Official Title: Phase 1 Study of INCB099280 in Combination With Adagrasib in Adults With Advanced Solid Tumors Harboring a KRASG12C Mutation

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Statistical Analysis Plan

INCB 99280-204

A Phase 1 Study of INCB099280 in Combination With Adagrasib in Adults With Advanced Solid Tumors Harboring a $KRAS^{G12C}$ Mutation

IND Number:	[redacted]
EU CT Number:	**2023-503223-26-00**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803** **United States**
Protocol Version:	**Protocol Amendment 4 dated 21 FEB 2024**
CRF Approval Date:	**01 AUG 2023**
SAP Version:	**Original**
SAP Author:	[redacted] [redacted]**, Biostatistics**
Date of Plan:	**26 JUN 2025**

This study is being conducted in compliance with Good Clinical Practice, including the archiving of essential documents.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AUC	area under the curve
$AUC_{(0-\tau)}$	area under the steady-state plasma or serum concentration-time curve over 1 dose interval
AUC_{0-12h}	area under the steady-state plasma or serum concentration-time curve from Hour 0 to 12
BID	twice daily
BMI	body mass index
BOR	best overall response
CI	confidence interval
CL/F	apparent oral dose clearance
CL_{ss}/F	apparent oral dose clearance at steady state
$C_{ave,ss}$	average plasma concentration at steady state
$C_{max,ss}$	maximum plasma concentration at steady state
$C_{min,ss}$	minimum plasma concentration at steady state
CR	complete response
CRC	colorectal cancer
CRF	Case Report Form
CSR	Clinical Study Report
C_{tau}	plasma concentration at time tau (ie, 12 hours for twice daily regimens or 24 hours for once daily regimens) at steady state
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor deoxyribonucleic acid
DCR	disease control rate
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DOR	duration of response
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
FAS	Full Analysis Set
FDA	Food and Drug Administration
$KRAS^{G12C}$	KRAS glutamine to cysteine mutation at codon 12
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
NCA	noncompartmental analysis
NCI	National Cancer Institute
NE	not evaluable
NSCLC	non–small cell lung cancer
ORR	objective response rate
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PT	preferred term
QD	once daily
RDE	recommended dose for expansion
RECIST	Response Evaluation Criteria in Solid Tumours
SAP	Statistical Analysis Plan
SD	stable disease
SOC	system organ class
TEAE	treatment-emergent adverse event
$t_{max,ss}$	time to maximum concentration at steady state
ULN	upper limit of normal
V_z/F	apparent oral dose volume of distribution at steady state
WHO	World Health Organization

1. INTRODUCTION

This is a Phase 1 multicenter, open-label study to be conducted in 2 parts, a dose-finding part (Part 1) followed by a dose-expansion part (Part 2), in adults with $KRAS^{G12C}$-mutated advanced solid tumors whose disease has progressed after at least 1 prior line of systemic therapy. Additional details regarding the study design are provided in Section 3.

This study was closed to further enrollment owing to a strategic decision by the sponsor during Part 1. At this time, only 6 participants had been dosed at 2 dose levels. Part 2 will not be conducted.

The purpose of this SAP is to provide details of the statistical analyses that have been outlined in the INCB 99280-204 Protocol.

2. STUDY INFORMATION, OBJECTIVES, AND ENDPOINTS

2.1. Protocol and Case Report Form Version

This SAP is based on INCB 99280-204 Protocol Amendment 4 dated 21 FEB 2024 and CRFs approved 01 AUG 2023. Unless superseded by an amendment, this SAP will be effective for all subsequent Protocol amendments and eCRF versions.

2.2. Study Objectives and Endpoints

Table 1 presents the objectives and endpoints.

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of INCB099280 in combination with adagrasib. • To establish the MTD or identify RDE(s) for the combination of INCB099280 and adagrasib.	• DLTs. • TEAEs. • Impact of TEAEs on study drug administration, assessed by treatment interruptions, dose reductions, and permanent discontinuation.
Secondary	
• To characterize the PK of INCB099280 and adagrasib when administered in combination. • To assess whether clinically effective dose(s) of INCB099280 can be coadministered with adagrasib.	• Descriptive summary of PK concentration data for INCB099280 and adagrasib. • INCB099280 PK parameters including $C_{max,ss}$, $T_{max,ss}$, $C_{min,ss}$, AUC_{0-12h}, CL/F, and V_z/F from observed INCB099280 plasma concentration-time profiles, summarized and analyzed [redacted].
To assess the antitumor activity of INCB099280 in combination with adagrasib in participants with $KRAS^{G12C}$-mutant advanced solid tumors, including NSCLC and CRC.	• Objective response, defined as having a BOR of CR or PR assessed per RECIST v1.1 by the investigator. • Disease control, defined as having a BOR of CR, PR, or SD ≥ 15 weeks (from the start of combination treatment) assessed per RECIST v1.1 by the investigator. • DOR, defined as the time from the first CR or PR until disease progression (assessed per RECIST v1.1 by the investigator) or death from any cause, whichever occurs earlier. • Six-month and 12-month PFS, defined as absence of disease progression (assessed per RECIST v1.1 by the investigator) or death from any cause from start of combination treatment to 6 or 12 months.

[redacted]

3. STUDY DESIGN

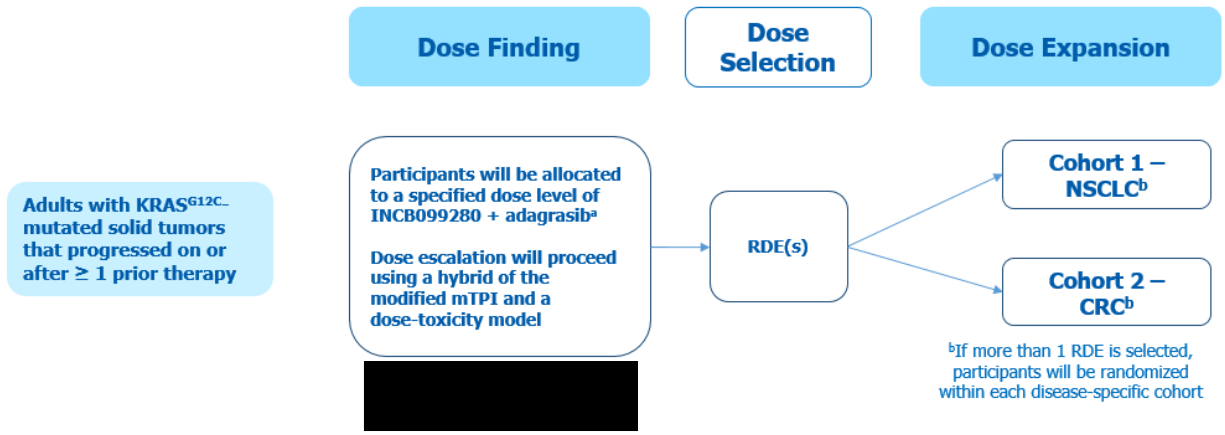
This is a Phase 1, multicenter, open-label study to be conducted in 2 parts: a dose-finding part (Part 1) followed by a dose-expansion part (Part 2; see Figure 1). However, the study was closed to further enrollment owing to a strategic decision by the sponsor; therefore, Part 2 will not be conducted.

In Part 1, the safety, tolerability, and PK of escalating doses of INCB099280 in combination with adagrasib will be evaluated in approximately 45 DLT-evaluable participants with previously treated KRAS^{G12C}-mutant advanced solid tumors. These data will support the identification of an MTD and/or RDE(s) for further evaluation in the dose-expansion part of the study.

[redacted] the starting dose regimen (Dose Level 1) will be INCB099280 50 mg QD and adagrasib 400 mg BID. [redacted]

Dose-escalation decisions will be guided by emergent safety and tolerability data, taking the PK results into consideration. The [redacted] for the participants enrolled in Dose Level 1 will be reviewed and the assignment of the next dose-escalation level (Dose Level 2) will be selected based [redacted]. A hybrid of the modified mTPI design and a dose-toxicity model will be used to make dose-escalation, de-escalation, and dose-elimination decisions (refer to INCB 99280-204 Protocol Section 4.1.1.2).

Figure 1: Study Design Schema



3.1. Randomization

Not applicable.

3.2. Control of Type I Error

All statistical analyses are exploratory in nature. Unless otherwise specified, all CIs provided will be at the 95% confidence level.

3.3. Sample Size Considerations

Dose escalation will follow a hybrid design (Liao et al 2022) with a target DLT rate of 30%. Cohorts of at least 3 DLT-evaluable participants will be initially enrolled into each dose level in Part 1, and the dose-escalation procedure may be stopped if the number of evaluable participants treated at any dose level is ≥ 9. The planned total sample size for Part 1 is approximately 45 evaluable participants, and the exact number of participants treated will depend on the number of participants required per dose level and the number of dose levels tested before the RDE(s) is established.

3.4. Schedule of Assessments

Refer to Protocol Amendment 4 dated 21 FEB 2024 for a full description of all study procedures and assessment schedules for this study.

4. DATA HANDLING DEFINITIONS AND CONVENTIONS

4.1. Scheduled Study Evaluations and Study Periods

4.1.1. Day 1

Day 1 is the start date of combination treatment, which is the date that the first dose of adagrasib is administered to the participants. [redacted]

4.1.2. Study Day

If a visit/reporting date is on or after Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (visit/reporting date − Day 1 date + 1).

If the visit/reporting date is before Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (visit/reporting date − Day 1 date).

A study day of −1 indicates 1 day before Day 1.

4.1.3. Baseline Value

Baseline is the last nonmissing measurement obtained before the first administration of INCB099280 or adagrasib, unless otherwise defined.

When scheduled assessments and unscheduled assessments occur on the same day and the time of the assessment or time of first dose is not available, use the following convention to determine baseline:

- If both a scheduled and an unscheduled visit are available on the day of the first dose and the time is missing, use the scheduled assessment as baseline.
- If all scheduled assessments are missing on the day of the first dose and an unscheduled assessment is available, use the unscheduled assessment as baseline.

4.1.4. Handling of Missing and Incomplete Dates

In general, values for missing dates will not be handled unless methods for handling missing dates are specified in this section or relevant sections. The original reported dates collected on the eCRF should be used in all relevant listings. The following rules will be used for handling partial dates for analyses requiring dates.

[redacted]

4.1.5. Cycle Length and Duration

Different administration schedules of INCB099280 such as QD and BID may be explored. Cycle 1 Day 1 is the day that the first dose of adagrasib is administered. The scheduled cycle length is 28 days. The actual Day 1 of subsequent cycles will correspond with the first day of administration of INCB099280 or adagrasib in that cycle; thus, treatment cycles may become out of sync with the originally planned schedule, and the cycle length may be different from 28 days. The date of the Day 1 of subsequent cycles recorded on the eCRF will be used as the Day 1 of the subsequent cycles.

4.2. Variable Definitions

4.2.1. Body Mass Index

Body mass index will be calculated as follows:

BMI (kg/m^2) = [weight (kg)] / [height (m)]^2.

4.2.2. Prior and Concomitant Medication

Prior medication is defined as any nonstudy medication started before the first dose of INCB099280 or adagrasib.

Concomitant medication is defined as any nonstudy medication that is started accordingly:

- Before the date of first administration of INCB099280 or adagrasib and is ongoing throughout the study or ends on/after the date of first study drug administration.
- On/after the date of first administration of INCB099280 or adagrasib and is ongoing or ends during the course of study.

A prior medication could also be classified as "both prior and concomitant medication" if the end date is on or after first dose of INCB099280 or adagrasib. In the listing, it will be indicated whether a medication is only prior, only concomitant, or both prior and concomitant.

For the purposes of analysis, all medications will be considered concomitant medications unless the medications can unequivocally be defined as not concomitant.

5. STATISTICAL METHODOLOGY

5.1. General Methodology

Unless otherwise noted, SAS® software (SAS Institute Inc, Cary, NC; v9.4 or later) will be used for the generation of all tables, graphs, and statistical analyses. Descriptive summaries for continuous variables will include but not be limited to the number of observations, mean, standard deviation, median, minimum, and maximum. Descriptive summaries for categorical variables will include the number and percentage of participants in each category.

Interim analyses are planned for this study as defined in Section 10.

5.2. Treatment Groups

Part 1 will be an open-label dose escalation to assess the safety, tolerability, and DDI of INCB099280 and adagrasib combination therapy in participants with $KRAS^{G12C}$-mutated advanced solid tumors and to determine MTD and/or RDE(s). Safety data will be summarized overall and by dose level based on the actual treatment that participants received. Efficacy data will be summarized overall and by dose level based on the assigned treatment.

5.3. Analysis Populations

Table 2 presents the analysis populations for primary and secondary endpoints.

Table 2: Analysis Populations for Primary and Secondary Endpoints

Analysis Population	Endpoint(s)	Population-Level Summary Metric(s)
DLT-Evaluable	DLTs	Proportion of participants having DLTs
Safety	TEAEs	Proportion of participants having TEAEs
	Impact of TEAEs on study drug administration, assessed by treatment interruptions, dose reductions, and permanent discontinuation	Proportion of participants having treatment interruptions, dose reductions, and discontinuation of study drug due to TEAEs
PK-Evaluable	INCB099280 PK parameters, including $C_{max,ss}$, $t_{max,ss}$, $C_{min,ss}$, $AUC_{(0-\tau)}$, CL/F, and V_z/F	• Concentration of INCB099280 and adagrasib • Estimated INCB099280 PK parameters using NCA
FAS	Objective response, defined as having a BOR of CR or PR assessed per RECIST v1.1 by the investigator.	ORR
	Disease control, defined as having a BOR of CR, PR, or SD ≥ 15 weeks (from the start of combination treatment) assessed per RECIST v1.1 by the investigator.	DCR
	DOR, defined as the time from the first CR or PR until disease progression (assessed per RECIST v1.1 by the investigator) or death from any cause, whichever occurs earlier.	Median DOR
	Six-month and 12-month PFS, defined as absence of disease progression (assessed per RECIST v1.1 by the investigator) or death from any cause from start of treatment to 6 or 12 months.	• 6-month PFS rate • 12-month PFS rate

5.3.1. All-Screened Population

The all-screened population will include all participants who signed the informed consent form.

5.3.2. Full Analysis Set

The FAS will include all participants who received at least 1 dose of INCB099280 or adagrasib. Participants will be analyzed according to the treatment to which they have been initially assigned.

The FAS will be used for summary of demographics, participant disposition, baseline characteristics, and efficacy analyses.

5.3.3. Dose-Limiting Toxicity–Evaluable Population

The DLT-Evaluable Population will include all participants in Part 1 who meet 1 of the following criteria:

- Had a DLT by the end of the first treatment cycle (ie, Day 1 to Day 28 inclusive)
- Received at least 75% of the planned doses (ie, ≥ 42 doses) of both INCB099280 and adagrasib during the first treatment cycle (ie, Day 1 to Day 28 inclusive)
- Discontinue study treatment owing to a DLT or a TEAE after receiving at least 1 dose of INCB099280, even if adagrasib was not started

The DLT-Evaluable Population will be used for making dose escalation/de-escalation decisions and for the summary of DLTs.

5.3.4. Safety Population

The Safety Population will include all participants who received at least 1 dose of INCB099280 or adagrasib. Treatment groups for this population will be determined according to the actual treatment the participant received regardless of assigned study drug treatment.

All safety analyses and summary of exposure will be conducted using the Safety Population.

5.3.5. Pharmacokinetic-Evaluable Population

The PK-Evaluable Population will include all participants who received at least 1 dose of INCB099280 and provided at least 1 postbaseline plasma sample (1 PK measurement). The study pharmacokineticist may review data listings of study drug administration and sample records to identify participants to be excluded from analyses of PK data.

All PK analyses and summary of plasma concentrations will be conducted using the PK-Evaluable Population.

6. BASELINE, EXPOSURE, AND DISPOSITION

Appendix A provides a list of data displays. Sample data displays are included in a separate document.

6.1. Demographics, Baseline Characteristics, and Disease History

6.1.1. Demographics and Baseline Characteristics

The following demographics and baseline characteristics will be summarized for the FAS: age, sex, race, ethnicity, weight, height, and BMI.

6.1.2. Baseline Disease Characteristics and Disease History

The baseline ECOG performance status, cancer type, time since initial diagnosis, time since advanced/metastatic diagnosis, stage at initial diagnosis, current stage, disease histology/histopathology, primary site of disease, and site of metastatic disease at baseline will be listed for all participants in the FAS.

Time since diagnosis will be calculated as follows:

Time since diagnosis (years) = (Day 1 date − date of diagnosis + 1) / 365.25.

6.1.3. Medical History

For participants in the FAS, medical history will be listed by assigned treatment group.

6.2. Disposition of Participant

The number and percentage of participants who were treated, who were ongoing with study treatment, who discontinued study treatment with a primary reason for discontinuation, who discontinued only 1 drug component of the combination therapy with a primary reason for discontinuation, who were still in the study, who completed the study, and who withdrew from the study with a primary reason for withdrawal will be summarized for the FAS. The number of participants enrolled by country and/or site will also be provided by dose level.

6.3. Protocol Deviations

Protocol deviations will be listed.

6.4. Exposure

For participants in the Safety Population, dosing changes and missed doses will be listed. Total exposure to INCB099280 and adagrasib will be listed as the following:

- **Duration of treatment with INCB099280 (days)**: date of last nonzero dose of INCB099280 − date of first dose of INCB099280 + 1.
- **Duration of treatment with adagrasib (days)**: date of last nonzero dose of adagrasib − date of first dose of adagrasib + 1.

The unit used for defining duration of treatment may be changed to week or month if needed. One month is equal to 30.4375 days.

6.5. Prior and Concomitant Medication

Prior medications and concomitant medications will be coded using the WHO Drug Dictionary and will be listed for the FAS.

7. EFFICACY

Appendix A provides a list of data displays. Sample data displays are included in a separate document.

7.1. General Considerations

All secondary efficacy analyses will be conducted using the FAS unless otherwise specified. Efficacy endpoints will be listed and/or summarized by dose level.

7.2. Efficacy Hypotheses

Not applicable.

7.3. Analysis of the Primary Efficacy Parameters

Not applicable.

7.4. Analysis of the Secondary Efficacy Parameters

7.4.1. Response Criteria

Overall disease status will be categorized using RECIST v1.1 for solid tumors (Eisenhauer et al 2009). Participants will have their overall response evaluated as CR, PR, SD, PD, or NE at each postbaseline radiologic assessment.

7.4.1.1. Best Overall Response

In general, under RECIST v1.1, BOR is the best response recorded postbaseline prior to and including the first PD, in the order of CR, PR, SD, PD and NE. Responses do not need to be confirmed. In order to have a BOR of SD, overall response must meet the SD criteria at least once after at least 15 weeks (105 days) since the start of combination therapy (ie, Day 1).

The BOR will be determined from response assessments prior to and including the date of starting new anticancer therapy. If any alternative cancer therapy is taken while on study, any subsequent assessments will be excluded from the BOR determination (ie, the while-on-treatment strategy for handling intercurrent events).

7.4.1.2. Objective Response Rate

Objective response rate is defined as the percentage of objective responders, participants having a BOR of CR or PR at any postbaseline visit before first PD as determined by investigator per RECIST v1.1. The ORR will be estimated with exact 95% CI overall and by dose level using the Clopper-Pearson (1934) method.

7.4.1.3. Disease Control Rate

Disease control rate is defined as the percentage of participants having a BOR of CR, PR, or SD after ≥ 15 weeks since the start of combination therapy as determined by investigator per RECIST v1.1. The DCR will be estimated with exact 95% CI overall and by dose level using the Clopper-Pearson (1934) method.

7.4.1.4. Duration of Response

For objective responders, the DOR is the time from the first overall response contributing to an objective response to the earlier of the participant's death or first overall response of PD as assessed by RECIST v1.1 occurring after the first overall response contributing to the objective response. Partial dates of death and new anticancer treatment start will be handled using the rules described in Section 4.1.4. Censoring of DOR will follow the algorithm outlined in Table 3 based on FDA guidance (FDA 2015, FDA 2018).

Table 3: Evaluation and Censoring of Duration of Response

Situation	Outcome	Date of Progression or Censoring
Progression documented between scheduled response assessments	Progressed	Date of first overall response of PD
No progression	Censored	Date of last valid radiologic assessment (not NE and not missing)
Study discontinuation for undocumented progression	Censored	Date of last valid radiologic assessment (not NE and not missing)
Study discontinuation for toxicity or other reason	Censored	Date of last valid radiologic assessment (not NE and not missing)
New anticancer treatment started	Censored	Date of last valid radiologic assessment (not NE and not missing) on/before starting a new anticancer treatment
Death before first progressive response assessment	Progressed	Date of death
Death between adequate response assessments	Progressed	Date of death
Death or progression after 2 or more missed assessments	Censored	Date of last valid radiologic assessment (not NE and not missing)

The Kaplan-Meier estimate of median DOR will be presented with its 95% CI overall and by dose level. The 95% CI will be calculated using the generalization of Brookmeyer and Crowley's (1982) method with log-log transformation (Klein and Moeschberger 1997).

Summary and analysis of DOR for a particular category will be presented only if the number of responders is ≥ 5. Otherwise, only subject-level listings will be provided.

7.4.1.5. Progression-Free Survival

Progression-free survival is defined as the time from the start of the combination therapy (ie. Day 1) to the earliest date of disease progression, as determined by investigator assessment per RECIST v1.1, or death due to any cause if occurring sooner than progression. Partial dates of death and new anticancer treatment start will be handled using the rules described in Section 4.1.4. Censoring of PFS will follow the algorithm outlined in Table 4.

Table 4: Evaluation and Censoring of Progression-Free Survival

Situation	Outcome	Date of Progression or Censoring
No baseline tumor assessments	Censored	Day 1
No valid postbaseline response assessment	Censored	Day 1
Progression documented between scheduled response assessments	Progressed	Date of first overall response of PD
No progression	Censored	Date of last valid radiologic assessment (not NE and not missing)
Study discontinuation for undocumented progression	Censored	Date of last valid radiologic assessment (not NE and not missing)
Study discontinuation for toxicity or other reason	Censored	Date of last valid radiologic assessment (not NE and not missing)
New anticancer treatment started	Censored	Date of last valid radiologic assessment (not NE and not missing) on/before starting a new anticancer treatment
Death before first progressive response assessment	Progressed	Date of death
Death between adequate response assessments	Progressed	Date of death
Death or progression after 2 or more missed assessments	Censored	Date of last valid radiologic assessment (not NE and not missing)

The Kaplan-Meier estimate of median PFS and 6-month and 12-month PFS rates will be presented with their 95% CIs overall and by dose level. The 95% CI of median PFS will be calculated using the generalization of Brookmeyer and Crowley's (1982) method with log-log transformation (Klein and Moeschberger 1997).

8. PHARMACOKINETICSAND PHARMACODYNAMICS

8.1. Pharmacokinetic Analyses

8.1.1. Noncompartmental Analysis and Descriptive Analysis

Standard noncompartmental PK methods will be used to analyze the plasma concentration data using Phoenix WinNonlin v8.3.4 or higher (Certara USA, Princeton, NJ) or other functionally equivalent software applications. The actual times of postdose sample collections will be used. Predose PK samples will be assigned time 0.

The following steady-state PK parameters will be calculated from the plasma concentrations of INCB099280:

- $C_{max,ss}$
- $t_{max,ss}$
- $C_{min,ss}$
- $AUC_{(0-\tau)}$
- $C_{ave,ss}$, derived as $AUC_{(0-\tau)}$ divided by tau (hours)
- C_{tau}
- CL_{ss}/F
- V_z/F

The plasma concentrations of INCB099280 will be summarized by dose level, visit, and time. The PK parameters estimated by NCA methods will be summarized by dose level and visit.

The plasma concentrations of adagrasib will be summarized by cohort or INCB099280 dose level, visit, and time.

The descriptive summary statistics include but are not limited to the number of observations, mean, standard deviation, standard error of the mean, coefficient of variation, median, minimum, maximum, geometric mean, and geometric coefficient of variation.

[redacted]

9. SAFETY AND TOLERABILITY

Appendix A provides a list of data displays. Sample data displays are included in a separate document.

9.1. General Considerations

The clinical safety data (ie, vital signs, ECGs, routine laboratory tests, and TEAEs) will be either listed or summarized using descriptive statistics (eg, mean, frequency) using the Safety Population.

9.2. Adverse Events

9.2.1. Adverse Event Definitions

A TEAE is any AE either reported for the first time or worsening of a pre-existing event after the first dose of study drug up to 104 days after the last dose of study treatment or until the start of new anticancer therapy, whichever occurs first. Analysis of AEs (as discussed below) will be limited to TEAEs, but data listings will include all AEs regardless of their timing in relation to study drug administration. For purposes of analysis, all AEs will be considered TEAEs unless the AE can unequivocally be defined as not treatment-emergent.

Adverse events will be tabulated by MedDRA PT and SOC. Severity of AEs will be graded using the NCI CTCAE v5.0 using Grades 1 through 5. The CTCAE reporting guidelines and grading details are available on the Cancer Therapy Evaluation Program website.

The subset of AEs considered by the investigator to be related to INCB099280 or adagrasib will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to a study drug, the AE will be considered to be related to that study drug. The incidence of AEs and treatment-related AEs will be tabulated. In addition, serious TEAEs will also be tabulated.

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

- An unresolved missing causality will be considered treatment-related.
- An unresolved missing severity will be identified as an unknown severity.

Immune-related adverse events are TEAEs that are flagged as potentially immune-related by the investigator.

9.2.2. Dose-Limiting Toxicities

The participants with DLTs and the type of DLT will be listed by dose level.

9.2.3. Adverse Event Summaries

An overall summary of TEAEs by treatment group will include the following:

- Number (%) of participants who had any TEAEs
- Number (%) of participants who had any serious TEAEs
- Number (%) of participants who had any Grade 3 or higher TEAEs
- Number (%) of participants who had any treatment-related TEAEs
  - Number (%) of participants who had any TEAEs related to INCB099280
  - Number (%) of participants who had any TEAEs related to adagrasib
- Number (%) of participants who had a Grade 3 or higher treatment-related TEAE
  - Number (%) of participants who had a Grade 3 or higher TEAE related to INCB099280
  - Number (%) of participants who had a Grade 3 or higher TEAE related to adagrasib
- Number (%) of participants who had a TEAE leading to dose interruption of INCB099280
- Number (%) of participants who had a TEAE leading to dose reduction of INCB099280
- Number (%) of participants who had a TEAE leading to discontinuation of INCB099280
- Number (%) of participants who had a TEAE leading to dose interruption of adagrasib
- Number (%) of participants who had a TEAE leading to dose reduction of adagrasib
- Number (%) of participants who had a TEAE leading to discontinuation of adagrasib
- Number (%) of participants who had any fatal TEAEs

The following summaries will be produced by MedDRA term (if 10 or fewer participants appear in a table, a listing may be appropriate):

- Summary of TEAEs by MedDRA SOC and PT
- Summary of TEAEs by MedDRA PT in decreasing order of frequency

9.3. Clinical Laboratory Tests

Laboratory values and change from baseline values will be listed by visit for hematology, chemistry, coagulation, and endocrine. Baseline will be determined according to Section 4.1.3. If there are multiple values that meet the criteria for baseline, additional rules may be provided after consultation with the medical monitor to delineate which value will be defined as baseline.

Laboratory test values will be assessed for severity based on the numerical component of CTCAE v5.0.

Any laboratory test results and associated normal ranges from local laboratories will be converted to SI units. For the limited number of cases for which the associated normal ranges from a local laboratory cannot be obtained despite due diligence, a set of standard normal ranges based on documented reference ranges will be applied to facilitate reporting the test results.

9.4. Vital Signs

Values at each scheduled visit, change, and percentage change from baseline for vital signs, including systolic blood pressure, diastolic blood pressure, pulse, temperature, respiratory rate, and weight will be listed.

9.5. Electrocardiograms

Twelve-lead ECGs including PR, RR, QT, QRS, QTcB, and QTcF intervals will be obtained for each participant at different study visits and timepoints during the study. Values at each scheduled visit and timepoint, change, and percentage change from baseline will be listed. If there are multiple values recorded for a parameter at the same visit timepoint (eg, triplicate ECG), the average will be the analysis value for that visit timepoint. Baseline will be determined as the average of all nonmissing values, including those from unscheduled visits, before the first administration of INCB099280 or adagrasib.

10. INTERIM ANALYSES

10.1. Overview of Interim Analyses

In Part 1, dose-escalation decisions from the hybrid design based on the available data will be made before the end of the study. In other words, after each dose-level cohort in the dose-escalation procedure, the next dose level will be chosen depending on the observed accumulated data.

11. CHANGES AND MODIFICATIONS TO THE ANALYSIS PLAN

All versions of the SAP are listed in Table 5.

Table 5: Statistical Analysis Plan Versions

SAP Version	Date
Original	26 JUN 2025

11.1. Changes to Protocol-Defined Analyses

[redacted]

11.2. Changes to the Statistical Analysis Plan

Not applicable.

12. REFERENCES

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics 1982;38:29-41.

Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26:404-413.

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-247.

Food and Drug Administration. Guidance for Industry: Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics. 2015.

Food and Drug Administration. Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. 2018.

Klein JP, Moeschberger ML. Survival analysis: techniques for censored and truncated data. New York: Springer-Verlag. 1997.

Liao JJZ, Z Zhou F, Zhou H, Petruzzelli L, Hou K, Asatiani E. A hybrid design for dose-finding oncology clinical trials. Int J Cancer 2022;151:1602-1610.

APPENDIX A. PLANNED TABLES AND LISTINGS