti-Tumor or Investigational Drugs

Additional systemic anti-tumor therapy is not permitted while subjects are receiving study therapy.

5.4.2. Anti-Diarrheal, Anti-Emetic Therapy

Primary prophylaxis of diarrhea, nausea, and vomiting is not permitted in the first cycle in the Phase 1b portion of the study. Primary prophylaxis in subsequent cycles is at the Investigator's discretion. The choice of the prophylactic drug as well as the duration of treatment is up to the Investigator with Sponsor approval assuming there is no known or expected drug-drug interaction and assuming the drug is not included in the Prohibited Concomitant Medications section.

5.4.3. Anti-Inflammatory Therapy

Anti-inflammatory or narcotic analgesic may be offered as needed assuming there is no known or expected drug-drug interaction and assuming the drug is not included in the Concomitant Treatments section.

5.4.4. Corticosteroids

Chronic systemic corticosteroid use (prednisone ≥ 12.5 mg/day or dexamethasone ≥ 2 mg/day) for palliative or supportive purpose is not permitted (unless administered for adrenal insufficiency). Acute emergency administration, topical application, inhaled sprays, eyedrops or local injections are permitted.

6. STUDY ASSESSMENTS

6.1. Informed Consent

Prior to conducting any protocol-specific procedures for Phase 1b and Phase 2, written informed consent and any other authorizations must be signed and dated by the subject or subject's legal representative (Section 12.4).

6.2. Tumor Molecular Alteration

Perform molecular testing as per Section 4.1 and the Schedule of Activities (Table 1).

Molecular testing to determine eligibility can be performed in advance with no time limit (e.g., the subject can be tested while being treated on another anticancer therapy).

Source documents (molecular pathology report detailing the specific test that confirms KRAS mutational status) should be submitted for the Sponsor's approval of eligibility.

Adequate archival tissue should be available for shipment to the Sponsor's designated central laboratory. A fresh biopsy is required if no adequate previously taken and stored tumor sample is not available.

6.3. Tumor Treatment History

All prior therapies, including duration and best response of targeted therapies, prior chemotherapy, and/or immunotherapy regimens and will be recorded in the applicable eCRF. If brain metastases are present, prior radiation and methods of radiation (e.g., whole brain radiation, stereotactic radiosurgery) should also be recorded.

6.4. Demographics

Demographic information (e.g., date or year of birth and race) will be recorded at Screening, as allowed per local country privacy law regulations.

6.5. Medical History

Relevant medical history, including history of current disease, other pertinent clinical conditions, and information regarding underlying disease will be recorded at Screening.

6.6. Physical Examination

A complete physical examination, including neurological examination will be performed by either the Investigator or a sub-Investigator according to the Schedule of Activities (Table 1).

The neurological examination will include assessments of the following symptoms: dizziness, dysgeusia, paresthesia, ataxia, headache, neuralgia, extrapyramidal disorder, memory impairment, concentration impairment, somnolence, and cognitive disturbance.

Height and weight will be collected as part of the physical exam. Height will be collected at Screening only.

Clinically significant abnormal findings must be recorded in the applicable eCRF and followed by the Investigator, sub-Investigator, or other qualified site staff at the next scheduled visit or earlier as clinically indicated.

6.7. Ophthalmologic Examination

All subjects must undergo a baseline, standard ophthalmologic exam at Screening. The exam will include direct and indirect fundoscopic exams, visual acuity (corrected), visual field examination, and tonometry, with special attention to any retinal abnormalities that are predisposing factors for RVO or CSR. After Screening, additional ophthalmologic exams will be performed only as symptomatically warranted.

6.8. Performance Status

The ECOG performance status will be assessed at Screening and according to the Schedule of Activities (Table 1).

6.9. Vital Signs

Body temperature, blood pressure, heart rate, and respiratory rate will be performed at timepoints outlined in the Schedule of Activities (Table 1).

6.10. Subject Diary and Compliance

All doses of study drugs (i.e., repotrectinib and trametinib) and dosing diaries will be dispensed by the appropriately designated study staff at the investigational site.

Subjects will be required to bring the dosing diary and all empty and partially used study drug bottles and any leftover study drug to every visit. The number of capsules and/or tablets returned by the subject will be counted, documented, and recorded. Treatment compliance will be evaluated by noting the discrepancy among the assigned dose, the dose administered, and the reason for the discrepancy will be recorded in the source documents.

6.11. Laboratory Assessments

Laboratory assessments as described in Table 7 below will be performed per the Schedule of Activities (Table 1).

Table 7: Safety Laboratory Tests

Hematology	Complete blood count with differential: hemoglobin, platelets, WBC, absolute neutrophils, absolute lymphocytes, absolute monocytes, absolute eosinophils, absolute basophils
Chemistry	ALT, AST, ALP, sodium, potassium, magnesium, chloride, total calcium, total bilirubin, BUN or urea, creatinine, uric acid, glucose (nonfasted), lipid panel (total cholesterol, LDL, HDL, triglycerides), albumin, phosphorus or phosphate, bicarbonate, total protein, lactate dehydrogenase, amylase, lipase
Coagulation	PT or INR, PTT
Urinalysis	Urine dipstick for urine protein: If positive and clinically significant, microscopic (Reflex Testing) Urinalysis includes the analysis of protein, glucose, ketones, blood, and specific gravity. A microscopic (white blood cells/high-power field [HPF], red blood cells/HPF, and any additional findings) exam need be performed only if the urinalysis result is abnormal.
Pregnancy Test	Serum pregnancy test for female subjects of childbearing potential (Section 6.12)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; HDL = high-density lipoprotein; INR = International normalized ratio; LDL = low-density lipoprotein; PT = prothrombin time; PTT = partial thromboplastin time; WBC = white blood cell.
Note: For potential Hy's Law cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/INR, alkaline phosphatase, total bile acids and acetaminophen drug and/or protein adduct levels.

6.12. Pregnancy Test

For female subjects of childbearing potential, a serum pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed as per the Schedule of Activities (Table 1). Only subjects with negative serum pregnancy test results can enroll in the study.

Following a negative pregnancy test result at Screening, appropriate contraception must be commenced, and another negative pregnancy test result will then be required at the baseline visit before a subject may receive study drug. Additional pregnancy tests may also be undertaken if requested by Institutional Review Boards/Ethics Committees or if required by local regulations. In case of a confirmed pregnancy, the subject will be withdrawn from study drug but may remain in the study.

6.13. Cardiac Safety Monitoring

6.13.1. Electrocardiogram

Triplicate 12-lead (with a 10-second rhythm strip) tracings will be used for all ECGs. It is preferable that the machine used has a capacity to calculate the standard intervals automatically. At each timepoint, 3 consecutive ECGs will be performed at approximately 2 minutes apart to determine the mean QTc interval. See the Schedule of Activities (Table 1).

When coinciding with blood sample draws for PK, the ECG assessment should be performed prior to blood sample collection such that the blood sample is collected at the nominal time.

If the mean QTc is prolonged (> 500 msec [i.e., CTCAE Grade 3]), then the ECGs should be re-evaluated by a qualified person at the site for confirmation as soon as the finding is made, including verification that the machine reading is accurate. If manual reading verifies a QTc of > 500 msec, immediate correction for reversible causes (including electrolyte abnormalities,

hypoxia, and concomitant medications with the potential to prolong the QTc interval) should be performed. Study drug will be held until the QTc interval decreases to ≤ 500 msec. Subjects will then re-start the study drug if no other cause for QTc prolongation is found or is considered drug-related resume treatment at 1 dose level lower (Table 4). If the QTc interval has still not decreased to < 500 msec after 2 weeks, or if at any time a subject has a QTc interval > 515 msec or becomes symptomatic, the subject will be removed from the study. Additional triplicate ECGs may be performed as clinically indicated.

Prior to concluding that an episode of prolongation of the QTc interval is due to study drug, thorough consideration should be given to potential precipitating factors (e.g., change in subject clinical condition, effect of concurrent medication, electrolyte disturbance) including possible evaluation by a specialist. If subject experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke), an ECG (triplicate) should be obtained at the time of the event.

Additional ECG timepoints may be included based on the emerging data. Interpretation of the tracing will be made by a central ECG laboratory. Each ECG tracing should be labeled with the study number, subject initials, subject number, and date, and kept in the source documents at the study site. Only clinically significant abnormalities will be recorded in the AE CRF page. Clinically significant abnormalities at Screening/baseline should be recorded on the relevant medical history/current medical conditions CRF page and must be discussed with the Sponsor's Medical Monitor before enrolling the subject in the study.

6.13.2. Echocardiogram/MUGA Scan

To monitor potential left ventricular ejection fraction dysfunction, an echocardiogram or multigated acquisition (MUGA) scan will be performed at timepoints specified in the Schedule of Activities (Table 1). The same method of evaluation should be utilized throughout the study.

6.14. Pharmacokinetics

For the determination of study drug (i.e., repotrectinib and trametinib) plasma concentrations, 5 mL of blood will be collected for each PK sample. Plasma PK samples will be analyzed using a validated bioanalytical method at a Good Laboratory Practice (GLP) compliant bioanalytical laboratory designated by the Sponsor.

Blood samples for PK assessments during the Phase 1b and Phase 2 potions of the study will be collected as specified in the Schedule of Activities (Table 1).

Additional PK samples may be collected from subjects when experiencing unexpected and/or serious AEs and the date/time should be documented in the CRFs. In addition, the PK sampling scheme may be modified by the Sponsor pending emerging PK data.

All reasonable efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. However, samples obtained within 10% of the nominal time (e.g., within 6 minutes of the 60-minute sample) from dosing will not be considered as a protocol deviation, and the exact time of the sample collection noted on the source document and data collection tool (e.g., CRF).

For the PK samples collected, after sample analysis, the remaining samples may be used for the purposes of exploratory metabolite scouting and potential exploratory protein biomarker testing.

Details regarding the collection, processing, storage, and shipping of the PK samples will be provided in the Study Manual.

6.15. Pharmacodynamics/Biomarkers

In all subjects, blood samples for circulating cell-free DNA (ccfDNA) will be collected at Screening, Cycle 3 Day 1 (in conjunction with tumor assessment evaluation), and either at the time of radiographic disease progression or at the EOT (whichever occurs earlier) as specified in the Schedule of Activities (Table 1).

Circulating cell-free DNA (ccfDNA) will be isolated from blood to study changes of circulating tumor levels (i.e., assessed by modulations of minor allele frequency [MAF] of genomic alterations), and explore resistance mechanisms as well as clonal evolution.

Blood will be collected across two 10 mL Streck Cell-Free DNA Blood Collection Tubes (for ccfDNA analysis). Circulating cell-free DNA (ccfDNA) will be isolated from blood.

Details for handling of these specimens including processing, storage, and shipment will be provided in the Laboratory Manual.

6.16. Tumor Assessments

Imaging studies will include a computerized tomography (CT) or magnetic resonance imaging (MRI) scan of the brain, chest, abdomen, pelvis. For subjects diagnosed with primary brain tumors, only the MRI of the brain will be required at Screening and during the study.

Tumor assessments will include all known or suspected disease sites and will be performed per specified timepoints according to the Schedule of Activities (Table 1). For all tumor assessments, the method of assessment that was used at Screening should be the same method used throughout the study. Tumor assessment will be assessed locally by Investigator and by BICR.

For all subjects, radiographic confirmation of objective tumor response or disease progression will be based on RECIST v1.1 and assessed locally by Investigator (Section 6.16.4).

At the EOT visit, the subject must undergo an EOT tumor assessment evaluation CT or MRI (if more than 4 weeks have passed since the last imaging assessment) to evaluate for radiologic disease progression if treatment is being discontinued for an alternate reason other than confirmed radiographic disease progression.

For subjects demonstrating radiographic response (PR or CR) during treatment, subject responses will be confirmed ≥ 4 weeks later (ideally, the confirmation scan should be scheduled at end of the next cycle, i.e., 28 days) after the initial documentation of response by the Investigator.

For subjects discontinuing study treatment before documented radiographic progression, tumor assessments should continue at the current scan interval at the time of treatment discontinuation until radiographic evidence of disease progression, the start of a subsequent anticancer therapy, withdrawal of consent, or decision to no longer treat (e.g., supportive care only), whichever is first.

For subjects discontinuing the study treatment due to documented radiographic progression, survival status will be obtained via a phone call or medical chart review, including information

about subsequent anticancer therapies (including best response) every three months until death, loss of follow-up, or withdrawal of consent, whichever comes first.

6.16.1. CT/MRI of Chest/Abdomen/Pelvis

Intravenous (IV) contrast is required when not medically contraindicated. Subjects who have a contraindication to IV contrast may have MRI exams of the abdomen, and pelvis performed in lieu of CTs and a non-contrast CT of the chest. Positron emission tomography (PET)/CT may be used to document baseline and new disease, but the CT portion of a PET/CT may not be used in lieu of a diagnostic CT, unless it is performed with IV contrast. Additional requirements are provided in the Imaging Manual.

Every effort should be made to maintain the assessment scheduling relative to Cycle 1 Day 1, regardless of any dosing interruptions.

6.16.2. Brain CT or MRI

At Screening, a CT/MRI of the brain should be obtained to rule out newly diagnosed, untreated brain metastases or to document stability of previously treated brain metastases.

CT/MRI brain scans should be performed at every on-study tumor assessment for subjects with brain metastases.

6.16.3. Bone Scan

At Screening, a bone scan should be obtained if bone metastases are suspected. For subjects with bone metastases at baseline, a bone scan should only be repeated to check for residual disease when assessing for complete response unless the bone scan is used to determine RECIST v1.1 response assessment. The bone scan should be performed at the same time as the chest, abdomen and pelvis CT (C/A/P) scans. If a bone scan has been performed within 28 days prior to Cycle 1 Day 1 the scan can be used for Screening. Radiographic confirmation of objective tumor response or disease progression will be based on RECIST v1.1. The same imaging modality should be used at Screening and on study.

6.16.4. Blinded Independent Central Review (BICR)

All scans will be submitted to a third-party central imaging laboratory for independent review of tumor response and disease progression during the study according to an Imaging Review Charter to be prepared by the core imaging laboratory in consultation with Turning Point Therapeutics Medical Monitor.

It is important to the integrity of the study that all imaging studies are forwarded to the central imaging laboratory in a timely manner throughout the study, within 1 week of collection whenever possible. Further details can be found in the Imaging Manual.

6.17. Other Clinical Assessments

All AEs, whether reported by the subject or noted by study personnel, will be recorded in the subject's medical record and on the Adverse Event CRF at each subject contact. After the informed consent for the clinical trial has been obtained but prior to initiation of study drug, only SAEs related to protocol-mandated assessments should be reported. After initiation of study

drug, all AEs, regardless of relationship to study drug, will be reported until at least 28 days after the last dose of study treatment. AEs will be graded according to CTCAE version 5.0. The type, incidence, severity, timing, seriousness, and relatedness of AEs and laboratory abnormalities will be reported. Refer to Section 8 for a description of procedures for AE assessments.

Refer to Section 5.4 for information regarding concomitant treatments and Section 7.7 (Long-Term Follow-up) for survival follow-up procedures.

7. STUDY CONDUCT

Scheduled protocol-related activities will be performed at specified timepoints and within windows as outlined in the Schedule of Activities (Table 1). If a visit is missed for any reason, the next scheduled visit should occur as originally planned.

7.1. Screening and Eligibility

All subjects being considered for screening must provide informed consent prior to completing any study-specific procedures. A subject number will be assigned. After signing informed consent, subjects will be screened to confirm eligibility.

The following items must be completed as part of the screening procedures:

- An eligibility checklist must be completed for each subject and sent to the Sponsor for eligibility confirmation before enrollment
- Source documents of molecular pathology report, detailing the specific test that confirms KRAS mutational status, should be submitted for the Sponsor's approval of eligibility (refer to Section 6.2 for additional information)
- Imaging studies (CT or MRI of the chest, abdomen, and pelvis and MRI of the brain) should be submitted for BICR assessment

7.2. Timing of Clinical Procedures

On visits that require in-clinic dosing, clinical assessments should be conducted as described in Section 7.2.1.

7.2.1. Pre-Dose Assessments

- Record any AEs
- Review and record concomitant medications and non-drug supportive interventions taken since the time of Informed Consent Form (ICF) signing
- Assess study drug compliance
- Perform a complete physical examination and record vital signs and body weight
- Perform ECOG performance status
- Collect blood for clinical laboratory assessments, (hematology, chemistry, and coagulation profile)
- Collect blood for ccfDNA

- For WOCBP, collect blood for pregnancy test
- Collect urine for urine analysis
- Perform and record pre-dose triplicate 12-lead ECGs approximately 2 minutes apart
- Collect pre-dose PK sample

7.3. Subject Discontinuation and Withdrawal from Study

A subject may be discontinued from study treatment at any time if the subject, the Investigator, or the Sponsor Medical Monitor determine that it is not in the subject's best interest to continue on study. The following is a list of possible reasons for early discontinuation of study treatment:

- Disease progression (unless there is reasonable evidence of clinical benefit to justify continuation on treatment - which must be previously discussed with the Sponsor)
  - Subjects should remain on study treatment until there is confirmed radiographic progression
  - Subject may be allowed to continue repotrectinib or trametinib beyond RECIST-defined progression if, in the clinical judgment of the Investigator, the subject continues to derive clinical benefit from the study drug(s) (with approval from Turning Point Therapeutics; see Section 7.4)
- Any adverse event (AE) that cannot be adequately managed with dose modifications, including dose interruption > 28 days (unless there is reasonable evidence of clinical benefit to justify continuation on the protocol–which must be previously discussed with Turning Point Therapeutics) (Section 3.5)
- Protocol violation requiring discontinuation of study treatment
- Subject is not compliant with study procedures
- Lost to follow-up
- Subject withdrawal of consent for further treatment
- Turning Point Therapeutics' early termination of study. Reasons for terminating the study may include, but are not limited to, the following:
  - All enrolled subjects have discontinued study treatment
  - The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects
  - Subject enrollment is unsatisfactory

Data to be collected for the EOT visit are described in the Schedule of Activities (Table 1).

Subjects will be followed for at least 28 calendar days after the last dose of study drug (i.e., repotrectinib and trametinib). If a subject is discontinued from treatment due to an AE, the subject will be followed until the AE has resolved or stabilized as per Section 8.4.

7.4. Study Treatment Discontinuation

For subjects discontinuing the study treatment prior to documented radiographic progression, tumor assessments should continue on the schedule approximately every 2 months or at the current scan interval at the time of treatment discontinuation until radiographic evidence of disease progression, the start of a subsequent anticancer therapy, or decision to no longer treat (e.g., supportive care only), whichever is first. At this time, subjects should transition into long-term follow-up (see Section 7.7).

7.5. Withdrawal of Consent

A subject may withdraw consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Subjects should notify the Investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the Investigator, as to whether the withdrawal is only from further receipt of the investigational product or also from study procedures and/or post-treatment study follow-up and entered on the appropriate CRF page. If vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.6. Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of 2 documented phone calls, faxes, or emails as well as lack of response by the subject to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use locally permissible methods to obtain the date and cause of death. If the Investigator's use of a third-party representative to assist in the follow-up part of the study has been included in the subject's informed consent, then the Investigator may use a Sponsor retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up part of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, to obtain updated contact information. If, after all attempts, the subject remains lost to follow up, then the last known alive date as determined by the Investigator should be reported and documented in the subject's medical records.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The Investigator should inquire about the reason for withdrawal, request that the subject return all unused investigational product, request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved AEs.

If the subject refuses further visits, the subject should continue to be followed for survival (if applicable) unless the subject withdraws consent for disclosure of future information or for

further contact. In this case, no further study-specific evaluations should be performed, and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent.

7.7. Long-Term Follow-Up

For subjects discontinuing the study treatment due to documented radiographic progression, survival status will be obtained via phone call or medical chart review, including information about subsequent anticancer therapies (including best response) every 3 months until death, lost to follow-up, or withdrawal of consent, whichever comes first.

7.8. Restrictions

7.8.1. Concomitant Medications

Please refer to Section 5.4.1 for Prohibited Concomitant Medications.

7.8.2. Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time passed between surgery and study drug required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping study drug is recommended for at least 2 days prior to surgery. Postoperatively, the decision to reinitiate study drug treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

7.8.3. Palliative Radiation

Palliative radiotherapy on study is permitted, following agreement with the Sponsor, for the treatment of painful bony lesions provided the lesions were known at the time of study entry and the Investigator clearly indicates that the need for palliative radiotherapy is not indicative of disease progression. In view of the current lack of data about the interaction of study drug with radiotherapy, study drug treatment should be interrupted during palliative radiotherapy, stopping 1 day before palliative radiotherapy and resuming treatment 1 day after completion of palliative radiotherapy and recovery from any acute radiation toxicities to baseline.

7.8.4. Supportive Care

Palliative and supportive care for disease-related symptoms may be administered at the Investigator's discretion and according to available American Society of Clinical Oncology (ASCO) guidelines.

7.8.5. Contraception

Women of childbearing potential (WOCBP) must have a negative serum pregnancy test during Screening and be neither breast feeding nor intending to become pregnant during study participation. A female will be considered to be of childbearing potential unless they have undergone permanent sterilization or are postmenopausal. Postmenopausal is defined as at least 12 months without menses with no other medical reasons (e.g., chemical menopause due to anticancer treatment).

For WOCBP, agreement must be provided to use a highly effective contraceptive method from the time of screening throughout the study until 4 months (WOCBP) after administration of the last dose of any study drug. Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (i.e., perfect use) and include the following:

- Established use of combined (estrogen and progestogen containing) hormonal methods of contraception (intravaginal, or transdermal) provided the subject remains on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure inhibition of ovulation.
- Progestogen-only hormonal contraception (injectable, or implantable) provided the subject remains on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure inhibition of ovulation.
- Correctly placed copper containing intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- Vasectomized partner with appropriately confirmed absence of sperm in the post-vasectomy ejaculate.
- Bilateral tubal ligation or bilateral salpingectomy.
- Sexual abstinence is acceptable if evaluated as consistent with the preferred and the usual lifestyle of the subject. Periodic abstinence is not an acceptable method of contraception.

All male study subjects must agree to condom use throughout the study and for 6 months following the last dose of study drug. Male partners of WOCBP subjects must agree to condom use throughout the study and for 4 months following the last dose of study drug.

8. SAFETY ASSESSMENTS

Safety assessments will consist of monitoring and recording AEs, including serious adverse events (SAEs), measurement of protocol-specified clinical laboratory assessments and vital signs, and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to Turning Point Therapeutics, as outlined in Section 8.3.

8.1. Adverse Events

According to the ICH guideline for Good Clinical Practice (GCP), an AE is any untoward medical occurrence in a clinical investigation subject administered a medicinal product, regardless of causal attribution. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 8.2.5.9
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- AEs that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

8.1.1. Serious Adverse Events (Immediately Reportable to Turning Point Therapeutics)

An SAE is any AE that meets any of the following criteria:

- Fatal (i.e., the AE actually causes or leads to death)
- Life-threatening (i.e., the AE, in the view of the Investigator, places the subject at immediate risk of death). This does not include any AE that, had it occurred in a more severe form or was allowed to continue, might have caused death
- Requires or prolongs in-patient hospitalization (see Section 8.2.5.10)
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug

- Significant medical event in the Investigator's judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are **not** synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to CTCAE; see Section 8.2.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each AE recorded on the CRF.

SAEs are required to be reported by the Investigator to Turning Point Therapeutics Medical Monitor immediately (i.e., no more than 24 hours after learning of the event; see Section 8.3 for reporting instructions).

8.2. Methods and Timing for Capturing and Assessing Safety Parameters

The Investigator is responsible for ensuring that all AEs are recorded on the Adverse Event CRF and reported to Turning Point Therapeutics.

For each AE recorded on the Adverse Event CRF, the Investigator will make an assessment of seriousness (Section 8.1.1), severity (see Section 8.2.3), and causality (see Section 8.2.4).

8.2.1. Adverse Event Reporting Period

All AEs, whether reported by the subject or noted by study personnel, will be recorded in the subject's medical record and on the Adverse Event CRF at each subject contact.

After informed consent for the clinical trial has been obtained but prior to initiation of study drug, only SAEs related to protocol-mandated assessments should be reported.

After initiation of study drug, all AEs, regardless of relationship to study drug, will be reported until at least 28 days after the last dose of study treatment. Any SAEs occurring any time after the reporting period must be promptly reported if a causal relationship to the study drug is suspected.

8.2.2. Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting AE information at all subject evaluation timepoints. Examples of non-directive questions include the following:

"How have you been feeling since your last clinic visit?"

"Have you noticed any new or changed health problems since you were last here?"

8.2.3. Assessment of Severity of Adverse Events

The AE severity grading scale for the CTCAE v5.0 will be used for assessing AE severity. Table 8 will be used for assessing severity for AEs that are not specifically listed in the CTCAE.

Table 8: Grading of Severity of Adverse Events

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by subjects who are not bedridden.
[c] If an event is assessed as a "significant medical event," it must be reported as a SAE per the definition of SAE.
[d] Grade 4 and 5 events must be reported as SAEs per the definition of SAE.

8.2.4. Assessment of Causality of Adverse Events

Investigators should use their knowledge of the subject, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the study drugs (e.g., repotrectinib-related, trametinib-related, etc.), indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 9):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the subject or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 9: Causation Attribution

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

8.2.5. Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording AEs on the Adverse Event CRF. Avoid colloquialisms and abbreviations. Only one AE term should be recorded in the event field on the Adverse Event CRF.

8.2.5.1. Diagnosis Versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event CRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event CRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

8.2.5.2. Adverse Events That Are Secondary to Other Events

In general, AEs that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary AE that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event CRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy subject, then only vomiting should be reported on the CRF
- If vomiting results in severe dehydration, then both events should be reported separately on the CRF
- If a severe gastrointestinal hemorrhage leads to renal failure, then both events should be reported separately on the CRF
- If dizziness leads to a fall and consequent fracture, then all 3 events should be reported separately on the CRF

- If neutropenia is accompanied by an infection, then both events should be reported separately on the CRF

All AEs should be recorded separately on the Adverse Event CRF if it is unclear as to whether the events are associated.

8.2.5.3. Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, across cycles. When this occurs, the initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent AE becomes more or less severe, the initial event should be closed and a new event with the new severity should be recorded on the Adverse Event CRF. Similarly, if the event becomes serious, the initial event should be closed and a new event recorded on the Adverse Event CRF, completing all data fields related to SAEs. The SAE should be reported to Turning Point Therapeutics Medical Monitor immediately (i.e., no more than 24 hours after learning that the event became serious).

A recurrent AE is one that resolves between treatment cycles and subsequently recurs. Each recurrence of an AE should be recorded as a separate event on the Adverse Event CRF.

8.2.5.4. Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an AE. A laboratory test result must be reported as an AE if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Results in more frequent follow-up assessments or further diagnostic investigation
- Clinically significant in the Investigator's judgment

It is the Investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., increased alkaline phosphatase (ALP) and bilirubin at 5 × Upper Limit of Normal [ULN] associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event CRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event CRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event CRF unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated as described in Section 8.2.5.3.

8.2.5.5. Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an AE. A vital sign result must be reported as an AE if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Clinically significant in the Investigator's judgment

It is the Investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event CRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event CRF unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated as described in Section 8.2.5.3.

8.2.5.6. Abnormal Liver Function Tests

Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values > 3 × ULN concurrent with a total bilirubin value > 2 × ULN with no evidence of hemolysis and an ALP value ≤ 2 × ULN or not available.
- For subjects with preexisting ALT OR AST OR total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:

  - For subjects with preexisting AST or ALT baseline values above the normal range, AST or ALT value ≥ 2 times the baseline values and ≥ 3 × ULN, or ≥ 8 × ULN (whichever is smaller).

- Concurrent with
  - For subjects with preexisting values of total bilirubin above the normal range: Total bilirubin increased from baseline by an amount of ≥ 1 × ULN or if the value reaches ≥ 3 × ULN (whichever is smaller).

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment. The possibility of hepatic neoplasia (primary or secondary) should be considered. In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), ALP, and total bile acids and acetaminophen drug and/or protein adduct levels. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (e.g., biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for LFT abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs.

8.2.5.7. Deaths

Death due to disease progression will not be reportable as an SAE. The immediate cause of death will be the serious reported term.

All deaths, regardless of relationship to study drug, must be recorded on the Death CRF and on the Adverse Event CRF if considered an AE and occurred within the 28-day AE reporting window. Deaths reported as "disease progression" are not to be reported as SAEs if they occur within the 28-day window.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event CRF. Generally, only one such event should be reported. The term "**sudden death**" should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a subject with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the subject was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the Adverse Event CRF. If the cause of death later becomes available (e.g., after autopsy), "**unexplained death**" should be replaced by the established cause of death.

8.2.5.8. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the Screening visit for this study. Such conditions should be recorded on the Medical History CRF.

A preexisting medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event CRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "worsening headaches").

8.2.5.9. Lack of Efficacy or Worsening of the Malignancy Under Study

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be reflected as objective radiographic progression according to RECIST v 1.1 criteria. In rare cases, the determination of disease progression will be based predominantly on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE.

8.2.5.10. Hospitalization or Prolonged Hospitalization

Any AE that results in hospitalization (i.e., in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as a SAE, except as outlined below.

The following hospitalization scenarios are **not** considered to be AEs:

- Hospitalization for respite care or social admissions (e.g., lack of housing, economic inadequacy, family circumstances)
- Hospitalization solely for coordination of care, including hospice arrangements
- Hospitalization due solely to progression of the underlying cancer
- Hospitalization that was necessary solely because of subject requirement for outpatient care outside of normal outpatient clinic operating hours
- Hospitalization for same day surgeries (as outpatient/same day/ambulatory procedures)
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)
- Hospitalization for a preexisting condition, provided that the hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease and the subject has not experienced an AE

8.2.5.11. Exposure During Pregnancy

For investigational products and for marketed products, an exposure during pregnancy occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (e.g., because of treatment or environmental exposure) to the investigational

product; or the female becomes, or is found to be pregnant after discontinuing and/or being exposed to the investigational product. An example of environmental exposure would be a case involving direct contact with investigational product in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

- A male subject has been exposed (e.g., because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the Investigator must submit this information to Premier Research Pharmacovigilance (Premier PV) on a SAE Report Form (if applicable) and Pregnancy Data Collection Form. In addition, the Investigator must submit information regarding environmental exposure to an investigational product in a pregnant woman (e.g., a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage). This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all Pregnancy Data Collection Forms with an unknown outcome. The Investigator will follow the pregnancy until completion or until pregnancy termination and notify Premier PV of the outcome as a follow-up to the initial Pregnancy Data Collection Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for the termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (i.e., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise or a neonatal death]), the Investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion.
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the Investigator assesses the infant death as related or possibly related to exposure to investigational product.

Additional information regarding the exposure during pregnancy may be requested by the Investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the Investigator will provide the study subject with the pregnant partner release of information form to deliver to his partner. The Investigator must document in the source

documents that the subject was given the pregnant partner release of information form to provide to his pregnant partner.

8.2.5.12. Occupational Exposure

An occupational exposure occurs when during the performance of job duties, a person (whether a healthcare professional or otherwise) has unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to safety within 24 hours of Investigator's awareness, using the SAE Report Form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a CRF, however a copy of the completed SAE Report Form is maintained in the study master file.

8.2.5.13. Adverse Events Associated with an Overdose or Incorrect Administration of Study Drug

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an AE, but it may result in an AE. All AEs associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event CRF. If the associated AE fulfills serious criteria, the event should be reported to Turning Point Therapeutics Medical Monitor immediately (i.e., no more than 24 hours after learning of the event).

8.3. Immediate Reporting Requirements from Investigator to Turning Point Therapeutics

Certain events require immediate reporting to allow Turning Point Therapeutics to take appropriate measures to address potential new risks in a clinical trial. The Investigator must report such events to Turning Point Therapeutics immediately; under no circumstances should reporting take place more than 24 hours after the Investigator learns of the event. The following is a list of events that the Investigator must report to Turning Point Therapeutics within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious AE (whether or not deemed drug-related or expected).
- Pregnancy of female subject or partner of male subject of childbearing potential.
- Occupational Exposure (regardless of whether there is an associated AE/SAE)

The Investigator must report new significant follow-up information for these events to Premier Research GPV immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery

- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting SAEs to the local health authority and IRB/EC.

8.3.1. SAE Reporting

After informed consent has been obtained but prior to initiation of study drug, only SAEs related to protocol-mandated procedures should be reported.

After initiation of study drug, SAEs will be reported until at least 28 days after the last dose of study drug.

Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the SAE Report Form and submit the report via fax or email (please refer to the Study Manual).

8.3.2. Immediate Reporting Requirements for Pregnancies

8.3.2.1. Pregnancies in Female Subjects

Female subjects or partners of male subjects of childbearing potential will be instructed to immediately inform the Investigator if they become pregnant during the study or within 4 months after the last dose of study drug. A Pregnancy Data Collection Form should be completed by the Investigator no more than 24 hours after learning of the pregnancy and submitted using the same process as for SAEs. Refer to Section 8.2.5.11 for further information on reporting requirements for exposure during pregnancy.

The Investigator should discontinue study drug and counsel the subject or partner of a male subject, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring should continue until conclusion of the pregnancy. Any SAEs associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported and submitted within 24 hours. Refer to Section 8.2.5.11 for additional information regarding follow-up and SAE reporting requirements for exposure during pregnancy.

8.3.2.2. Congenital Anomalies/Birth Defects and Abortions

Any congenital anomaly/birth defect in a child born to a female subject or partner of a male subject exposed to study drug should be classified as an SAE and reported as such. Any spontaneous abortion or miscarriage should be reported in the same fashion (therapeutic abortions are excluded from expedited reporting and would be captured as pregnancy outcome information). Refer to Section 8.2.5.11 for additional information regarding follow-up and SAE reporting requirements for exposure during pregnancy.

8.4. Follow-Up of Subjects After Adverse Events

8.4.1. Investigator Follow-Up

The Investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the Investigator, the subject is lost to follow-up, or the subject

withdraws consent. Every effort should be made to follow all SAEs considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of AEs (with dates) should be documented on the Adverse Event CRF and in the subject's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

8.4.2. Turning Point Therapeutics Follow-Up

For SAEs and pregnancies, Turning Point Therapeutics or a designee may follow-up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

8.5. Post-Study Adverse Events

Turning Point Therapeutics should be notified if the Investigator becomes aware of any SAE that occurs after the end of the AE reporting period (defined as 28 days after the last dose of study drug) if the event is believed to be related to the study drug.

The Investigator should report these events directly to Turning Point Therapeutics or its designee using the SAE Report Form.

8.6. Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Ethics Committees

Turning Point Therapeutics will promptly evaluate all SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single AE cases, Turning Point Therapeutics will assess the expectedness of these events using the IB.

Turning Point Therapeutics will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the Investigator's assessment of causality and seriousness, with allowance for upgrading by Turning Point Therapeutics as needed.

9. STATISTICAL METHOD ANALYSIS

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a Statistical Analysis Plan (SAP), which will be maintained by the Sponsor or their designee. The SAP may modify the initial analysis plan outlined in the protocol; however, any major modifications of the primary endpoint and/or analysis methods will also be reflected in a protocol amendment.

9.1. Analysis Sets

9.1.1. Full Analysis Set

The Full Analysis Set (FAS) consists of all subjects who receive at least one full or partial dose of both study drugs. This will be the same as the Safety Analysis Set. The FAS set will be used for the summary of subject disposition, demographics, and baseline characteristics, and safety analysis. For Phase 2, the FAS set will also be used for primary efficacy analysis if subjects have received repotrectinib.

Subjects will be classified according to the assigned treatment dose levels. Subjects who were screened but never started treatment will be listed in the subject data listing as screening failure, and reasons for screening failure will be included.

9.1.2. Efficacy Evaluable Analysis Set

Efficacy Evaluable (EE) Analysis Set will include all enrolled subjects who (1) have received at least one dose of study treatment with repotrectinib; (2) *KRAS* mutation determined by a qPCR or NGS test performed in a CLIA laboratory or equivalently accredited diagnostic laboratory; (3) have a baseline tumor assessment with measurable disease and have at least 1 on-study tumor assessment per RECIST v1.1; and (4) have no major protocol violations that could affect efficacy.

The EE Analysis Set will be used for efficacy analyses for Phase 1b, and sensitivity analysis of efficacy endpoints for Phase 2.

9.1.3. Safety Analysis Set

The Safety Analysis Set includes all enrolled subjects who receive at least one dose of either study drug. This will be the same as the FAS. Subjects will be classified according to the actual treatment (dose levels or cohorts). Each subject will be classified into and analyzed consistently within one treatment group, unless otherwise specified.

9.1.4. Pharmacokinetic Concentration Analysis Set

The PK Concentration Analysis Set is defined as all enrolled subjects who receive at least one dose of study drug and have at least one concentration of study drug.

9.1.5. Pharmacokinetic Parameter Analysis Set

The PK Parameter Analysis Set is defined as all enrolled subjects who receive at least one dose of study drug and have sufficient information to estimate at least one of the PK parameters of interest.

9.2. Sample Size Determinations

9.2.1. Repotrectinib + Trametinib

9.2.1.1. Phase 1b Dose Escalation

For dose escalation, 3 to 6 DLT-evaluable subjects will be enrolled per dose level. Therefore, it is expected that approximately 24 – 30 subjects will be enrolled to determine the RP2D of repotrectinib in combination with trametinib.

9.2.1.2. Phase 2 Expansion

For Phase 2 expansion, sample size will be determined using Pearson-Clopper exact confidence interval method. A total of approximately 50 subjects will be enrolled. In addition, up to 6 locally advanced or metastatic *KRAS*-mutant NSCLC subjects treated at the RP2D in Phase 1b will be pooled for the efficacy analysis. If 21 subjects out of 56 subjects have a confirmed objective response (ORR = 38%; 95% CI: 25 – 51) where the lower limit of the 95% CI is > 23%, repotrectinib in combination with trametinib will be considered superior than the currently approved chemotherapy in the second-line setting for NSCLC in this expansion cohort, including the combination of docetaxel + ramucirumab (Cyramza® USPI, 2020) which has demonstrated a best ORR of 23% (95% CI: 20 – 26) in the second-line setting.

9.3. Study Endpoints

9.3.1. Primary Endpoint for Phase 1

- Incidence of first cycle (28 days) DLTs to determine MTD and/or RP2D.

9.3.2. Secondary Endpoints for Phase 1

- ORR assessed by the Investigator using RECIST v1.1
- Pharmacokinetic parameters of repotrectinib
- Pharmacokinetic parameters of trametinib

9.3.3. Primary Endpoint for Phase 2

- ORR assessed by Investigator using RECIST v1.1.

9.3.4. Secondary Endpoints for Phase 2

- DOR, TTR, and CBR by the Investigator
- Intracranial objective response rate (IC-ORR) assessed according to modified RECIST v1.1 in subjects with brain metastases
- PFS and OS
- Type, incidence, severity, timing, seriousness, and relatedness (to each study drug) of AEs and laboratory abnormalities
- Pharmacokinetic parameters of repotrectinib

- Pharmacokinetic parameters of trametinib

9.3.5. Exploratory Endpoints for Phase 1b and Phase 2

- ORR and PFS by modulation of circulating tumor levels and genomic alterations observed pre- and post-dosing.

9.4. Statistical Analysis

9.4.1. General Considerations

Full descriptions of analyses to be performed will be included in the SAP and will supersede any analysis described here.

9.4.1.1. Missing Data

All analyses and descriptive summaries will be based on the observed data. Unless otherwise specified, missing data will not be imputed. Partial dates for AEs and concomitant medications will be imputed using the most conservative rules. Further details regarding missing data will be included in the SAP.

9.4.2. Efficacy Analyses

9.4.3. Analysis of Primary Endpoint

For Phase 1b, efficacy analysis will be performed in EE population. For Phase 2, the FAS analysis set will be used as the primary analysis for efficacy, and analyses using the EE population will be used as sensitivity analysis. Primary efficacy data will be based on the radiologic assessments evaluated by the Investigator. Data from BICR may be analyzed as supportive.

For Phase 2, the primary efficacy endpoint is ORR of repotrectinib in combination with trametinib in subjects with advanced/metastatic solid tumors harboring *KRAS* mutations potential biomarkers, including genomic alterations that could predict efficacy or resistance to the study drugs, may be explored.

9.4.3.1. Objective Response Rate

The ORR will be defined as the proportion of subjects with a confirmed CR or PR. A confirmed response is a response that persists on a repeat imaging performed at least 4 weeks after initial documentation of response. Subjects with a confirmed objective response (CR or PR) will be referred to as responders. Non-responders will include subjects without a confirmed objective response, SD, progressive disease (PD), not evaluable (NE), or non-CR/non-PD (NN). The ORR will be reported as the proportion of responders by RECIST v1.1 along with the corresponding two-sided 95% Clopper-Pearson exact CI.

9.4.4. Analysis of Secondary Endpoints

The secondary efficacy endpoints include DOR, TTR, CBR, intracranial response, PFS, and OS of repotrectinib in combination with trametinib in subjects with advanced or metastatic solid tumors harboring *KRAS* mutations. Potential biomarkers, including genomic alterations that

could predict efficacy or resistance to the study drugs, may be explored. Further details regarding these secondary efficacy analyses will be included in the SAP.

9.4.5. Safety Analyses

Safety analyses will be performed using the Safety Analysis Set for each cohort, as well as for all cohorts combined. Further descriptions of the analyses of safety endpoints including adverse events coded to Medical Dictionary for Regulatory Affairs (MedDRA) version 23.0 or higher, deaths, laboratory results, ECG results, vital signs, and left ventricular ejection fraction (LVEF) will be described in the SAP.

9.4.6. Analysis of Pharmacokinetics

9.4.6.1. Single-and Multiple-Dose Repotrectinib and Trametinib Pharmacokinetic Analysis

Repotrectinib and trametinib plasma concentration-time data will be analyzed using non-compartmental methods to estimate the following PK parameters in individual subjects: maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under the plasma concentration-time curve (AUC). If data permit or if considered appropriate, area under the plasma concentration versus time curve to infinity (AUC_{inf}), terminal elimination half-life ($t_{½}$), apparent plasma clearance (CL/F), apparent volume of distribution (Vz/F), and accumulation ratio (R_{acc}) will be estimated. The single- and multiple-dose PK parameters will be summarized descriptively by dose, cycle, and day.

Repotrectinib and trametinib concentrations will be summarized descriptively (n, mean, standard deviation, CV, median, minimum, maximum, geometric mean and its associated CV) by dose, cycle, day and nominal time. Individual, mean, and median profiles of the concentration-time data will be plotted by dose, cycle and day (single-dose, and multiple-dose) using nominal time. Median and mean profiles will be presented on both linear and log-linear scales.

Dose normalized AUC_{inf}, (AUC_{τ} at steady state), AUC_{last}, and C_{max} will be plotted against dose (using a logarithmic scale) by cycle and day. These plots will include individual subject values and the geometric means for each dose. These plots will be used to help understand the relationship between PK exposure and dose.

The observed R_{acc} will be summarized descriptively. It will be analyzed after natural log transformation using a one-way analysis of variance with a single term for dose. The means and 90% confidence intervals (CIs) obtained from the model will be back-transformed to provide means and 90% CIs for the accumulation and linearity ratios for each dose.

Trough concentrations will be plotted for each dose using a box-whisker plot by cycle and day within cycle to assess the attainment of steady state.

9.5. Interim Analysis

Periodic reviews of the preliminary data may be performed for executive, regulatory, and/or conference presentation purposes.

In addition, for Phase 2, an interim futility analysis of the ORR will be performed after approximately 15 subjects are evaluable for tumor response to safeguard future patients from

exposure to a potentially ineffective treatment. Depending on the enrollment rate, it is anticipated that approximately 20-30 subjects will be enrolled at the interim analysis.

The interim futility stopping rule for the maximum number of responders (R) required among the 15 (N) evaluable subjects with the cumulative probability of observing ≤ R responders under the targeted ORR (P1) and futility ORR (P0) is shown in Table 10. If ≤ 2 responders (confirmed CR or PR) are observed from 15 evaluable subjects, the expansion cohort will be stopped for futility. If ≥ 3 responders are observed, this cohort may continue depending on the overall benefit and risk assessment at the interim analysis. If the true ORR in this cohort is as targeted at 38%, the probability of observing ≤ 2 responders is 3.8%. If the true ORR is significantly lower than the target ORR (i.e., 10% instead of 38%), the probability is 81.6%.

Table 10: Stopping Rule for Interim Futility Analysis of ORR in Phase 2

N	R	Target ORR (P1)	Futility ORR (P0)	Probability Under P1	Probability Under P0
15	2	38%	10%	0.038	0.816

Abbreviations: EXP = expansion; ORR = overall response rate; P1 = target overall response rate; PO = futility overall response rate.
Note: N is the number of evaluable patients for tumor response at the interim futility analysis and R is the maximum number of responders (confirmed CR or PR) for futility stop. If the number of responders is ≤ R, the cohort will be stopped for futility.

10. QUALITY CONTROL AND QUALITY ASSURANCE

It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported for each subject. Source documentation supporting the data should indicate the subject's participation in the study and should document the dates and details of study procedures, AEs, and subject status.

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. Queries will be entered, tracked, and resolved directly through the electronic data capture (EDC) system. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

11.2. Study Monitoring, Audits, and Inspections

Site visits will be conducted by an authorized Sponsor representative, who will inspect study data, subjects' medical records, and CRFs according to GCP, the Food and Drug Administration (FDA), and the International Conference on Harmonisation (ICH) guidelines. In addition to monitoring by the Sponsor or its designees, the study may be audited by representatives of the FDA or other regulatory authorities, who will also be permitted access to study documents. The

Investigator should immediately notify the Sponsors' Clinical Operations department or designee of any proposed or scheduled audits by regulatory authorities.

The Investigator will permit authorized representatives of the Sponsor or designee and national or local health authorities to inspect facilities and records relevant to this study.

The Investigator must obtain Institutional Review Board (IRB)/EC approval for the investigation. Initial IRB/IEC approval and all materials approved by the IRB/EC for this study, including the subject consent form and recruitment materials, must be maintained by the Investigator and made available for inspection.

11.3. Inspection of Records

The Sponsor and designees of the Sponsor will be allowed to conduct site visits to the investigational facilities for monitoring any aspect of the study. The Investigator agrees to allow Sponsor representatives to inspect the drug storage area, investigational product inventory, drug accountability records, subject charts and study source documents, and other records relative to the study conduct.

11.4. Record Retention

The Investigator will coordinate with the study site to ensure all documentations relating to the study for a period of 2 years after marketing application approval or, if not approved, 2 years after the notification to the FDA of the discontinuance of the investigational product for investigation. If it becomes necessary for the Sponsor or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

The records should be retained by the Investigator according to ICH, local regulations, or as specified in the Clinical Trial Agreement, whichever is longer; but at a minimum, all study documentation must be retained for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of repotrectinib.

12. ETHICS

12.1. Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB/IEC, as appropriate. The Investigator must submit written approval to the Sponsor before he or she can present informed consent and begin screening activities for any subject in the study.

The Investigator is responsible for informing the IRB/IEC of any amendment(s) to the protocol in accordance with local requirements. In addition, the IRB/IEC must approve all advertising used to recruit subjects for the study, if applicable. The protocol must be re approved by the IRB/IEC upon receipt of amendments and annually, as local regulations require.

The Investigator is also responsible for providing the IRB/IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The Sponsor will provide this information to the Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB/IEC according to local regulations and guidelines.

12.2. Protocol Compliance

The Investigator will conduct the trial in compliance with the protocol provided by the Sponsor. Modifications to the protocol may not be made without agreement of both the Investigator and the Sponsor. Changes to the protocol will require a written IRB/IEC approval/favorable opinion before implementation, except when the modification is needed to eliminate an immediate hazard(s) to subjects. The IRB/IEC may provide and expedite review, if applicable and as regulatory authority(ies) permit, the approval/favorable opinion for minor change(s) in ongoing trials that have the approval/favorable opinion of the IRB/IEC.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to subjects, the Investigator will contact the Sponsor/Designee and/or the Study Monitor, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented on the appropriate CRF and in the source documentation and reported to the IRB/IEC per institutional and/or local requirements.

12.3. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements, and the Sponsors' (or its designee's) applicable policies and standard operating procedures (SOPs).

12.4. Written Informed Consent

The Investigator at the study center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk(s), and benefit(s) of the study. Subjects must also be notified that they are free to withdraw from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated ICF must be obtained before conducting any study procedures (Section 6.1).

The Investigator must maintain the original signed ICF. A copy of the signed ICF must be given to the subject.

12.5. Subject Confidentiality

To maintain subject privacy, data capture tools, investigational product accountability records, study reports, and communications will identify the subject only by initials and the subject number assigned at Screening. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records, including medical history, laboratory studies, and medication administrations, for verification of data gathered and to audit the data collection process. This information will be accessed for the duration of the research study for data reconciliation purposes. The subject's

confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

13. PUBLICATION OF STUDY RESULTS

All information regarding the investigational product supplied by the Sponsor to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for any other purposes without written consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used toward the development of the Sponsors' investigational product program and may be disclosed to regulatory authority(ies), other Investigators, corporate partners, shareholders, or consultants as required.

Additionally, the Investigator should obtain authorization from the clinical trial subjects in writing and ensure that all 18 identifiers (outlined in the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule (November 26, 2012)) have been removed from the data.

It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer-reviewed scientific or medical journal. Investigator publication rights will be provided in the Clinical Trial Agreement.

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APPENDIX 1. STRONG CYP3A INHIBITORS OR INDUCERS, SENSITIVE CYP3A SUBSTRATES AND MEDICATIONS THAT CAUSE QTC PROLONGATION

Strong CYP3A Inhibitors or Inducers

Strong CYP3A Inhibitors	Strong CYP3AInducers
Macrolide antibiotics: clarithromycin and telithromycin	Carbamazepine
	Efavirenz
Anti-fungal: itraconazole, ketoconazole, voriconazole, posaconazole	Phenobarbital
	Phenytoin
Anti-virals: lopinavir, indinavir, nelfinavir, ritonavir, saquinavir, amprenavir	Rifampin
	Rifabutin
Conivaptan	Rifapentin
Mibefradil	St John's wort
Nefazodone	
Troleandomycin	
Miscellaneous: Grapefruit juice	

Sensitive CYP3A Substrates

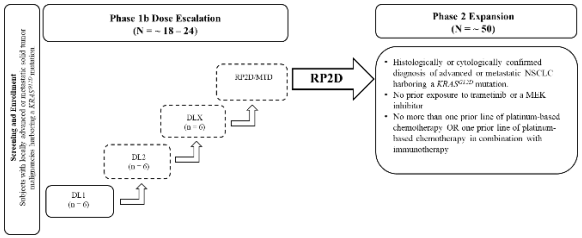
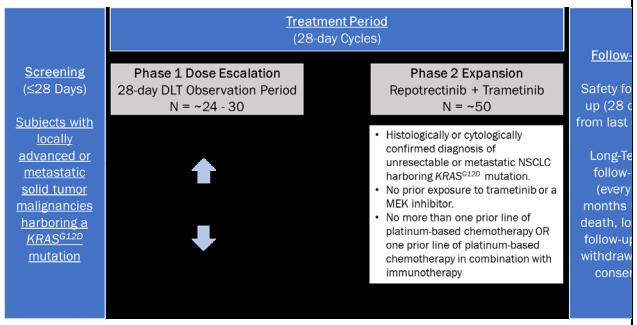
alfentanil	avanafil	buspirone	conivaptan
darifenacin	darunavir	ebastine	everolimus
ibrutinib	lomitapide	lovastatin	midazolam
naloxegol	nisoldipine	saquinavir	simvastatin
sirolimus	tacrolimus	tipranavir	triazolam
vardenafil	budesonide	dasatinib	dronedarone
eletriptan	eplerenone	felodipine	indinavir
lurasidone	maraviroc	quetiapine	sildenafil
ticagrelor	tolvaptan		

Medications That Cause QTc Prolongation

Amiodarone	Astemizole	Azithromycin	Chlorpromazine
Disopyramide	Terfenadine	Clarithromycin	Haloperidol
Dofetilide	Chloroquine	Erythromycin	Mesoridazine
Flecainide	Halofantrine	Moxifloxacin	Pimozide
Ibutilide	Probucol	Sparfloxacin	Thioridazine
Procainamide	Pentamidine	Domperidone	Levomethadyl
Quinidine	Bepridil	Droperidol	Methadone
Sotalol	Arsenic trioxide	Vavdetanib	Citalopram
Cisapride			

APPENDIX 2. SUMMARY OF CHANGES

Summary of Changes for Version 2.0 to Version 3.0. This Summary of Changes details the substantive changes to TPX-0005-13 Subprotocol 1. Minor changes for editorial clarifications, or for administrative corrections of typographic errors, reformatting, abbreviations or section/table re-numbering are not included in this summary. Text removed from the original version (Version 2.0) is indicated with ~~strikethrough text~~. Text added to the new version (Version 3.0) is indicated by **bold text**.

Protocol Section	Original Text with Deletions	Revised Text	Justification
Title Page	Medical Monitor: ~~Naseem Zojwalla, M.D.~~ ~~Vice President, Clinical Development~~	Medical Monitor: **Amit Reddy, MBBS** **Associate Medical Director, Clinical Development**	Change of Medical Monitor
Sponsor Approval Page, Signatory	~~Naseem Zojwalla, M.D.~~ ~~Vice President, Clinical Development~~	**Minal Mehta, MBBS** **Executive Director, Clinical Development**	Change of Sponsor Signatory
Synopsis, Exploratory Objectives (All Phases) **Section 2.3 Exploratory Objectives (All Phases)**	• Evaluate biomarkers potentially predictive of response in subjects treated with repotrectinib in combination with other anticancer therapies. • Explore the potential prognostic utility of genomic alterations and characterize intrinsic or acquired resistance in subjects treated with repotrectinib in combination with other anticancer therapies using liquid biopsy samples	• Evaluate biomarkers potentially predictive of response in subjects treated with repotrectinib in combination with other anticancer therapies. • Explore the potential prognostic utility of genomic alterations and characterize intrinsic or acquired resistance in subjects treated with repotrectinib in combination with other anticancer therapies using **tissue-based or** liquid-**based** biopsy samples	Clarified acceptance of liquid-based biopsy explicitly stated as it allows adequate analytical performance for mutation testing
Synopsis, Overall Study Design **Section 3.1, Table 2 – Subprotocol 1 Study Design**			Revised and clarified the study schematic to reflect the overall study design.
Synopsis, Overall Study Design	Phase 1b Dose Escalation Subjects with locally advanced or metastatic solid tumor malignancies harboring a KRASG12D mutation will be	Phase 1b Dose Escalation Subjects with locally advanced or metastatic solid tumor malignancies harboring a KRASG12D mutation will be	The study will utilize a more conservative 3+3

<table>
<tr><th>Protocol Section</th><th>Original Text with Deletions</th><th>Revised Text</th><th>Justification</th></tr>
<tr><td></td><td>enrolled into the Phase 1b dose escalation portion of the study to determine the MTD/RP2D of repotrectinib in combination with trametinib. Dose escalation will follow a ~~rolling 6~~ design.</td><td>enrolled into the Phase 1b dose escalation portion of the study to determine the MTD/RP2D of repotrectinib in combination with trametinib. Dose escalation will follow a traditional 3+3 design</td><td>dose escalation design to guide dose finding in Phase 1b.</td></tr>
<tr><td>Synopsis, Phase 1b Dose Escalation Study Design

Section 3.2, Phase 1b Dose Escalation Study Design</td><td>Initially, approximately ~~18~~ 24 subjects with locally advanced or metastatic solid tumor malignancies harboring a KRAS^{G12D} mutation will be enrolled.
Dose escalation will follow a ~~rolling 6~~ design. ~~At least~~ six subjects at each dose level will be administered daily (QD) doses of repotrectinib in combination with trametinib according to the table below (starting with Dose Level 1 [DL1]) and evaluated for dose-limiting toxicities (DLTs) during Cycle 1 (i.e., for 28 days). After the first 3 subjects have completed their first cycle of study treatment (Cycle 1), a safety evaluation will be conducted by a Safety Review Committee to determine if enrollment of subjects in the next dose level (DL2) may begin. If no subjects experience a DLT within the first 28 days of DL1 treatment, then dose escalation ~~will~~ proceed to the next dose level ~~concurrent with enrollment at DL1~~, according to the table below. If 1 of the 3 initial subjects at DL1 experiences a DLT, then the next 3 subjects will be enrolled prior to escalating to the next dose level. ~~Rolling enrollment~~ into all subsequent dose levels will follow the same procedure. If ≥ 33% ~~in at least 6~~ subjects at any dose level experience a DLT within the first 28 days of treatment, the ~~doses~~ will be ~~reduced~~ according to the table below. If ~~≥ 2 of 6~~ subjects ~~experience a DLT within the first 28 days of treatment at DL 1, then the study~~ will be ~~terminated~~. See Section 3.2 for further details of dose finding.

Dose-finding Dose Levels
<table>
<tr><th></th><th>Repotrectinib</th><th>Trametinib</th></tr>
<tr><td>~~Dose Level~~ 3</td><td>160 mg QD/BID[a]</td><td>2 mg QD</td></tr>
</table></td><td>Initially, approximately ~~24~~ 30 subjects with locally advanced or metastatic solid tumor malignancies harboring a KRAS^{G12D} mutation will be enrolled.
Dose escalation will follow a traditional 3+3 design. Three to six DLT-evaluable subjects at each dose level will be administered daily (QD) doses of repotrectinib in combination with trametinib according to the table below (starting with Dose Level 1) and evaluated for dose-limiting toxicities (DLTs) during Cycle 1 (i.e., for 28 days). After the first 3 subjects have completed their first cycle of study treatment (Cycle 1), a safety evaluation will be conducted by a Safety Review Committee to determine if enrollment of subjects in the next dose level (Dose Level 2) may begin. If no subjects experience a DLT within the first 28 days of Dose Level 1 treatment, then dose escalation may proceed to the next dose level, according to the table below. If 1 of the 3 initial subjects at Dose Level 1 experiences a DLT, then the next 3 subjects will be enrolled prior to escalating to the next dose level. Enrollment into all subsequent dose levels will follow the same procedure. If ≥ 33% of subjects at any dose level experience a DLT within the first 28 days of treatment, the dose levels will be de-escalated to Dose Level -2 or -3 according to SRC recommendation and following approval by the Sponsor, as detailed in the table below. If Dose Level -2 is tolerable, testing of alternate escalating dose levels (-2a, -2b) may occur as outlined in the table below. If Dose Level -2 is not tolerable, subjects will be de-escalated to Dose Level -3. If Dose Level -3 is tolerable, testing of alternate escalating dose levels (-3a, -3b) may occur as outlined in the table below. Alternative regimens or additional dose levels or dose level increments may be explored</td><td>Based on review of available safety and PK data from 2 patients treated with repotrectinib and trametinib at Dose Level 1, the SRC recommended a dose level de-escalation to Dose Level -2 and recommended alternate dose finding levels. Furthermore, the study will utilize a more conservative 3+3 dose escalation design to guide dose escalation decisions.

The PK data showed that in combination with 120 mg QD repotrectinib, the exposure of trametinib was double that of the 2 mg trametinib single-agent exposure.</td></tr>
</table>

<table>
<tr><th>Protocol Section</th><th>Original Text with Deletions</th><th>Revised Text</th><th>Justification</th></tr>
<tr><td></td><td>
<table>
<tr><td>~~Dose Level~~ 2</td><td>160 mg QD</td><td>2 mg QD</td></tr>
<tr><td>~~Dose Level~~ 1 (Starting Dose)</td><td>120 mg QD</td><td>2 mg QD</td></tr>
<tr><td>~~Dose Level~~ -1</td><td>120 mg QD</td><td>1.5 mg QD</td></tr>
</table>
</td><td>
based on emergent clinical safety, efficacy, and PK data. See Section 3.2 for further details of dose finding.

Dose-finding Dose Levels
<table>
<tr><th>Dose Level</th><td>Repotrectinib</td><td>Trametinib</td></tr>
<tr><td>3</td><td>160 mg QD/BID[a]</td><td>2 mg QD</td></tr>
<tr><td>2</td><td>160 mg QD</td><td>2 mg QD</td></tr>
<tr><td>1 (Starting Dose)</td><td>120 mg QD</td><td>2 mg QD</td></tr>
<tr><td>(-2b)</td><td>160 mg QD/BID[a]</td><td>1.0 mg QD</td></tr>
<tr><td>(-2a)</td><td>160 mg QD</td><td>1.0 mg QD</td></tr>
<tr><td>-2</td><td>120 mg QD</td><td>1.0 mg QD</td></tr>
<tr><td>(-3b)</td><td>160 mg QD/BID[a]</td><td>0.5 mg QD</td></tr>
<tr><td>(-3a)</td><td>160 mg QD</td><td>0.5 mg QD</td></tr>
<tr><td>-3</td><td>120 mg QD</td><td>0.5 mg QD</td></tr>
</table>
</td><td></td></tr>
<tr><td>Synopsis, Number of subjects (planned)</td><td>Phase 1b Dose Escalation: approximately ~~18 –~~ 24 subjects
Phase 2 Expansion: approximately 50 subjects</td><td>Phase 1b Dose Escalation: approximately 24 – 30 subjects
Phase 2 Expansion: approximately 50 subjects</td><td>To account for the possible alternate dose finding levels that may be explored.</td></tr>
<tr><td>Synopsis, Inclusion Criteria</td><td>Added text</td><td>Phase 1 AND Phase 2</td><td>Clarified that IC #1 through #13 are required for Phase 1 and Phase 2</td></tr>
<tr><td>Synopsis, Inclusion Criteria #1

Section 4.1, Inclusion</td><td>1. Subject must have a histologically or cytologically confirmed diagnosis of unresectable or metastatic solid tumor malignancy harboring a KRAS mutation.
• Documented KRAS^{G12D} mutation as determined by a quantitative polymerase chain reaction (qPCR) or next-generation sequencing (NGS)</td><td>1. Subject must have a histologically or cytologically confirmed diagnosis of unresectable or metastatic solid tumor malignancy harboring a KRAS mutation.
• Documented KRAS^{G12D} mutation as determined by a quantitative polymerase chain reaction (qPCR) or next-generation sequencing</td><td>Clarification: Acceptance of tissue based or liquid biopsy as local test (was and) should be explicitly stated as there’s</td></tr>
</table>

Protocol Section	Original Text with Deletions	Revised Text	Justification
Criteria #1	test performed in a Clinical Laboratory Improvement Amendments (CLIA) laboratory or equivalently accredited diagnostic laboratory.	(NGS) test performed in a Clinical Laboratory Improvement Amendments (CLIA) laboratory or equivalently accredited diagnostic laboratory. **Local tissue-based or liquid biopsy diagnostic testing will be permitted.**	adequate analytical performance for mutation testing
Synopsis, Inclusion Criteria #5 **Section 4.1, Inclusion Criteria #5**	5. At least 1 measurable target lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 ~~prospectively confirmed by Blinded Independent Central Radiology Review (BICR) PRIOR to enrollment~~. Subjects with central nervous system (CNS)-only measurable target lesion ≥ 5 mm as defined by RECIST v1.1 are eligible.	5. At least 1 measurable target lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Subjects with central nervous system (CNS)-only measurable target lesion ≥ 5 mm as defined by RECIST v1.1 are eligible.	As this is a signal-finding study, radiographic disease confirmation by BICR is not needed.
Synopsis, Inclusion Criteria #6 **Section 4.1, Inclusion Criteria #6**	~~6.~~ Subject must have received prior standard therapy appropriate for their tumor type and stage of disease, or in the opinion of the Investigator, would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy. • Subject must have received no more than 3 prior systemic regimens. • Maintenance therapy will not be counted as a separate regimen. • Adjuvant chemotherapy or chemotherapy administered as part of concurrent chemotherapy and radiation therapy will not count as a prior regimen of systemic therapy as long as recurrence occurred more than 6 months after the last day of chemotherapy.	**Additional Inclusion Criteria for Phase 1 only:** **13**. Subject must have received prior standard therapy appropriate for their tumor type and stage of disease, or in the opinion of the Investigator, would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy. • Subject must have received no more than 3 prior systemic regimens. • Maintenance therapy will not be counted as a separate regimen. • Adjuvant chemotherapy or chemotherapy administered as part of concurrent chemotherapy and radiation therapy will not count as a prior regimen of systemic therapy as long as recurrence occurred more than 6 months after the last day of chemotherapy.	Clarification that criterion applies to Phase 1 only
Synopsis, Inclusion Criteria #7 **Section 4.1, Inclusion Criteria #7**	7. Baseline laboratory values fulfilling the following requirements: … Total Serum Bilirubin: < 1.5 x ULN …	7. Baseline laboratory values fulfilling the following requirements: … Total Serum Bilirubin: < 1.5 x ULN **(≤ 3.0 × ULN for patients with Gilbert's Syndrome or liver metastases)**	Clarified requirement for patients with Gilbert's Syndrome or liver metastases

Protocol Section	Original Text with Deletions	Revised Text	Justification
Synopsis, Inclusion Criteria #10 **Section 4.1, Inclusion Criteria #10**	~~10~~. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test during screening and be neither breastfeeding nor intending to become pregnant during study participation. Female patients will be considered to be of childbearing potential unless they have undergone permanent sterilization or are postmenopausal. Postmenopausal is defined as at least 12 months without menses with no other medical reasons (e.g., chemical menopause due to anticancer treatment). For WOCBP and for men, agreement to use a highly effective contraceptive method from the time of screening throughout the study until 4 months (WOCBP) or 6 months (men) after administration of the last dose of any study drug. Highly effective contraceptive methods consist of prior sterilization, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), injectable or implantable contraceptives. All ~~males (~~study subjects ~~and partners of female subjects)~~ must agree to use condoms throughout the study and 6 months after administration of the last dose. True abstinence is acceptable if evaluated as consistent with the preferred and the usual lifestyle of the subject. Periodic abstinence is not an acceptable method of contraception.	~~9~~. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test during screening and be neither breastfeeding nor intending to become pregnant during study participation. Female patients will be considered to be of childbearing potential unless they have undergone permanent sterilization or are postmenopausal. Postmenopausal is defined as at least 12 months without menses with no other medical reasons (e.g., chemical menopause due to anticancer treatment). For WOCBP and for men, agreement to use a highly effective contraceptive method from the time of screening throughout the study until 4 months (WOCBP) or 6 months (men) after administration of the last dose of any study drug. Highly effective contraceptive methods consist of prior sterilization, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), injectable or implantable contraceptives. All **male** study subjects must agree to use condoms throughout the study and 6 months after administration of the last dose. **Male partners of WOCBP subjects must agree to condom use throughout the study and for 4 months following the last dose of study drug.** True abstinence is acceptable if evaluated as consistent with the preferred and the usual lifestyle of the subject. Periodic abstinence is not an acceptable method of contraception.	Clarify that male partners of WOCBP subjects only need to agree to 4 months of condom use after their partner has taken the last dose of study drug.
Synopsis, Inclusion Criteria #6 **Section 4.1, Inclusion Criteria #6**	~~6. Subject must have received prior standard therapy appropriate for their tumor type and stage of disease, or in the opinion of the Investigator, would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy.~~ ~~• Subject must have received no more than 3 prior systemic regimens.~~ ~~• Maintenance therapy will not be counted as a separate regimen.~~ ~~• Adjuvant chemotherapy or chemotherapy~~	**Additional Criteria for Phase 1 Only** **13. Subject must have received prior standard therapy appropriate for their tumor type and stage of disease, or in the opinion of the Investigator, would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy.** • **Subject must have received no more than 3 prior systemic regimens.** • **Maintenance therapy will not be counted as a separate regimen.**	Clarified that prior lines of therapy requirement is different for Phase 1 and Phase 2 patients (ie, move IC#6 down to be a requirement for Phase 1 patients only)

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	~~administered as part of concurrent chemotherapy and radiation therapy will not count as a prior regimen of systemic therapy as long as recurrence occurred more than 6 months after the last day of chemotherapy.~~	• **Adjuvant chemotherapy or chemotherapy administered as part of concurrent chemotherapy and radiation therapy will not count as a prior regimen of systemic therapy as long as recurrence occurred more than 6 months after the last day of chemotherapy.**	
Synopsis, Inclusion Criteria #14 **Section 4.1, Inclusion Criteria #14**	Additional Inclusion Criteria for Phase 2 only: 14. Histologically or cytologically confirmed diagnosis of advanced or metastatic NSCLC harboring a *KRAS*^{G12D} mutation. • Subject must have a documented *KRAS*^{G12D} mutation as determined by a qPCR or NGS test performed in a CLIA laboratory or equivalently accredited diagnostic laboratory.	Additional Inclusion Criteria for Phase 2 only: 14. Histologically or cytologically confirmed diagnosis of advanced or metastatic NSCLC harboring a *KRAS*^{G12D} mutation. • Subject must have a documented *KRAS*^{G12D} mutation as determined by a qPCR or NGS test performed in a CLIA laboratory or equivalently accredited diagnostic laboratory. **Local tissue-based or liquid biopsy diagnostic testing will be permitted.**	Clarification: Acceptance of liquid biopsy qPCR / NGS as local test (was and) should be explicitly stated as there's adequate analytical performance for mutation testing
Synopsis, Exclusion Criteria #10 **Section 4.2, Subject Exclusion Criteria #10**	10. ~~History of extensive, disseminated, bilateral, or presence of CTCAE any grade interstitial fibrosis or interstitial lung disease including a history of pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, and pulmonary fibrosis~~.	10. **Currently have or had a history of ILD, radiation pneumonitis that required steroid treatment, or drug-related pneumonitis**	Clarified exclusionary criteria for subjects who have or had a history of ILD.
Synopsis, Criteria for Evaluation **Section 9.3, Study Endpoints**	Secondary Endpoints for Phase 1: • ORR assessed by ~~BICR and~~ Investigator using RECIST v1.1 Phase 2 Primary Endpoint: • ORR assessed ~~by BICR~~ per RECIST v1.1. Phase 2 Secondary Endpoints: • ~~ORR by Investigator~~ • DOR, TTR, and CBR by ~~BICR and~~ Investigator.	Secondary Endpoints for Phase 1: • ORR assessed by **the** Investigator using RECIST v1.1 Phase 2 Primary Endpoint: • ORR assessed **by Investigator** per RECIST v1.1. Phase 2 Secondary Endpoints: • DOR, TTR, and CBR by **the Investigator** • Intracranial objective response rate (IC-ORR) assessed according to modified RECIST v1.1 in	Since the study is a signal finding study, radiographic disease assessment by PI per RECIST v1.1 is sufficient to assess efficacy signal. BICR assessments will still be performed and may be analyzed.

<table>
<tr><th>Protocol Section</th><th>Original Text with Deletions</th><th>Revised Text</th><th>Justification</th></tr>
<tr><td></td><td>• Intracranial objective response rate (IC ORR) assessed ~~by BICR~~ according to modified RECIST v1.1 in subjects with brain metastases.
• …
Exploratory Endpoints (All Phases):
• ~~Association~~ of circulating tumor levels and genomic alterations ~~at baseline~~ and ~~after~~ dosing ~~with ORR and PFS~~</td><td>subjects with brain metastases.
• …
Exploratory Endpoints (All Phases0
• <u>ORR and PFS by modulation</u> <u>of circulating tumor levels and genomic alterations</u> <u>observed pre-</u> <u>and</u> <u>post-</u><u>dosing</u></td><td></td></tr>
<tr><td>Synopsis, Sample Size Determination

Section 9.2.1.1, Sample Size Determination, Phase 1b Dose Escalation</td><td>Phase 1b Dose Escalation
For dose escalation, ~~at least 6~~ subjects will be enrolled per dose level. ~~Assuming 3 dose levels to be evaluated~~, it is expected that approximately ~~18 –~~ 24 subjects will be enrolled to determine the RP2D of repotrectinib in combination with trametinib.</td><td>Phase 1b Dose Escalation
For dose escalation, 3 to 6 subjects will be enrolled per dose level. Assuming 3 dose levels to be evaluated, it is expected that approximately 18 – 24 subjects will be enrolled to determine the RP2D of repotrectinib in combination with trametinib</td><td>To account for the possible alternate dose finding levels that may be explored.</td></tr>
<tr><td>Schedule of Activities, Tumor Assessment. Cycle 4 and Beyond</td><td><table><tr><td></td><td>Cycle 4 and Beyond</td></tr><tr><td>Tumor Assessment</td><td></td></tr><tr><td>CT or MRI (chest/abdomen/pelvis)</td><td>X</td></tr><tr><td>CT or MRI of Brain</td><td>X</td></tr></table></td><td><table><tr><td></td><td>Cycle 4 and Beyond</td></tr><tr><td>Tumor Assessment</td><td></td></tr><tr><td>CT or MRI (chest/abdomen/pelvis)</td><td></td></tr><tr><td>CT or MRI of Brain</td><td></td></tr></table></td><td>Correction to align with footnote that CT or MRI assessments occur every 2 cycles from Cycle 2</td></tr>
<tr><td>Schedule of Activities, Footnote 8</td><td>Added text</td><td>8. Dispense Repotrectinib (C1D15): For subjects assigned to repotrectinib BID dosing regimens (Dose Level 3, -2b, or -3b), repotrectinib will be dispensed on Day 15 following physician assessment of safety to confirm escalation from QD to BID dosing.</td><td>Footnote added to Schedule of Activities based on review of available safety and PK data from 2 patients treated with repotrectinib and trametinib at Dose Level 1, the SRC recommended a</td></tr>
</table>

Protocol Section	Original Text with Deletions	Revised Text	Justification
			dose level de-escalation to Dose Level -2 and recommended alternate dose finding levels
Schedule of Activities, Footnote 18 – Bone Scan **Section 6.16.3, Bone Scan**	~~18~~ Bone Scans: Bone scans (or bone MRI if preferred by Investigator) will be performed at baseline (28 days prior to Cycle 1 Day 1) if bone metastases are suspected. In addition, bone scans can be performed if clinically indicated per Investigator's discretion. These scans are only repeated for subjects having a baseline scan, to confirm the absence of bone metastases in case of a Complete Response (CR). Subject responses will be confirmed ≥ 4 weeks later after the initial documentation of response by the Investigator ~~and confirmed by BICR~~.	**21**. Bone Scans: Bone scans (or bone MRI if preferred by Investigator) will be performed at baseline (28 days prior to Cycle 1 Day 1) if bone metastases are suspected. In addition, bone scans can be performed if clinically indicated per Investigator's discretion. These scans are only repeated for subjects having a baseline scan, to confirm the absence of bone metastases in case of a Complete Response (CR). Subject responses will be confirmed ≥ 4 weeks later after the initial documentation of response by the Investigator.	Since the study is a signal finding study, radiographic disease confirmation by BICR is not needed.
Section 1.5.1, Study TPX-0005-09: Mass Balance, Pharmacokinetics, and Metabolism of Repotrectinib in healthy Male Subjects	Section added	**TPX-0005-09 was conducted as a 2-part, 2-treatment, fixed-sequence study in 7 healthy male volunteers to investigate the mass balance, PK, and metabolism of a single oral dose and PK of an intravenous tracer of [^{14}C]repotrectinib in healthy male subjects. The treatments were administered after an overnight fast of at least 10 hours. Below is a summary of key findings. Refer to the Investigator's Brochure for further details.** **Following concomitant administration of a single oral dose of 160-mg repotrectinib capsule formulation and intravenous administration of tracer [^{14}C]repotrectinib in study TPX-0005-09 (Period 1), the geometric mean absolute bioavailability of repotrectinib based on $AUC_{0-¥}$ was approximately**	Provide updated PK half-life information for the IV formulation (32.5 h) and the oral capsule dose (36.2 h) of repotrectinib.

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		45.7%. The geometric means $t_{1/2}$ of the IV formulation and the oral capsule dose were 32.5 and 36.2 hours, respectively. **Following oral administration of a 160 mg of [^{14}C]repotrectinib (100 µCi) dose (TPX-0005-09, Period 2), the mean total recovery of radioactivity in excreta was 93.7% with radioactivity recoveries in feces and urine of 88.8% and 4.84%, respectively. No metabolite exceeded 10% of total circulating drug-related radioactivity. All detected metabolites had been previously detected in rat and/or cynomolgus monkey following oral administration; therefore, there were no unique human metabolites.**	
Section 1.6.1, Repotrectinib in Combination with Trametinib	Therefore, the starting dose of repotrectinib in combination with trametinib for the Phase 1b dose escalation portion of the study will be ~~160 mg~~ daily (QD), and the starting dose of trametinib will be ~~1.5 mg~~ QD, ~~one dose level below the standard trametinib monotherapy and combination dose to minimize possible safety risks in the initial evaluation of the combination therapy~~.	Therefore, the starting dose of repotrectinib in combination with trametinib for the Phase 1b dose escalation portion of the study will be **120 mg** daily (QD), and the starting dose of trametinib will be **2 mg** QD.	Modify the current dose finding levels in Subprotocol 1 to allow assessment of repotrectinib with lower doses of trametinib
Section 3.4, Study Duration	Subjects will remain on study treatment until ~~Blinded Independent Central Review (BICR)~~ confirmed radiographic disease progression, development of unacceptable toxicity, or withdrawal of consent. There is no limit to the number of cycles of treatment with repotrectinib or trametinib.	Subjects will remain on study treatment confirmed radiographic disease progression, development of unacceptable toxicity, or withdrawal of consent. There is no limit to the number of cycles of treatment with repotrectinib or trametinib.	Since the study is a signal finding study, radiographic disease confirmation by BICR is not needed.
Section 3.5.1, Dose Interruptions and Delays,	[1] If subjects are assigned to the ~~DL 1~~ dose level, further dose reductions will not be implemented. Subjects will be discontinued if a dose reduction is required	[1] If subjects are assigned to the **Dose Level -3**, further dose reductions will not be implemented. Subjects will be discontinued if a dose reduction is required	Clarified dose modification guidelines for subjects assigned

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Table 4 Repotrectinib Dose Modification Guidelines for Adverse Events (CTCAE v5.0), Footnote 1			to Dose Level -3 with CTCAE adverse events
Section 5.4, Concomitant Medications	Added text	**Note on COVID-19 Vaccination: The use of vaccines is not a restriction for this study. Currently enrolled and potential adult clinical trial subjects are allowed to receive the COVID-19 vaccine with no impact on their eligibility or ability to remain on study treatment. This guidance will also apply to pediatric and adolescent patients once vaccine approval is available for these populations. In addition, there is not a required wash-out period for the vaccine. The risk-benefit for COVID-19 vaccination while on study should be determined by the treating physician. Administration of the COVID-19 vaccine will be recorded in the medical history or the concomitant medications CRF, as applicable, as well as any adverse events related to the vaccine.**	Provide guidance regarding COVID-19 vaccination for study participants.
Section 6.15 Pharmacodynamic/Biomarkers	Circulating cell-free DNA (ccfDNA) will be isolated from blood to study changes of circulating tumor levels (i.e., assessed by modulations of ~~major~~ allele frequency [MAF] of genomic alterations), and explore resistance mechanisms as well as clonal evolution	Circulating cell-free DNA (ccfDNA) will be isolated from blood to study changes of circulating tumor levels (i.e., assessed by modulations of **minor** allele frequency [MAF] of genomic alterations), and explore resistance mechanisms as well as clonal evolution	Correction to assessment by modulation of minor allele frequency
Section 6.16, Tumor Assessments	Tumor assessments will include all known or suspected disease sites and will be performed per specified timepoints according to the Schedule of Activities (Table 1). For all tumor assessments, the method of	Tumor assessments will include all known or suspected disease sites and will be performed per specified timepoints according to the Schedule of Activities (Table 1). For all tumor assessments, the method of	Clarified that tumor assessment by BICR will still be conducted on

Protocol Section	Original Text with Deletions	Revised Text	Justification
	assessment that was used at Screening should be the same method used throughout the study. For all subjects, radiographic confirmation of objective tumor response or disease progression will be based on RECIST v1.1 and assessed locally by Investigator ~~and by BICR~~ (Section 6.16.4). At the EOT visit, the subject must undergo an EOT tumor assessment evaluation CT or MRI (if more than 4 weeks have passed since the last imaging assessment) to evaluate for radiologic disease progression if treatment is being discontinued for an alternate reason other than ~~BICR~~ confirmed radiographic disease progression.	assessment that was used at Screening should be the same method used throughout the study. **Tumor assessment will be assessed locally by Investigator and by BICR.** For all subjects, radiographic confirmation of objective tumor response or disease progression will be based on RECIST v1.1 and assessed locally by Investigator (Section 6.16.4). At the EOT visit, the subject must undergo an EOT tumor assessment evaluation CT or MRI (if more than 4 weeks have passed since the last imaging assessment) to evaluate for radiologic disease progression if treatment is being discontinued for an alternate reason other than confirmed radiographic disease progression.	study but since the study is a signal finding study, radiographic disease confirmation by BICR is not needed.
Section 7.1, Screening and Eligibility	• Imaging studies (CT or MRI of the chest, abdomen, and pelvis and MRI of the brain) should be submitted. ~~and confirmed by~~ BICR	• Imaging studies (CT or MRI of the chest, abdomen, and pelvis and MRI of the brain) should be submitted **for** BICR **assessment**.	Clarified that tumor assessment by BICR will still be conducted on study but since the study is a signal finding study, radiographic disease confirmation by BICR is not needed.
Section 7.3, Subject Discontinuation and Withdrawal from Study	Subjects should remain on study treatment until there is ~~BICR~~ confirmed radiographic progression.	Subjects should remain on study treatment until there is confirmed radiographic progression.	Since the study is a signal finding study, radiographic disease confirmation by BICR is not needed.

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Section 7.8.3 Palliative Radiation	Palliative radiotherapy on study is permitted for the treatment of painful bony lesions ~~providing~~ the lesions were known at the time of study entry and the Investigator clearly indicates that the need for palliative radiotherapy is not indicative of disease progression. In view of the current lack of data about the interaction of study drug with radiotherapy, study drug treatment should be interrupted during palliative radiotherapy, stopping 1 day before palliative radiotherapy and resuming treatment 1 day after completion of palliative radiotherapy and recovery from any acute radiation toxicities to baseline	Palliative radiotherapy on study is permitted**, following agreement with the Sponsor**, for the treatment of painful bony lesions **provided** the lesions were known at the time of study entry and the Investigator clearly indicates that the need for palliative radiotherapy is not indicative of disease progression. In view of the current lack of data about the interaction of study drug with radiotherapy, study drug treatment should be interrupted during palliative radiotherapy, stopping 1 day before palliative radiotherapy and resuming treatment 1 day after completion of palliative radiotherapy and recovery from any acute radiation toxicities to baseline	Clarified that palliative radiotherapy permitted for pre-existing bony lesions following Sponsor agreement
Section 7.8.5. Contraception	All ~~fertile~~ male ~~(~~study subjects ~~and partners of female subjects of WOCBP)~~ must agree to condom use throughout the study and for 6 months following the last dose of study drug. ~~Fertile~~ male partners of WOCBP must agree to condom use throughout the study and for 4 months following the last dose of study drug. .	All male study subjects must agree to condom use throughout the study and for 6 months following the last dose of study drug. Male partners of WOCBP **subjects** must agree to condom use throughout the study and for 4 months following the last dose of study drug.	Clarified contraception requirement for males partners of female study subjects. Aligned with the synopsis inclusion criteria.
Section 8.2.5.11, Exposure During Pregnancy	If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the Investigator must submit this information to Premier Research Pharmacovigilance (Premier PV) on a SAE Report Form (if applicable) and Pregnancy Data Collection Form~~, regardless of whether an SAE has occurred~~. … Additional information regarding the exposure during pregnancy may be requested by the Investigator. Further	If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the Investigator must submit this information to Premier Research Pharmacovigilance (Premier PV) on a SAE Report Form (if applicable) and Pregnancy Data Collection Form. … Additional information regarding the exposure during pregnancy may be requested by the Investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays). In the case of paternal	Revised to clarify the language and instructions for reporting of pregnancy during the study.

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	follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the Investigator will provide the study subject with the ~~Pregnancy Data Collection Form~~ to deliver to his partner. The Investigator must document in the source documents that the subject was given the ~~Pregnancy Data Collection Form~~ to provide to his pregnant partner.	exposure, the Investigator will provide the study subject with the **pregnant partner release of information form** to deliver to his partner. The Investigator must document in the source documents that the subject was given the **pregnant partner release of information form** to provide to his pregnant partner.	
Section 9.2.1.1, Phase 1b Dose Escalation	For dose escalation, ~~at least 6~~ subjects will be enrolled per dose level. ~~Assuming 3 dose levels to be evaluated~~, it is expected that approximately ~~18 –~~ 24 subjects will be enrolled to determine the RP2D of repotrectinib in combination with trametinib	For dose escalation, **3 to 6 DLT-evaluable** subjects will be enrolled per dose level. **Therefore,** it is expected that approximately 24 **– 30** subjects will be enrolled to determine the RP2D of repotrectinib in combination with trametinib	To account for the possible alternate dose finding levels that may be explored.
Section 9.4.3, Analysis of Primary Endpoint	For Phase 1b, efficacy analysis will be performed in EE population. For Phase 2, the FAS analysis set will be used as the primary analysis for efficacy, and analyses using the EE population will be used as sensitivity analysis. Primary efficacy data will be based on the radiologic assessments evaluated by ~~the BICR.~~ Data from ~~the Investigator will~~ be analyzed as supportive~~.~~	For Phase 1b, efficacy analysis will be performed in EE population. For Phase 2, the FAS analysis set will be used as the primary analysis for efficacy, and analyses using the EE population will be used as sensitivity analysis. Primary efficacy data will be based on the radiologic assessments evaluated by **the Investigator**. Data from **BICR may** be analyzed as supportive~~.~~	Clarified that tumor assessment by BICR will still be conducted on study and may be analyzed as supportive, but since the study is a signal finding study, radiographic disease confirmation by BICR is not needed.