# Statistical Analysis Plan

# (SAP)

## -Part 1 & Part 2-

**Scheme Number: BG02-2101**

# Phase I/II Clinical Study on Tolerability and Bioavailability of Utidelone Capsule in Patients with Advanced Solid Tumors

Version: 1.0

Date: 2025-10-11

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# 1. Overview

This statistical analysis planis basedontheprotocol (Protocol No.: BG02-2101), Version 4.0, dated January 22, 2024.

## 1.1. Research Objective

**Primary research objective:**

To evaluate the safety and tolerability of utidelone capsules in patients with advanced solid tumors, and to determine the maximum tolerated dose and dose-limiting toxicities.

To evaluate the objective response rate (ORR) of utidelone capsules in combination with capecitabine for patients with advanced metastatic breast cancer.

**Secondary research objective:**

1) To evaluate the absolute bioavailability of Utedron capsules relative to Utedron injection.

2) To evaluate the pharmacokinetic characteristics of utidelone capsules in patients with advanced solid tumors.

3) To conduct a preliminary evaluation of the efficacy and safety of Utedron capsules in patients with advanced solid tumors.

4) Recommend the dose and dosing regimen for subsequent clinical trials.

5) To evaluate the efficacy, safety, and pharmacokinetic profile of utidelone capsules in combination with capecitabine for patients with advanced metastatic breast cancer.

## 1.2. Research Plan

### 1.2.1. Overall Design

This study is a Phase I/II clinical trial. The study design was conducted in strict accordance with the relevant requirements of regulatory documents issued by the NMPA, including the "Good Clinical Practice for Drug Clinical Trials" [1], the "Guiding Principles for the Management of Phase I Clinical Trials of Drugs (Trial)" [2], and the "Technical Guidance Principles for Clinical Pharmacokinetic Studies of Chemical Drugs" [3], to evaluate the tolerability, safety, pharmacokinetic profile, and efficacy of Utedron capsules in patients with advanced solid tumors.

Part 1, the dose-escalation study, is an open-label,single-center design, while Part 2, the pharmacokinetic comparison and dietary impact study, is an open-label, controlled, multicenter design. Detailed trial procedures are outlined in the protocol.

### 1.2.2. Randomization and Blinding

Part 1Dose-Escalation Study:

Randomization is not performed. During screening, participants are identified by a screening number, formatted as S + trial number + center number+ a three-digit Arabic numeral; for Part 1, the trial number is 1, e.g., S11001. Enrollment occurs on Day −1 of the trial, and eligible participants are assigned an enrollment number in ascending order based on their screening number. In this trial, dose levels serve as study arms, and enrollment numbers are designated as trial number + arm number + a two-digit Arabic numeral. For Arm 1, enrollment numbers are 1101, 1102, and so forth; for Arm 2, they are 1201, 1202, and so forth; for Arm 3, they are 1301, 1302, and so forth, and so on.

Part 2: Pharmacokinetic Comparison and Dietary Influence Study:

A randomizationscheme was developed by statisticians, and a participant randomization table (including randomization codes and group assignments) was generated using the PLAN procedure in SAS version 9.4 or later, employing block randomization. The resulting randomization table is reproducible, and the specified random-number seed parameter must be preserved.

During screening, participants are identified by a screening number, formatted as S+ trial number + center number + a three-digit Arabic numeral. For Part 2, the trial number is 2, e.g., S21001. Eligible participants are randomized on Day −1 of the study and assigned to different administration sequence groups, receiving a randomization code. The randomization code is structured as trial number + group identifier + a two-digit Arabic numeral: Group A–B is designated as 2101, 2102, etc.; Group B–A is designated as 2201, 2202, etc.

Prior to the completion of the trial, participants who discontinued due to non-drug-related toxicities—such as missed follow-up visits, errors in the supply of the investigational drug, medical conditions that prevent swallowing, or rapid disease progression—will be replaced. Replacement participants will be assigned new randomization and enrollment numbers in sequential order.

Participants who withdraw from this trial for any reason, if they have not received the investigational product, may be re-screened and, upon meeting eligibility criteria, enrolled in the trial with a new randomization/registration number. Participants who withdraw for reasons other than treatment failure, but who have received the investigational product, will retain their original randomization/registration number and will not be eligible for re-enrollment. Participants who withdraw due to treatment failure will also retain their

randomization/registration number; after a 3-month washout period, if they continue to meet the inclusion criteria and do not meet the exclusion criteria, they may be enrolled in the high-dose cohort following renewed informed consent, receiving a new registration number. Each participant may participate in no more than two dose-group cohorts.

This trial is an open-label study. Investigators, project managers, monitors, bioanalytical assay personnel, and data management and statistical analysis staff will all be unblinded.

### 1.3. Administration of medication

**Part 1: Dose-Escalation Study**

Ineachcycle, thedrug is administered once dailyfor 5 consecutivedays; in the dose group receiving treatment for 7 consecutive days per cycle, a 21-day period constitutes one treatment cycle.

**Part 2: Pharmacokinetic Comparison and Dietary Influence Study**

**Pharm**acokinetic Comparison: The 18eligible participants were randomly assigned in a1:1ratio to one of two administration sequences (Group A–B or Group B–A). During Cycle 0, the nine participants in Group A–B received oral ucedron capsules under fasting conditions, while the nine participants in Group B–A received intravenous infusion of ucedron injection, with a single dose administered and a 7-day washout period. On Day 8, Cycle 1 commenced: participants in Group A–B received intravenous infusion of ucedron injection, whereas those in Group B–A took oral ucedron capsules under fasting conditions, with once-daily dosing for 5 consecutive days followed by a 16-day observation period without treatment.

**Dieta**ry influence: On Day 29, participants entered Cycle 2. On Day 29, both groups received an oral dose of ublituzumab capsules after a high-fat meal; from Days 30 to 33, they took ublituzumab capsules on an empty stomach, with once-daily dosing for 5 consecutive days, followed by a 16-day observation period without medication.

**Post-t**reatment phase: After the participant has completed treatment and assessments for Cycle 0, Cycle 1, and Cycle 2 as described above, and provided the investigator determines that continued treatment would be beneficial, the participant may remain on the original regimen. Patients initially receiving Utedron injection may cross over to Utedron capsules during the post-treatment phase, continuing until disease progression, the occurrence of intolerable adverse events, voluntary withdrawal by the participant, or a decision by the investigator to discontinue the study drug.

**Administration conditions:**

During Cycles 0 and 1, all patients received an intramuscular or oral dose of 40 mg diphenhydramine 30–60 minutes prior to administration of utidelone injection, alongwith an intravenous bolus of 10 mg dexamethasone and either 300–400 mg cimetidine or 50 mg ranitidine as premedication. On the following day, depending on the patient's condition, the doses of dexamethasone and diphenhydramine could be halved or omitted. When administering utidelone capsules, participants took the medication in a fasted state (fasting for 2 hours before dosing and 1 hour after dosing), swallowing each capsule with one glass (approximately 240 mL) of warm water.

During the follow-up treatment phase, there are no special dietary requirements.

# 2. Endpoint indicator

## 2.1. Primary endpoint

Maximumtolerated dose (MTD), dose-limiting toxicity (DLT), and the objective response rate (ORR) of utidelone capsules in combination with capecitabine for patients with advanced metastatic breast cancer.

## 2.2. Secondary endpoint

1）The absolute bioavailability of Utedron capsules relative to Utedron injection is: F.

2）Pharmacokinetic parameters:

- $C_{max}$,$T_{max}$,$AU_{C0–}$t, $A_{UCi}$nf,$\lambda z,_{t}$1/2,$C_L$, Vd, etc.;
- $C_{max,ss}$,$AU_{C0\text{-}t,s}$s, $A_{UCinf,}$ss, $A_{UC0\text{-}\tau,}$ss, $A_{UC_\%Ext}$ra$_p$,$\lambda_{z,\ T}$1/2$_{z,}$CLs$_s$/F,$V_{z/F,\ C}$mi$_{n,ss,}$Cav,ss, and others.
- Urinary drug excretion: the product of the drug concentration in urine and the total urine volume for each time interval.
- Cumulative urinary excretion rate: the ratio of the cumulative amount of drug excreted in urine to the administered dose.
- Fecal drug excretion: the product of the fecal drug concentration at each time point and the total fecal weight.
- Cumulative fecal drug excretion rate: the ratio of the cumulative amount of drug excreted in feces to the administered dose.

3）Efficacy and safety outcomes of Utedron capsules in patients with advanced solid tumors:

- Efficacyevaluation criteria (RECIST1.1 objective response assessment): objective response rate (ORR);
- Safety assessment endpoints: vitalsigns, physical examination, laboratory tests,

electrocardiogram, ECOG performance status, adverse events, and serious adverse events.

4）Efficacy, safety, and pharmacokinetic characteristics of utidelone capsules in combination with capecitabine for the treatment of patients with advanced metastatic breast cancer:

- Progression-free survival (PFS): assessed according to RECIST 1.1 criteria;
- Disease Control Rate (DCR): assessed according to RECIST 1.1 criteria;
- Duration of Response (DoR): assessed according to RECIST 1.1 criteria;
- Safety endpoints: vital signs, physical examination, laboratory tests,ECOG performance status, adverse events (AEs), and serious adverse events (SAEs), among others. Adverse events were graded according to the NCI-CTCAE v5.0 criteria.

## 3. Sample size

Part 1is a dose-escalationstudy,planned to include at least three dose cohorts, with 14–26 participants enrolled.

Part 2consists of a pharmacokinetic comparison and a dietary impact study, with both an experimental group and a control group; a total of 18 participants are planned for enrollment.

## 4. Analysis Set

**Full Analysis Set (FAS):** The FAS comprises all participants who were enrolled and received at least one dose of the investigational product. In accordance with the intention-to-treat principle, analyses are performed based on the treatment assigned to each participant at the time of enrollment.

**Per Protocol Set (PPS):** This refers to the efficacy analysis set, which includes all participants who were enrolled, received at least two cycles of the investigational medicinal product, had measurable lesions according to RECIST 1.1 at baseline, and provided at least one post-dose efficacy assessment, while excluding any participants with significant protocol deviations that could affect the efficacy endpoints.

**Safety Set (SS):** All participants who have received at least one dose of the investigational product and for whom safety data are available following administration of the investigational product. Safety analyses are conducted based on the actual treatment received.

**DLTAnalysis Set (DLTS):** All enrolled participants who 1) completed Part 1 Cycle1 treatment and follow-upassessments with medication adherence of atleast 80% of the planned dose; or 2) discontinued or had their treatment interrupted during Part 1 Cycle 1 due to an adverse event related to the investigational drug, even if they did not complete all scheduled

follow-up visits for Part 1 Cycle 1 or had medication adherence below 80%. Only safety data from Part 1 Cycle 1 will be evaluated.

**Blood Pharmacokinetics Concentration Set (BPKCS):** All participants who were enrolled and received at least one dose of the investigational drug, and who had at least one valid post-dose blood concentration measurement during the study. Situations that may preclude inclusion in the pharmacokinetic analysis include: a) factors present during the study that could significantly affect PK concentration measurements; b) pre-dose concentrations exceeding 5% of the Cmax.

**Urinary Pharmacokinetics Concentration Set (UPKCS):** All participants who were enrolled and received at least one dose of theinvestigational drug, and who had at least one valid post-dose urinary drug concentration measurement during the study. Situations that may preclude inclusion in the urinary drug concentration analysis include: a) the presence of factors during the study that significantly interfere with PK concentration measurements.

**Feces Pharmacokinetics Concentration Set (FPKCS):** All participants who were enrolled and received at least one dose of the investigational drug, and who had at least one valid post-dose fecal drug concentration measurement during the study period. Exclusions from fecal drug concentration analysis include: a) any factors during the study that clearly interfere with the measurement of PK concentrations.

**Pharmacokinetics Parameter Set (PKPS):** All participants who were enrolled andreceived at least one dose of the investigational drug, with at least one valid PK parameter during the study period. Situations that maybe excluded from pharmacokinetic parameter analysis include: a) violations ofthe protocol's dosing requirements, such as incorrect blood-sampling times, concomitant use of prohibited medications, or ingestion of foods not specified in the protocol, which could affect PK parameter outcomes or render parameters unestimable; b) pre-dose concentrations exceeding 5% of Cmax; c) loss of three or more consecutive samples in either the absorption or elimination phase, or inability to report such data [if the absorption phase is adequately characterized, absorption-related parameters—such as Cmax and Tmax—will be calculated]; d) the first post-dose sample being Cmax, with no early-time samples (5–15 minutes post-dose) collected; e) extremely low concentrations (AUC0-t less than 5% of the geometric mean AUC0-t observed in other participants receiving the same dose); f) vomiting occurring within twice the median Tmax after administration of the investigational drug; g) errors in sample handling, transport, or storage between sample

collection and completion of bioanalytical testing, which compromise the accuracy of bioanalytical results.

Tolerabilitywill be assessed using the DLTS, safety will be evaluated using the SS, and efficacy will be analyzed using both the FAS and PPS; pharmacokinetic analyses will employ the corresponding datasets. Compliance and baseline characteristics will be analyzed using the FAS.

# 5. Statistical analysis methods

## 5.1. Overall Considerations

Pharmacokinetic parameters wereestimated using the Phoenix WinNonLin software (PharsightCorporation, version 8.2 or later) with a non-compartmental model. Statistical and other analyses were performed using SAS software (version 9.4 or later).

For measurement data, statistical descriptions are provided using counts, means, standard deviations, medians, minimum values, and maximum values;for categorical orordinal data, statistical descriptions are presented as counts and percentages. The minimum and maximum values retain the same number of decimal places as the original data, while the mean, standard deviation, and median are reported with one additional decimal place compared to the raw data. The upper and lower limits of confidence intervals maintain the same number of decimal places as the point estimate, and percentages are rounded to two decimal places. For items that are not applicable, use a hyphen (“–”); for statistics that cannot be estimated, use “NE”.

Baseline isdefined as the lastnon-missing value prior to the first dose in each treatment period; relative changefrom baseline = each visitvalue minus the baseline value; when summarizing analyses by visit, unscheduled visits are excluded; for clinical significance assessments using contingency tables, unscheduled visits are included, and the worst-case scenario following dosing is analyzed—defined as the most severe outcome in terms of clinical significance, with “abnormal with clinical significance” being more severe than “abnormal without clinical significance,” which in turn is more severe than “normal.”

**Early dropout and missing data**

**<u>Imputation of Missing Dates in AE</u>**

Themissing datesfor AEs are imputed as follows: this imputation is used solely for AE classification, and the original unimputed dates remain displayed when generating the AE-related data list.

- The AE start date is missing.

1) If the year and month are known and the year-month is earlier than the date of the first administration of the investigational drug, the last day of the known month shall be used for imputation.

2) If the year and month are knownand the year–month correspondsto the date of the first administration of the investigational drug, then set the AE onset date to the date of the first administration of the investigational drug (where “date” refers to “month day”).

3) If the year and month are known and the year-month is later than the date of the first administration of the investigational drug, the first day of the known month shall be used for imputation.

4) If only the year is known anditprecedes the year of the first administration of the investigational drug, “December 31” shall be used for imputation.

5) If only the year is known and the year equals the year ofthefirst administration of the investigational drug, then set the AE’s onset date to the date of the first administration of the investigational drug (where “date” refers to “month day”).

6) If only the year is known anditislater than the year of the first administration of the investigational drug, “January 1” is used for imputation.

7) If the year, month, and day are all missing, use the date of the first administration of the investigational drug as the corresponding start date.

8) All other cases are considered missing.

- The AE end date is missing.

If the outcome is classified as “recovered with no sequelae,” “recovered with sequelae,” “improved,” or “worsened,” it shall be coded according to the following rules:

1) If the year and month are known, fill in using the last day of the known month.

2) If only the yearis known, use “December 31” as the placeholder.

3) If the date on which the vacancy is filled falls after the following date, it shall be filled in accordance with the rules set forth below:

a. If the participant remains in the study and the imputed date is later than the data cut-off date, imputation shall be performed using the cut-off date.

b. If a participant completes the study or withdraws early, and the imputed date is later than any of the dates listed below, the imputation shall be based on the earliest of those dates:

-28 days after the last dose

-Date of initiation of new anticancer therapy

-Study completion date

-Date of death

4) If the start date of the filled-in period is later than the end date, the end date shall be taken as the corresponding start date.

5) All other cases are considered missing.

If the outcome is “death,” it shall be filled in accordance with the following rules:

1) If the date of death is known, use that date to impute.

2) If the date of death is unknown, impute the last known day of survival.

If the outcomeis “persistent” or “unknown,” the AE end date is considered missing.

**Imputation of missing dates for prior/combined medications**

Themissing dates for prior/combined medications are imputed as follows: imputation of missing dates for prior/combined medications is used solely for the purpose of categorizing such medications; when generating a list of data related to prior/combined medications, the imputed dates remain unreported.

- Previous/Concomitant medication start dates are missing.

1) If the year and month are known, fill in using the first day of the known month.

2) If only the yearis known, use “January 1” as the placeholder.

3) If the year, month, and day are all missing, do not fill them in.

4) All other cases are considered missing.

- Previous/Concomitant medication end dates are missing.

If “No” is selected for the continuity question, the following rules will be applied to impute the missing values:

1) If the year and month are known, fill in using the last day of the known month.

2) If only the yearis known, use “December 31” as the placeholder.

3) If the completion date of the imputation is later than the participant’s study end date or the data cut-off date, the imputation shall be performed according to the following rules:

a. If the participant remains in the study, imputation is performed using the data cut-off date for this analysis.

b. If the participant has completed the study or withdrawn from the study early, use the earliest of the following dates for imputation:

-28 days after the last dose;

-Study completion date;

-Date of death;

-Data cut-off date.

4) If the start date of the filled-in period is later than the end date, the end date shall be taken as the corresponding start date.

5) All other cases are considered missing.

If "Yes" is selected for the continuation status, the end date is treated as missing.

**Filling in missing dates for non-pharmacological treatments**

Fill inmissing dates by referring to the "Previous/Concomitant Medication Date Missing" rule.

**Derivation of laboratory test results**

If the result is ">xxx" or "≥xxx", the numeric value following ">" or "≥" will be included in the analysis.

If the result is "<xxx" or "≤xxx", the numeric value following "<" or "≤" will be extracted for analysis.

If the result is non-numeric—e.g., "not detected" or "below the limit of quantification"—it will be treated as 0 in the analysis.

If outliers are present, they shall be handled in accordance with the method determined during the data blind review meeting.

Part 1and Part 2 are analyzed separately.

**Group:**

Part 1 study: refers to the dose groups consisting of 50 mg/m²/day for 5days, 75 mg/m²/day for 5 days, 65 mg/m²/day for 7 days, 75 mg/m²/day for 7 days, and 85 mg/m²/day for 7 days.

Part 2 Study: For participantdistribution and baselineanalysis, thesequence refers to A–B (fasted: Utedron capsules – Utedron injection) and B–A (fasted: Utedron injection – Utedron capsules);for pharmacokinetic analysis, itrefers to formulation (PK comparison) and dietary state (dietary effect), namely fasted: Utedron capsules vs. Utedron injection, and Utedron capsules (fasted) vs. Utedron capsules (postprandial); for safety analysis, it refers to treatment period (single dose/multiple doses/subsequent treatment period) and formulation, specifically single dose (Cycle 0): Utedron capsules vs. Utedron injection; multiple doses (Cycle 1): Utedron capsules vs. Utedron injection; and Cycle 2 and subsequent treatment periods: Utedron capsules.

## 5.2. Participant distribution

### 5.2.1. Distribution

Provides the number of participants categorized as screened, screened but ineligible, screened and eligible, screened and eligible but not enrolled/randomized, and

enrolled/randomized. Summarized by group (by dose cohort in Part 1 studies and by sequence in Part 2 studies), it reports the number and percentage of participants across each category of administration and reason for treatment discontinuation, as well as the number and percentage of participants included in the FAS, SS, PPS, DLTS, BPKCS, UPKCS, FPKCS, and PKPS sets. Percentages are based on the number of participants who were enrolled/randomized.

#### 5.2.2. Plan deviation

Basedon the FAS, data were summarized by group (bydose cohort in Part 1 and by treatment period and formulation in Part 2), with a summary analysis of protocol deviation categories and subcategories, providing the number of cases, the total number of participants, and the corresponding percentages.

#### 5.2.3. Inclusion/Exclusion Criteria

A list ofdata that do not meet the inclusion/exclusion criteria will be provided.

### 5.3. Demographics and Baseline Characteristics

This section presents an analysisbasedon the FAS, summarized by group (in Part 1, by dose cohort; in Part 2, by sequence).

#### 5.3.1. Demography

Descriptive statistical measures of demographic characteristics are provided. For continuous variables such as age, height, weight, and body mass index, the number of cases, mean, standard deviation, median, minimum, and maximum values are reported. For categorical variables such as sex, age group, ethnicity, and marital status, the number of participants and the percentage for each category are presented.

#### 5.3.2. Baseline characteristics

History of solid tumors, including the primary site ofadvanced solid tumors, the current clinical stage of the tumor, and the initial tumor stage (Stage I, Stage II, Stage IIIA, Stage IIIB, Stage IIIC, Stage III, Stage IVA, Stage IVB, Stage IVC, Stage IV, or other). For each category—presence of metastases (none, bone metastases, brain metastases, or other metastases)—provide the number and percentage of participants.

Provide the number and percentage of participants with a prior history of antitumor (solid tumor) surgery, aprior history of antitumor (solid tumor) pharmacologic therapy (including prior treatment types, lines of therapy, and exposure to taxane-based agents), a prior history of nonpharmacologic antitumor (solid tumor) therapies, a prior surgical history (excluding the study-defined solid tumor), a history of hepatitis B, hepatitis C, HIV, or syphilis infection, an allergy history, a history of alcohol abuse, and a history of drug abuse.

The number and percentage of participants in each category of smoking history are provided.

Themedicalhistory provides the number and percentage of participants in each category, categorized according to SOC and PT.

Pregnancy tests and infectious disease screenings provide only a list of results.

## 5.4. Level of Exposure and Compliance

### 5.4.1. Investigational drug

Basedonthe SS, provide, by group (by dose cohortinPart 1 and by treatment period,formulation, and dietarystatus inPart 2), the number of participants, mean, standard deviation, median, minimum, and maximum for treatment duration, exposure time, and total exposure dose; also report the number and percentage of participants in each exposure-time category (those who received one treatment cycle, those who received two or more cycles).

Based on the FAS, the total planned dose, the total actual dose, and the number of participants with medication adherence are provided, along with their mean, standard deviation, median, minimum, and maximum values. Additionally, the number and percentage of participants falling into each medication-adherence category (<80%, 80%–120%, >120%) are reported.

Total planned dose (mg)=Cumulative planned doses across all cycles (mg); Totalactualdose (mg) = Cumulative actual doses across all cycles (mg); Medication adherence (%) = Total actual dose (mg) / Total planned dose (mg) × 100.

### 5.4.2. Past concomitant medications, past non-pharmacological treatments

Previous concomitant medications were coded using the Chinese version of the WHO Drug Dictionary.

Priorpharmacologic or nonpharmacologic therapies are defined as those that hadbeen discontinued prior to the first administration of the study drug; concomitant pharmacologic or nonpharmacologic therapies are defined as those initiated after the first administration of the study drug or still in use at that time. If the start or end date of a therapy or medication is incomplete and cannot be used to determine whether it qualifies as concomitant, it shall be classified as concomitant.

Basedon the FAS, the number and percentage of participants with prior medication use are provided by group (by dose cohort in Part 1 and by sequence in Part 2), summarized at ATC level 2 and level 4; the number and percentage of participants with prior non-pharmacologic treatment are also reported.

Basedonthe SS, provide the number and percentage of participants receiving concomitant medications, stratified by group (by dose cohort in Part 1 and by treatment period and formulation in Part 2), and summarized according to ATC level 2 and level 4 classifications; also provide the number and percentage of participants receiving non-pharmacologic therapies.

### 5.5. Efficacy Analysis

This section presents an analysisbased on the FAS and PPS, summarized by group (dose cohorts in Part 1; capsule dose cohorts in Part 2).

Effectiveness evaluation indicators:

At baseline, participants must have measurable tumor lesions. Efficacy is assessedaccordingtoRECIST 1.1criteria, with outcomes categorized as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Participants initially classified as CR or PR must undergo confirmatory assessment at least four weeks later.

| First Overall Efficacy | Next overall efficacy | Best Overall Efficacy | |
|---|---|---|---|
| CR | CR | CR | |
| CR | Public Relations | Confirmedas first-ever PR: Best response is PR. | |
| | | Meetthe minimum SD deadline: SD | Does not meet the minimum SD time limit: PD |
| CR | SD | Meetthe minimum SD deadline: SD | Does not meet the minimum SD time limit: PD |
| CR | PD | Meetthe minimum SD deadline: SD | Does not meet the minimum SD time limit: PD |
| CR | NE | Meetthe minimum SD deadline: SD | Does not meet the minimum SD time limit: PD |
| Public Relations | CR | PR | |
| Public Relations | Public Relations | Public Relations | |
| Public Relations | SD | SD | |
| PR | PD | Meetthe minimum SD deadline: SD | Does not meet the minimum SD time limit: PD |
| PR | NE | Meetthe minimum SD deadline: SD | Does not meet the minimum SD time limit: NE |
| NE | NE | NE | |

Note: If the first overall response isCR or PR at the last efficacy assessment, the best overall response is by default considered SD.

To classifythe best overall response as SD, the minimum duration requirement must be met—specifically, at least 6 weeks. If the confirmed assessment period is shorter than this minimum, the originally assigned SD classification should be revised to NE.

• Objective Response Rate (ORR): The proportion of participants achieving a best response of CR or PR, as assessed according to RECIST 1.1 criteria.

• Progression-free survival (PFS): As assessed according to RECIST 1.1 criteria, it is defined as the time from enrollment to the first radiologic evidence of diseaseprogression or death from any cause. If, at the study's cut-off date, the participant has neither experienced

progressive disease nor died, or if they have already initiated another anticancer therapy, the last efficacy assessment performed prior to the cut-off date or the start date of the alternative anticancer treatment—whichever occurs first—will be used as the censoring time. The median PFS (in months*) will be estimated using the Kaplan–Meier method, and a survival curve will be plotted.

**Table 5-1 Censoring Rules**

| Therapeutic efficacy indicators | Data situation | Censoring date |
|---|---|---|
| PFS | Randomized/No tumor assessment after enrollment | Randomization/Enrollment Date |
| PFS,DOR | Alive and without tumor disease progression as of the cutoff date. | Date of the last imaging assessment |
| PFS,DOR | Tumor disease progression or death occurs after two or more consecutive imaging assessments are missing. | Date of the last imaging assessment without progression prior to the first consecutive missing assessment. |
| PFS,DOR | Underwent other anti-tumor therapies prior to tumor disease progression or death. | Date of the last imaging assessment prior to initiation of other antitumor therapies |

• Disease Control Rate (DCR): The proportionof patients achieving a best response of CR, PR, or SD, as assessed according to RECIST 1.1 criteria, relative to the total number of patients.

• Duration of Response (DoR): Assessed according to RECIST 1.1 criteria, defined as the timefrom the first documented attainment of CR or PR (whichever occurs first) to the occurrence of progressive disease (PD) or death. The duration of response is calculated only for patients whose best response was CR or PR. The median DoR (in months*) is estimated using the Kaplan–Meier method, and a survival curve is plotted.

The number and percentage of participants in each category (CR, PR, SD, PD) were reported according to tumor response group; ORR and DCR were described using frequencies and percentages, with 95% confidence intervals calculated.

Create waterfall charts, spider charts, and swimmer charts.

*Note: One month is calculated as 30.4375 days.

### 5.6. Pharmacokinetic analysis

Key PK data-point definitions: For concentrations below the lower limit of quantification (BLQ), BLQ values observed prior to reaching Cmax will be assigneda value of “0”; BLQ values observed after Cmax will be marked as “missing.” When conducting pharmacokinetic concentration summary analyses, the planned sampling times shall be used regardless of

whether the actual sampling times deviate from the schedule. For the calculation of pharmacokinetic parameters, if the actual sampling times differ from the planned times but remain within the maximum allowable deviation, such deviations are considered irrelevant to the pharmacokinetic analysis, and the planned sampling times will continue to be used for parameter estimation; if the deviation exceeds this range, the actual sampling times will be employed for calculating the pharmacokinetic parameters.

This section presents a summary analysis by group: Part 1 analyzes data by dose cohort, while Part 2 examines formulations and dietary conditions, with analyses conducted separately for each investigational drug.

Drug Concentration (c)–Time(t) Data Analysis: Based on BPKCS, UPKCS, and FPKCS, the concentrations of utidelone or capecitabine in blood, urine, and feces, as well as those of at least one major metabolite, are described by group at each time point. For each parameter, the number of participants (N), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV), minimum value (Min), median, maximum value (Max), geometric mean (Geo_Mean), and geometric coefficient of variation (CV%-GM) are provided. Linear and semi-logarithmic plots are used to depict individual drug concentration–time profiles and the average drug concentration–time profile.

Pharmacokinetic parameter analysis: Based on PKPS, parametersare summarized by group, with the number of participants (N), arithmetic mean, standard deviation (SD), coefficient of variation (CV), minimum value (Min), median, maximum value (Max), geometric mean (Geo_Mean), and geometric coefficient of variation (CV%-GM) reported. Using the Power model approach, and also based on PKPS, the dose–exposure relationship (AUC, Cmax) following a single administration is evaluated for proportionality. Dose–PK exposure parameter scatter plots are generated. Urinary and fecal drug excretion and excretion rate analysis: Based on UPKCS and FPKCS, for each group, urinary excretion at each time point, cumulative urinary excretion and cumulative excretion rate over specified intervals, as well as cumulative fecal excretion and cumulative excretion rate over specified intervals, are described. The number of participants (N), arithmetic mean, standard deviation (SD), coefficient of variation (CV), minimum value (Min), median, maximum value (Max), geometric mean (Geo_Mean), and geometric coefficient of variation (CV%-GM) are provided. Individual and average curves of cumulative urinary/fecal drug excretion rates versus time are plotted.

## 5.7. Safety Analysis

This section presents an analysis based on SS, conducted by group (by dose cohort in Part 1 and by treatment period and formulation in Part 2).

### 5.7.1. Adverse event

Adverse events werecoded using MedDRA terminology. For the pooledanalysis, only adverse events occurring from the first dose of the study drug through 28 days after the last dose were included. Adverse events that occurred prior to the first dose of the study drug or more than 28 days after the last dose were excluded from the pooled analysis and are presented in a separate list.

Summary of the number ofoccurrences, cases, and percentagesforAEs:all adverse events; Grade 3 or higher adverse events; investigational product–related adverse events (classified as "definitely related," "probably related," or"uncertain" in relationtothe study treatment); Grade 3 or higher investigational product–related adverse events; adverse events leading to a reduction in the study treatment dose; adverse events resulting in temporary discontinuation of the study drug; adverse events leading to permanent discontinuation of the study drug; serious adverse events; serious investigational product–related adverse events; adverse events leading to withdrawal from the study; adverse events resulting in death; and serious adverse events related to the investigational product. For each of these AE categories, data are summarized by System Organ Class (SOC) and Preferred Term (PT), with the number of occurrences, cases, and percentages provided. Additionally, adverse events and investigational product–related adverse events are tabulated by System Organ Class (SOC) and Preferred Term (PT), along with their severity, with the number of occurrences, cases, and percentages reported. A corresponding list of data for each AE category is also provided.

### 5.7.2. DLTanalysis

Based on DLTS(applicable onlyto Part 1 of the study), the number and percentage of cases in each DLT category are provided.

### 5.7.3. Vital signs

Provide the number of cases, mean, standard deviation, median, minimum, and maximum for each visit's vital signs (body weight, body surface area, body temperature, respiratory rate, pulse, seated systolic blood pressure, and seated diastolic blood pressure), along with the corresponding changes from baseline; present cross-tabulations comparing baseline values with post-dose values (under worst-case scenarios) for clinical significance assessment; and furnish a summary table of newly observed clinically significant laboratory findings.

#### 5.7.4. Physical examination

The physical examination provides a cross-tabulation of baseline and post-administration (based on the worst-case scenario) clinical significance assessments, along with a summary table of newly detected abnormalities that are clinically significant.

#### 5.7.5. Laboratory tests

Provide the number of cases,mean, standard deviation, median, minimum, and maximum values for each laboratory test (complete blood count, urinalysis, serum biochemistry, stool analysis, and fecal occult blood); present cross-tabulations comparing baseline values with post-dose values (under worst-case scenarios) for clinical significance; and furnish a summary table of newly observed abnormalities that are clinically significant.

#### 5.7.6. 12-lead electrocardiogram

Provide the number of cases, mean, standard deviation, median, minimum, and maximum for each visit's 12-lead electrocardiogram results (heart rate, PR interval, QRS duration, QT interval, QTcB interval, and QTcF interval), along with the corresponding changes from baseline; present cross-tabulations summarizing the clinical significance assessments between baseline and post-dose visits (based on the worst-case scenario); and furnish a summary table of newly observed clinically significant abnormalities.

#### 5.7.7. ECOGperformance status

A cross-tabulation ofECOG performance status scores at baseline and at the post-dose visit (under the worst-case scenario) is provided.

## 6. Changes to be analyzed in the plan

None.

## 7. References

[1]. Wen-Zhao Zhong, Qun Wang, Wei-Min Mao, et al. Gefitinib versus vinorelbine plus cisplatin as adjuvant treatment for stage II–IIIA (N1–N2) EGFR-mutant NSCLC (ADJUVANT/CTONG1104): a randomised, open-label, phase 3 study. Lancet Oncol 2018; 19: 139–48.

[2].Dongsheng Yue, Shidong Xu, Qun Wang, et al. Erlotinib versus vinorelbine plus cisplatin as adjuvant therapy in Chinese patients with stage IIIA EGFR mutation-positive non-small-cell lung cancer (EVAN): a randomised, open-label, phase 2 trial. Lancet Respir Med 2018;6: 863–73.

[3]. Y-iLong Wu, Masahiro Tsuboi, Jie He, et al. Osimertinib in Resected EGFR-Mutated Non–Small-Cell Lung Cancer. The New England Journal of Medicine 2020; 383(18):1711-1723.