Protocol Title:	A Phase 1/2 Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of SNDX-5613 in Patients with Colorectal Cancer and Other Solid Tumors
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REVISION HISTORY

Version/Date	Section	Changes implemented
V1/15Mar2023	**The original version**	
V2/18Oct2024	Cover Page	Contact information for Study Responsible Physician replaced with those of the current Study Responsible Physician.
	List of Abbreviation	Adding new abbreviations.
	2.1 Primary Endpoints	Modified Phase 1 endpoint from "DCR6" to "DCR" to be aligned with the protocol.
	3 STATISTICAL HYPOTHESES	Added the primary and secondary hypothesis order for phase 2 based on protocol amendments.
	4 SAMPLE SIZE	Futility boundary for the Phase 1b in CRC patients was removed based on protocol amendment.
	4 SAMPLE SIZE	Revision of assumptions for Phase 1b in patients with CRC based on protocol amendment.
	5 Analysis Population	Revised the population definitions population based on protocol amendment.
	6.3.2 Baseline Characteristics	Baseline variables were updated based on team's comment.
	6.3.5 and 6.3.6 Prior Anti-Cancer treatment/procedures	Revised the contents of tables and listing.
	6.4 and 6.4.1 Administration of Study Drug	Revised Overall duration of exposure and total number of cycles definition.
	6.5 Efficacy Analyses	Updated DCR_6 to DCR according to protocol amendment. Added 'for patients who achieved CR or PR' for DOR analysis. Added 'Both PFS and OS will be tested at one-sided alpha of 0.1.'

Version/Date	Section	Changes implemented
	6.5.2 Analysis of Efficacy Endpoints	Added analyses for target lesions and non-target lesions. A footnote of the confirmation rules for the objective response of PR and CR was added. A swimmer plot was added for the response status in phase 1 patients
	6.5.2.3 Disease Control Rate (DCR)	Clarified the DCR definition and assessment duration.
	6.5.2.4 Progression-free Survival (PFS) 6.5.2.5 Overall Survival (OS)	Censoring rules for the two endpoints were revised. Checking proportional hazards assumptions were added.
	6.6.3 Clinical Laboratory Analysis	A table for liver lab related to Hy's law pattern was added.

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADaM	Analysis Dataset Model
AUC	Area under the plasma concentration versus time curve
$AUC_{0\text{-}inf}$	Area under the plasma concentration versus time curve from time 0 extrapolated to infinity
$AUC_{0\text{-}24}$	Area under the plasma concentration versus time curve from time 0 to 24 hours
$AUC_{0\text{-}t}$	Area under the plasma concentration versus time curve from time 0 to the last measurable concentration
CL/F	Apparent oral clearance
Cmax	Maximum observed concentration
Cmin	Minimum observed concentration
CSR	Clinical Study Report
CR	Complete response
CRC	Colorectal cancer
CT	Computed tomography
ctDNA	Circulating tumor DNA
DCR	Disease Control Rate
DLT	Dose limiting toxicity
DOR	Duration of Response
ECG	Electrocardiogram
ICH	International Council for Harmonisation
ITT	Intention-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institution
OR	Overall Response
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive disease
PFS	Progression free survival
PK	Pharmacokinetic
PR	Partial remission
PT	Preferred Term
RECIST	Response Evaluation Criteria in Solid Tumor
RDI	Relative dose intensity
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model
SOC	System Organ Class
t1/2	Apparent terminal elimination half-life
TEAE	Treatment-emergent adverse events
TID	Three times a day
T_{max}	Time to maximum plasma concentration
TRAE	Treatment-related treatment-emergent adverse event
Vz/F	Apparent volume of distribution during the terminal phase

1 INTRODUCTION

The purpose of this Statistical Analysis (SAP) is to provide detailed descriptions of the statistical methods, data derivations and data displays for study protocol SNDX-5613-0706 "A Phase 1/2 Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of SNDX-5613 in Patients with Colorectal Cancer and Other Solid Tumors" for Clinical Study Report (CSR) analysis.

Any derivations from this SAP will be described and justified in the Clinical Study Report (CSR). The preparation of this SAP has been based on International Council for Harmonisation (ICH) E9 guidelines.

All statistical analyses will be performed using SAS version 9.4[illegible] or later (SAS Institute Inc, Cary NC).

Study objectives and design can be found in Sections 3 and 4 of the Protocol.

2 STUDY ENDPOINTS

2.1 Primary Endpoints

- Phase 1
  - Occurrence of dose limiting toxicities (DLTs)
  - Frequency, duration, and severity of treatment-emergent adverse events (TEAEs), treatment-related TEAEs (TRAEs) and serious adverse events (SAEs)
  - Incidence and shifts of clinically significant clinical laboratory abnormalities
  - Change from baseline in other observations related to safety, including electrocardiogram (ECG) and vital signs
  - Disease control rate (DCR) by investigator assessment
  - Overall response rate (ORR) by investigator assessment
- Phase 2
  - Progression free survival (PFS) by blinded radiographic review

2.2 Secondary Endpoints

- Phase 1
  - PK parameters: maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under the plasma concentration versus time curve (AUC) from time 0 to t (AUC_{0-t}), AUC from time 0 to 24 hours (AUC_{0-24}), apparent oral clearance (CL/F), apparent volume of distribution (Vz/F), and half-life ($t_{1/2}$)
- Phase 2
  - Frequency, duration, and severity of TEAEs, TRAEs, and SAEs
  - Incidence and shifts of clinically significant clinical laboratory abnormalities
  - Change from baseline in other observations related to safety, ECGs and vital signs
  - PK parameters: C_{max}, T_{max}, AUC_{0-t}, AUC_{0-inf}, CL/F, Vz/F, and $t_{1/2}$
  - Overall survival (OS)
  - DCR_6 by both blinded radiographic and investigator assessments
  - ORR by Response Evaluation Criteria in Solid Tumor (RECIST), version 1.1 by both blinded radiographic and investigator assessments
  - Duration of response (DOR) by both blinded radiographic and investigator assessments
  - PFS by investigator assessment

2.3 Exploratory Endpoints

- Phase 1
  - Evaluate changes in circulating tumor DNA

  - PK parameters: C_{max}, T_{max}, AUC_{0-t}, AUC_{0-inf}, CL/F, Vz/F, and $t_{1/2}$ when administered in a tablet formulation compared to a capsule, and under fed and fasted condition
  - The ratio of the population geometric means between the formulations for AUC_{0-inf}, AUC_{o-t}, and C_{max} when administered in a tablet formulation compared to a capsule, and under fed and fasted condition
- Phase 2
  - Evaluate changes in circulating tumor DNA

3 STATISTICAL HYPOTHESES

There is no formal statistical hypothesis testing in Phase 1.

The Phase 2 portion will test the following hypotheses:

Primary hypothesis:

H_0: hazard ratio for PFS (SNDX-5613 versus control) is greater than or equal to 1 versus

H_a: hazard ratio for PFS is less than 1.

Secondary hypothesis:

H_0: hazard ratio for OS (SNDX-5613 versus control) is greater than or equal to 1 versus

H_a: hazard ratio for OS is less than 1.

The secondary hypothesis will only be tested if the primary hypothesis is significant.

4 SAMPLE SIZE

The actual number of patients to be enrolled in Phase 1 is dependent on the number of dose levels at which DLTs are reported and the number of dose levels evaluated in dose escalation. It is anticipated that approximately 56 patients will be enrolled in Phase 1, assuming the following:

- Approximately 36 patients in Phase 1a (assumes three dose escalation cohorts and 12 patients per cohort: six patients during the Rolling 6 dose escalation and six additional solid tumor patients when each dose level is expanded), and
- Approximately 20 patients in the CRC Phase 1b (the total number required to be enrolled in Phase 1b will be 20 patients though this may be reduced by however many eligible CRC patients were enrolled at that dose during Phase 1a),

As the Capsule versus Tablet and Food Effect evaluations will be completed by patients already being enrolled during Phase 1a and Phase 1b, these parts of the trial will not have an impact on the overall sample size.

For Phase 2, 78 PFS events are needed to provide 80% power with a 1-sided alpha of 0.1, assuming SNDX-5613 will improve the treatment effect in PFS from 3 months to 5 months (hazard ratio = 0.6) with 2:1 randomization ratio. One hundred two total patients will be enrolled and followed for 4 months for the PFS analysis.

5 ANALYSIS POPULATION

5.1 Intention-to-treat (ITT) Population

- For phase 1: All patients enrolled who provided the informed consent.
- For Phase 2: All randomized patients.

5.2 DLT-evaluable Population

All patients with data used for implementing the dose-escalation schedule (Phase 1a). These patients will have received 75% of all study drug doses in C1 (ie, the DLT evaluation period) or experienced a DLT during the DLT evaluation period.

5.3 Response Evaluable Population

All treated patients who have at least one post-baseline disease assessment or discontinued treatment due to clinical disease progression.

5.4 Safety Population

Consists of all enrolled patients who received at least 1 dose of study drug during the study.

5.5 Pharmacokinetic Population

All patients who receive at least one dose SNDX-5613 and have at least one valid plasma concentration of SNDX-5613 determined.

5.6 Food Effect Population

All patients who receive SNDX-5613 under fed and fasted conditions and have sufficient PK data to calculate Cmax, AUC0-t, and AUC0-inf following both conditions.

5.7 Tablet-to-Capsule

All patients who receive the tablet and capsule formulation of SNDX-5613 and have sufficient PK data to calculate Cmax and AUC0-6 following both conditions.

5.8 Pharmacodynamic Population

Patients who are exposed to SNDX-5613 and have sufficient samples collected to permit pharmacodynamic analyses.

6 STATISTICAL METHODS

6.1 General Statistical Conventions

Summary statistics for demographics, baseline characteristics, exposure, efficacy, and safety will be presented by study phase (Phase 1a, Phase 1b and Phase 2), by dose level in Phase 1a and by arm in Phase 2.

Continuous variables will be summarized using number of observations, mean, standard deviation, median, minimum and maximum. All mean, median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value. The minimum and maximum will be displayed to the same number of decimal places as the original data.

Categorical variables will be summarized using number (n) and percentage of non-missing values in each category.

Time-to-event data will be analyzed using the Kaplan-Meier method and results will be summarized by 25th, 50th (median) and 75th percentiles with associated 2-sided 95% confidence interval, as well as the percentage of censored observations.

Confidence interval (CIs) will be presented as 2-sided 95% CIs unless specified differently in specific analysis.

Unless otherwise noted, baseline is defined as the last non-missing value recorded prior to the first dose of trial drug.

All patients' data will be presented in individual patient data listing. In general, no imputed dates or values will be presented in listings unless specified.

6.2 Patient Disposition

The number of patients included in each analysis set will be summarized. The reason for exclusions from analysis sets will be listed. Primary reason for discontinuation will be summarized for patients discontinuing from study treatment and/or withdrawing from study participation. A listing of patient disposition will also be provided. Safety Population will be used for Phase 1 and ITT population will be used for Phase 2.

6.3 Demographics and Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be tabulated. Listings will also be provided. Safety Population will be used for Phase 1. The ITT population and safety population will be used in Phase 2.

6.3.1 Demographics

Demographic characteristics including age, sex, race, ethnicity, height, weight, and BMI will be summarized descriptively.

6.3.2 Baseline Characteristics

Baseline characteristics may be summarized descriptively including:

- Time from date of metastatic diagnosis to date of first dose (phase 1), or to the date of randomization (phase 2),
- Best response to last systemic anticancer therapy
- Prior anticancer treatment (Yes/No): anticancer surgery, radiation treatment, systemic anticancer treatment
- Prior treatment (Yes/No): bevacizumab, anti-EGFR, oxaliplatin, irinotecan, or other agents (regorafenib/lonsurf/fruguitinib, etc.)
- Number of prior regimens
- Disease status at screening (local advanced/metastases)
- Line of therapy
- Type of cancer
- ECOG
- ctDNA
- For CRC patients, microsatellite status (high, stable, low or unknown) and KRAS status (wild type, mutant or unknown)

Time from date of initial diagnosis to date of first dose (Phase 1)/date of randomization (Phase 2) = (Date of first dose or randomization – date of the first disease diagnosis + 1)/30.4375

6.3.3 Medical History

Medical history from the Medical History eCRF page will be coded with medical dictionary for regulatory activities (MedDRA) version 23.0 or above. All medical history will be listed and the number and percentage of patients with any medical history will be summarized for the Safety Population by primary system organ class (SOC) and preferred term (PT).

6.3.4 Prior and Concomitant Medications

Incomplete medications start and stop dates will be imputed as detailed in Section 6.10.2. Medications used in this study will be coded by the latest available version of the World Health Organization Drug Dictionary Enhanced (Enhanced 2019 March version, or higher).

Prior medications: A medication that stops prior to the date and time of first dose of study medication.

Concomitant medications: A medication that is ongoing at the start of study medication or starts on or after the time of the first study drug dose through 30 days after the last dose of the study drug.

If a medication starts before the date of first dose of study medication and is ongoing at the date of first dose of study medication, then the medication will be counted as both a prior and a concomitant medication.

If medication start and/or stop dates are missing, the dates will be compared as far as possible with the date of first dose of study medication. A medication will be assumed to be prior unless there is clear evidence to suggest that the medication started after the first dose of study medication. A medication will be assumed to be concomitant unless there is clear evidence to suggest that the medication stopped prior to the first dose of study medication. Prior and Concomitant medications will be summarized for the Safety Population by anatomical therapeutic chemical (ATC) level 2 and preferred term.

Listing for medications data will be produced for Safety Population.

6.3.5 Prior Systemic Anti-Cancer Treatments

The prior anti-cancer treatments will be summarized for the safety population. Prior regimens will be tabulated. Number of subjects with prior anti-cancer treatments, lines of prior anti-cancer treatments, time from last prior anti-cancer treatment to the first dose date or randomization date, best response to the last prior anti-cancer therapy before the first dose will be summarized for patients in safety population.

Listings will be presented for the patients with prior systemic anti-cancer treatments.

6.3.6 Prior Anti-Cancer Procedures (Radiotherapy and Anti-Cancer Surgery).

Number of subjects with prior radiation therapy and best response to the last prior radiation therapy before the first dose will be summarized for patients in safety population,

Patients having at least one prior surgery will be summarized for prior anti-cancer surgery in safety population.

Listings will be presented for the patients with prior anti-cancer radiotherapy and surgery, respectively.

6.4 STUDY TREATMENTS AND EXTENT OF EXPOSURE

Summary of exposure data and dose modifications will be presented for the safety population.

Listing of dose modifications and reasons will be presented.

6.4.1 Administration of Study Drug

The following parameters will be summarized for SNDX-5613, Lonsurf® and Stivarga® (Phase 2) separately:

- Overall duration of exposure (weeks)
- Total number of cycles started
- Cumulative administered dose
- Relative dose intensity (RDI)

Overall duration of exposure (weeks) = (Date of last administration of study drug – Date of first administration of study drug) + 1)/7

The total number of cycles started and the total number of cycles initiated by category >=1, >=2, >=3, so on) will be tabulated for each patient and summarized.

Actual cumulative administered dose = Sum of actual dose taken for each dosing day during the whole treatment period.

Assigned cumulative dose = Sum of assigned dose for each dosing day during the whole treatment period.

Relative dose intensity = (Actual cumulative administered dose / Assigned cumulative dose) * 100%

The exposure for Lonsurf® and Stivarga® (Phase 2) will be summarized separately.

6.4.2 Modification of Study Drug

The number and proportion of patients with 1 or more dose modifications will be tabulated along with the reason of the modification.

6.5 Efficacy Analyses

For Phase 1, efficacy analyses will be conducted in the response evaluable population and will be descriptive and graphical in nature. No formal statistical hypothesis testing will be performed. The point estimates and 95% exact binomial confidence intervals will be provided for ORR and DCR. DOR will be summarized using Kaplan-Meier method for patients who achieved confirmed CR or PR. The Phase 1 efficacy analyses may be repeated for the CRC subgroup.

For phase 2, efficacy analyses will use the ITT population. The efficacy analyses will be based on the arm that patients were randomized to. PFS and OS will be tested in a sequential fashion. If the treatment effect in PFS is statistically significant, the treatment effect in OS will be tested. Both PFS and OS will be tested at one-sided alpha of 0.1.

6.5.1 Analysis Methods

6.5.1.1 Analysis of Time-to-Event Endpoints

Time-to-event endpoints will be summarized using the Kaplan-Meier method and displayed graphically when appropriate. Estimated survival rate at 6, 12 and 24 months and median survival times with 2-sided 95% confidence intervals will also be provided when appropriate. Log-rank test will be used to test PFS and OS effects between arms in Phase 2.

6.5.1.2 Analysis of Binary Endpoints

The rates of binary endpoints will be provided along with the corresponding 2-sided confidence intervals using an exact method. Stratified Cochran-Mantel-Haenszel test will be used to test ORR and DCR_6 in Phase 2.

6.5.2 Analysis of Efficacy Endpoints

Disease assessments will be performed, and disease response assessed, every 8 weeks according to the standardized criteria RECIST v1.1. In Phase 1 and Phase 2, responses will be assessed by the site investigators for the purpose of treatment decision making, in phase 2, assessments will be confirmed by blinded radiographic review. Unless specified, responses by investigator review will be utilized for Phase 1 and responses by blinded radiographic review will be utilized for Phase 2. The disease response criteria for target and nontarget lesions can be found in Section 8.1 of the protocol.

In Phase 1, partial or complete responses should be confirmed by a repeat tumor imaging assessment no less than four weeks after the first indication of response, or at the next scheduled scan, whichever is clinically indicated. The confirmation rules for the objective response of PR and CR can be found in the table below:

Earlier Response (to be confirmed)	Later Response (confirmation)	Confirmed Response
CR	CR	CR
CR	SD or missing	SD provided minimum criteria for SD duration met, otherwise, PD[a]
PR	CR or PR	PR
PR	SD	SD
PR	PD or missing	SD provided minimum criteria for SD duration met, otherwise, PD[a]

a. Best response would depend on whether minimum duration for SD, which is defined as 6 weeks from date of first dose, was met.

Target lesions, non-target lesions and response status, sum of all target lesion diameters (mm) by investigator, non-target lesions response by investigator, initial appearance of new lesions by investigator at each timepoint, change and percent change from baseline of sum of all target lesion diameters (mm) by investigator will be listed for Phase 1.

The maximum of % change from baseline in the sum of all target lesion diameters (mm) by the investigator and by best overall response category will be presented in a waterfall plot for Phase 1. The % change from baseline in the sum of all target lesion diameters (mm) over time by the investigator and by best overall response category will be presented in a spider plot for Phase 1. A swimmer plot will be presented for Phase 1 response evaluable population.

6.5.2.1 Best Overall Response (BOR)

The patient incidence of best response (CR, PR, SD, PD, NE) per investigator review will be tabulated for Phase 1 response evaluable population. For Phase 2, BOR per blinded radiographic review will be tabulated for the ITT population. The disease response after the subsequent new anti-cancer therapy will not be included as the response to the study treatment.

6.5.2.2 Overall Response Rate (ORR)

The ORR is defined as the proportion of patients who achieved best overall response of PR or CR. 95% CI will be generated using the exact method.

6.5.2.3 Disease Control Rate (DCR)

For Phase 1 the DCR is defined as the proportion of patients with objective evidence of confirmed CR, confirmed PR, or SD.

6.5.2.4 Progression-free Survival (PFS)

PFS is defined as the time from the first dosing date for Phase 1 patients or randomization date for Phase 2 patients to the first documented progression or death due to any cause, whichever occurs first. The censoring rules are summarized in the table below:

Scenario	End Date	Outcome
Documented PD	Date of the first assessment that determined PD	PFS event
Death during the study in absence of PD	Date of death	PFS event
Without PD or death or new anticancer treatment as of data cut-off	Date of last tumor assessment	Censored
Without PD or death or new anticancer treatment, and no post baseline tumor assessments	Date of first dose for Phase 1/Date of randomization for Phase 2	Censored
New anticancer treatment started before PD or death if any, or new anticancer treatment without PD or death.	Date of last tumor assessment before start of new treatment	Censored
Death or PD after two or more missed tumor assessments	Date of the last tumor assessment before missed assessments	Censored
No baseline or unreadable baseline assessment but readable post baseline assessments	Date of first dose/Date of randomization	Censored

In Phase 1, PFS will be summarized using the Kaplan-Meier method and displayed graphically. In Phase 2, PFS will be analyzed using log-rank test for generation of the p-value. The hazard ratio (HR) and its confidence interval will be estimated from a Cox proportional hazards model and the CI calculated using a profile likelihood approach. The proportional hazards assumption will be checked using graphical diagnostics.

The number of patients with an event, number of patients censored, and reason for censoring will be summarized.

Summary statistics based on Kaplan-Meier method will be provided as below:

- Quartiles (25%, 50% and 75%) and 95% CI
- Progression-free survival rate at time points 6, 12 and 24 months.

The Kaplan-Meier curves will be displayed and total number of patients at risk at given points will be also included into the plot.

6.5.2.5 Overall Survival (OS)

OS is defined as the time from the date of first dosing of study treatment (Phase 1) or the date of randomization (Phase 2) to death due to any cause.

OS (months) will be calculated as (Death date – date of first dosing of study treatment [Phase 1] or randomization [Phase 2] + 1)/30.4375 if a patient died by cut-off date, or (date of last known survival follow-up – date of first dosing of study treatment [Phase 1] or randomization [Phase 2]+ 1)/30.4375 when a patient is censored.

OS will be analyzed using log-rank test for generation of the p-value. The hazard ratio (HR) and its confidence interval will be estimated from an unadjusted Cox proportional hazards model and the CI calculated using a profile likelihood approach. The proportional hazards assumption will be checked using graphical diagnostics.

The number of deaths and the reasons for OS censoring (alive, lost-to-follow-up or withdrew consent) will be summarized. The censoring rules are summarized in the table below:

Scenario	End Date	Outcome
Death before data cutoff date for analysis	Date of death	OS event
Alive up through data cutoff date	Last date known to be alive	Censored
Withdrawal of consent or lost to follow-up prior to data cutoff date	Last date known to be alive	Censored

Summary statistics based on Kaplan-Meier method will be provided as below:

- Quartiles (25%, 50% and 75%) and 95% CI
- Event-free survival rate at time points 6, 12 and 24 months.

The Kaplan-Meier curves will be displayed and total number of patients at risk at given points will be also included into the plot.

A table of Overall survival (OS) and Kaplan-Meier Curves will be conducted in phase 2 data as secondary analysis and added to phase 1 analysis as exploratory analysis.

6.5.2.6 Duration of Response (DOR)

DOR is defined as the time from the first documented response (CR or PR) to the first documented objective progressive disease (PD) or death due to any case. DOR will follow the censoring rules of PFS.

Summary statistics based on Kaplan-Meier method will be provided as below:

- Quartiles (25%, 50% and 75%) and 95% CI

6.6 Safety Analyses

All safety analyses will be performed using Safety Population. The safety assessment will be based on AEs, physical examinations, vital signs, Electrocardiograms, clinical safety laboratory assessments data.

The safety analyses involving changes from baseline to a specific time point in safety variables will only include patients from the Safety Population who have data available for both the baseline and time point under consideration unless otherwise specified.

6.6.1 Dose Limiting Toxicity

Toxicities will be assessed by the Investigator using the National Cancer Institution (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0.

The DLT will be summarized using the DLT-evaluable Population. The table will include numbers and percentage of patients with at least one DLT.

6.6.2 Adverse Events

AEs will be coded using the standard Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 or above.

Analyses of AEs will be based on the principle of treatment emergence. Treatment-emergent AEs (TEAEs) are defined as having onset on or after first study drug dosing date or a sign, symptom, or diagnosis that worsens on or after first study drug dosing date and no later than 30 days after the date of last study drug dosing.

TEAEs will be summarized based on the number and percentage of patients experiencing the event by System Organ Class (SOC) and Preferred Term (PT). If a patient experiences multiple AEs under the same PT (SOC), the patient will be counted only once for that PT (SOC).

AEs will be graded by the investigator according to the CTCAE version 5.0. If a patient experiences the same AE more than once with different toxicity grades, then the event with highest severity grade will be used for purpose of incidence tabulations. In addition, AEs with a missing intensity will be presented in the summary table as an intensity category of "Missing".

The causal relationship between the occurrence of an AE and study drug will be judged by the investigator based on his or her clinical judgement. The AE is classified as "Related", "Probably Related", "Possibly Related", "Unlikely Related" and "Not Related". If a patient reports the same AE more than once within that SOC/PT, the AE with strongest relationship to study medication will be used in the corresponding relationship summaries. Relationship would be summarized as "Related" and "Not Related". AEs with investigator indicated drug-event relationship of "Unlikely Related" and "Not Related" are classified as "Not Related" with the study medication, while AEs with investigator indicated drug-event relationship of "Related", "Probably Related" and "Possibly Related" are considered as "Related" with the study medication. TEAEs with a missing relationship to study medication will also be considered as "Related" with study medication.

An overview table (including only TEAEs) will be presented with the number (and percentage) of patients with:

- TEAEs
- Treatment related TEAEs (TRAEs)
- CTCAE grade 3 or higher TEAEs
- CTCAE grade 3 or higher treatment related TEAEs
- Serious AEs (SAEs)
- Treatment related SAEs
- TEAEs with action of study drug modifications (dose decreased, dose delayed, dose skipped)
- TRAEs with action of study drug modifications (dose decreased, dose delayed, dose skipped)
- TEAEs with action of study drug discontinued
- TRAEs with action of study drug discontinued
- TEAEs leading to death

- TRAEs leading to death
- AEs of special interest (AESIs)

The incidence rate for all TEAEs will also be summarized as below:

- TEAEs by SOC, PT
- TEAEs by PT
- CTC grade 3 or higher TEAEs by SOC, PT
- CTC grade 3 or higher TEAEs by PT and CTCAE grade
- Treatment related TEAEs by SOC, PT
- Treatment related TEAEs by PT
- CTC grade 3 or higher treatment related TEAEs by SOC, PT
- CTC grade 3 or higher treatment related TEAEs by PT and CTCAE grade
- Serious TEAEs by SOC, PT
- Serious TEAEs by PT
- Treatment Related Serious TEAEs by SOC, PT
- Treatment Related Serious TEAEs by PT
- TEAEs leading to drug modification (dose decreased, dose delayed, dose skipped) by PT
- TRAEs leading to drug modification (dose decreased, dose delayed, dose skipped) by PT
- TEAEs leading to study drug discontinuation by PT
- TRAEs leading to study drug discontinuation by PT
- TEAEs leading to death by PT
- TRAE leading to death by PT
- AESI

Listings will be provided as below:

- AEs
- AEs leading to death
- Serious AEs
- AEs leading to dose interruption, reduction and/or discontinuation
- AESI
- Death

6.6.3 Clinical Laboratory Analysis

Hematology and serum chemistries results including the change from baseline will be summarized in a descriptive manner.

Directional shifts in laboratory toxicity grades to compare baseline grade with worst post-baseline grade will be analyzed using standard shift tables, presenting number and proportion of patients and their maximum grade shift. For some specific parameters with CTCAE grading in both high and low direction, CTCAE in high and low directions will be presented separately.

For analytes without a toxicity grading scale, the shift table will present directional shifts from baseline to above or below the laboratory standard normal range using the maximum increase and/or decrease observed throughout the course of treatment.

In addition to the high and low quantitative laboratory assignments, safety laboratory assessments will also be evaluated as normal/abnormal, not clinically significant (NCS)/abnormal, clinically significant (CS) by investigator.

The following summary table will be produced for lab tests:

- Shift table from baseline to worst post-baseline value according to abnormality assessed by investigators (normal, NCS and CS)

For all the shift tables, values from post-baseline unscheduled visit will be considered when derive worst post-baseline value.

Summary of liver laboratory parameters related to potential Hy's law pattern will be provided.

6.6.4 Vital Signs

Vital sign assessments are performed to characterize basic body function. The following vital signs parameters will be reported for this study

- Systolic Blood Pressure
- Diastolic Blood Pressure
- Pulse
- Respiratory Rate
- Oxygen Saturation
- Temperature

Descriptive statistics of actual value and change from baseline will be presented each scheduled visit for each parameter. Maximum and minimum post-baseline value and change from baseline will be also presented. Values from post-baseline unscheduled visits will be considered when deriving maximum and minimum post-baseline value.

6.6.5 Physical Examinations

A complete physical examination will be conducted for all patients during Screening and at the Safety Follow-up visit. The complete physical examination is to be performed per institutional practice and should include general appearance, head/ears/eyes/nose/throat, lungs/chest, heart, abdomen, lymph nodes, musculoskeletal, extremities, and neurological examinations. Physical examination assessments will be listed for each patient.

6.6.6 Electrocardiograms

All ECGs are to be done in triplicate with each separated by 2 minutes. QTc will be calculated using Fridericia's correction: QTcF Interval (msec) = $QT/(RR^{0.33})$ where RR = 60 / heart rate (bpm). The average of the 3 ECGs will be used to calculate QTcF.

The following summarizes will be provided for ECG data:

- Descriptive statistics for the actual values and changes from baseline in ECGs will be tabulated by time point
- A categorical analysis of maximum QTcF and maximum changes from baseline will be performed by summarizing the number and percentage of patients in each QTcF category (< 450 msec, 450 – 480 msec, 481 – 500 msec, and >= 501 msec) and in categories of change from baseline (> 30 msec and > 60 msec).

All ECG findings include ECG abnormalities for each patient will be presented in a listing.

6.7 Pharmacokinetic Analysis

Plasma concentrations of SNDX-5613 will be determined with a validated bioanalytical assay. The following parameters will be derived by conventional non-compartmental analysis when sufficient data are available:

$AUC_{0\text{-}inf}$	Area under the plasma concentration versus time curve from time 0 extrapolated to infinity.
$AUC_{0\text{-}t}$	Area under the plasma concentration versus time curve from time 0 to the last measurable concentration.
$AUC_{0\text{-}24}$	Area under the plasma concentration versus time curve from time 0 to 24 hours, estimated as three times $AUC_{0\text{-}t}$ with TID dosing
C_{max}	Maximum observed concentration
T_{max}	Time to maximum observed concentration
$T_{1/2}$	Apparent terminal elimination half-life (whenever possible).
CL/F	Apparent oral clearance
Vz/F	Apparent volume of distribution during the terminal phase

Details of any additional PK analyses will be provided in a separate PK SAP.

6.7.1 Food Effect Analyses

The food effect analysis planned for this study is a mixed effect model with treatment (fed or fasted) as fixed effects and subject within treatment sequence as a random effect. Natural log (ln) transformed PK parameters ($AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and C_{max}) will be calculated and used as the response variable in the model. Least squared (LS) means and the difference between treatment LS means, as well as their corresponding 90% confidence intervals will be computed from the model. The geometric mean ratios and their 90% CIs of the PK parameter for each treatment comparison will be constructed using the exponentiation of the difference and the CIs from the mixed effect model. The comparison of interest is fed compared with fasted.

6.7.2 Tablet-to-Capsule Analyses

The tablet versus capsule analysis planned for this study is a mixed effect model with treatment (tablet or capsule) as fixed effects and subject within treatment sequence as a random effect. Natural log (ln) transformed PK parameters ($AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and C_{max}) will be calculated and used as the response variable in the model. Least squared (LS) means and the difference between treatment LS means, as well as their corresponding 90% confidence intervals will be computed from the model. The geometric mean ratios and their 90% CIs of the PK parameter for each treatment comparison will be constructed using the exponentiation of the difference and the CIs from the mixed effect model. The comparison of interest is tablet compared with capsule.

6.8 Pharmacodynamics Analysis

Continuous summary (absolute and change from baseline) of all the pharmacodynamics assessments will be presented at all scheduled visits and time point per protocol.

Pharmacodynamics assessments will also be presented for each patient in a data listing. Actual sampling time points will be displayed for the assessments.

Based on data availability pharmacodynamic, and biomarker exploratory analyses will be described in a separate analysis plan and presented in a separate report.

6.9 Interim Analysis

No formal interim analysis is planned in this study.

Analyses may be performed before the final analysis to support regulatory interactions for SNDX-5613, for example, NDA submissions and safety update.

6.10 Handling of Missing Data and Outliers

6.10.1 Missing Data Analysis Methods

Missing data will not be imputed in listings. The listings will only present the data recorded on the original Case Report Form.

6.10.2 Handling of Missing or Incomplete Dates

Initial disease diagnosis date

Partial date of initial disease diagnosis will be imputed as below:

- If year is missing (or completely missing), do not impute
- 15th of the month will be used to impute the initial diagnosis date if only the day is missing
- June 15th of the year will be used to impute as the initial diagnosis date if both the day and the month are missing

The imputed date will be compared to reference start date (i.e. enrolled date). If it is later than the reference start date, the reference start date will be used to impute the incomplete date.

AE start and stop date

If the imputed stop date is before the AE start date then the imputed stop date will be equal to the start date.

Partial Missing Start or Stop Date	Imputed Start Date	Imputed Stop Date
Missing DAY, but YEAR and MONTH are present	• If the year and month are the same as the year and month of first dose date and full or partial AE stop date is not before the first dose date or AE stop date is missing, impute the AE start day as the day of first dose date • Otherwise, impute the AE start day as 1	• If the month and year of the partial stop date are the same as the month and year of the last dose date of study medication, then the day of the last dose date will be assigned to the missing day • If the month and year of the partial stop date are before the month and year of the last dose date of study medication, then the last day of month will be assigned to the missing day • If the month and year of the partial stop date are after the month and year of the last dose date of study medication, then the

		first day of the month will be assigned to the missing day
Missing DAY and MONTH, and the YEAR is present	• If the year is the same as the year of first dose date and full or partial AE stop date is not before the first dose date or AE stop date is missing, impute the AE start month and day as the month and day of first dose date • Otherwise, impute the AE start month as January and the day as 1	• If the year of the partial stop date is the same as the year of the last dose date of study medication, then the day and month of the last dose date will be assigned to the missing fields • If the year of the partial stop date is prior to the year of the last dose date of study medication, then December 31 will be assigned to the missing fields • If the year of the partial stop date is after the year of the last dose date of study medication, then January 1 will be assigned to the missing field
YEAR missing	If the year of AE start date is missing or AE start date is completely missing, then query site with no imputation. Also compare the partial AE stop date to the first dose date. If the AE stop date is before the first dose date, then the AE should be considered as pre-treatment AE. Otherwise, the AE will be considered as TEAE	No imputation

Medication start and stop date

Missing or partial medication start date:

- If only DAY is missing, use the first day of the month
- If DAY and MONTH are both missing, use a date/month before the first dose date/month or medication stop date/month whichever is earlier, or use June 15th of the year if both the reference date/month are missing
- If DAY, MONTH and YEAR are all missing, use the date/month/year before the first dose date/month/year or medication stop date/month/year whichever is earlier

Missing or partial medication stop date:

- If only DAY is missing, use the last day of the month
- If DAY and MONTH are both missing, use the last day of the year
- If DAY, MONTH and YEAR are all missing, assign "continuing" status to stop date

7 CHANGES TO PLANNED ANALYSIS FROM STUDY PROTOCOL

8 REFERENCES

9 APPENDICES

SNDX-5613-0706 SAP_V2_21Apr2025

Final Audit Report 2025-04-22

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By:	[redacted]
Status:	Signed
Transaction ID:	CBJCHBCAABAASE75I7LoBvppJxQ6taKv-49zyahqV-EU

"SNDX-5613-0706 SAP_V2_21Apr2025" History

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Document emailed to [redacted] for signature
2025-04-21 - 7:58:11 PM GMT

Email viewed by [redacted]
2025-04-21 - 7:58:13 PM GMT- IP address: [redacted]

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Challenge: The user opened the agreement.
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2025-04-22 - 5:42:10 PM GMT

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[redacted] authenticated with Adobe Acrobat Sign.

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Signing reason: I am an approver.

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