STATISTICAL ANALYSIS PLAN

Protocol Number:	SGNTUC-022
Version:	1.0
Date	17JAN2024
Protocol Title:	MOUNTAINEER-02: A randomized, double-blind, placebo-controlled, active comparator Phase 2/3 study of tucatinib in combination with trastuzumab, ramucirumab, and paclitaxel in subjects with previously treated, locally-advanced unresectable or metastatic HER2+ gastric or gastroesophageal junction adenocarcinoma
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APPROVAL SIGNATURES

Product:	Tucatinib
Protocol Number/Amendment:	SGNTUC-022/Amendment 2
SAP Version:	1.0
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The individuals signing below have reviewed and approve this statistical analysis plan.

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LIST OF ABBREVIATIONS

ADI	absolute dose intensity
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{last}	AUC to the time of the last quantifiable concentration
BID	twice daily
CI	confidence interval
C_{max}	maximum observed concentration
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough concentration
DCR	disease control rate
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EOT	end of treatment
GEC	gastric or gastroesophageal junction adenocarcinoma
IDI	intended dose intensity
IV	intravenous
KM	Kaplan-Meier
LLOQ	lower limit of quantification
MRAUC	metabolic ratio based on AUC
NCI	National Cancer Institute
NGS	next generation sequencing
ORR	objective response rate
PD	progression of disease
PFS	progression-free survival
PR	partial response
PT	preferred terms
RDI	relative dose intensity
SMC	Safety Monitoring Committee
SOC	system organ classifications
TEAE	treatment-emergent adverse event
T_{max}	time of the maximum observed concentration
ULN	upper limit of normal

1 INTRODUCTION

This document outlines the statistical methods to be implemented within the scope of Protocol SGNTUC-022, entitled "MOUNTAINEER-02: A randomized, double-blind, placebo-controlled, active comparator Phase 2/3 study of tucatinib in combination with trastuzumab, ramucirumab, and paclitaxel in subjects with previously treated, locally-advanced unresectable or metastatic HER2+ gastric or gastroesophageal junction adenocarcinoma (GEC)". Results of the proposed analyses will become the basis of the clinical study report for this protocol.

The purpose of this plan is to provide specific guidelines from which the analysis will proceed. All planned analyses specified in this document will be performed. Any changes to this plan, in the form of "post hoc" or "data driven" analyses will be identified as such in the final clinical study report. Any changes will either be reflected in amendments to this plan before the database lock or specifically documented in the clinical study report.

After completion of the Phase 2 dose optimization stage, further enrollment to the study was closed by the sponsor. A recommended paclitaxel dose will not be identified, and the study will be terminated upon the last subject completing the last visit. This document only includes statistical analysis plan of the Phase 2 dose optimization portion of the study.

2 STUDY OBJECTIVES

2.1 Primary Objectives

- To determine the recommended dose of paclitaxel when administered in combination with tucatinib, trastuzumab, and ramucirumab.
- To evaluate the safety and tolerability of tucatinib in combination with trastuzumab, ramucirumab, and paclitaxel.

2.2 Secondary Objectives

- To evaluate the preliminary activity of tucatinib in combination with trastuzumab, ramucirumab, and paclitaxel in subjects with previously treated locally-advanced unresectable or metastatic GEC that is HER2+ according to blood-based next generation sequencing (NGS) assay of circulating tumor DNA (ctDNA).
- To evaluate the pharmacokinetics (PK) of tucatinib and the tucatinib metabolite ONT-993.
- To evaluate the PK of paclitaxel and its metabolites in the presence and absence of tucatinib.

3 STUDY ENDPOINTS

3.1 Primary Endpoints

- Frequency of dose-limiting toxicities (DLTs) during the first cycle of treatment with tucatinib, trastuzumab, ramucirumab, and paclitaxel.

- Type, incidence, severity, seriousness, and relatedness of adverse events (AEs) and laboratory abnormalities.
- Vital signs and other relevant safety variables.
- Frequency of dose holds, dose reductions, and discontinuations of tucatinib, paclitaxel, trastuzumab, and ramucirumab.

3.2 Secondary Endpoints

3.2.1 Efficacy Endpoints

- Objective response rate (ORR; complete response [CR] or partial response [PR]) per RECIST version 1.1 according to investigator assessment.
- Confirmed ORR per RECIST version 1.1 according to investigator assessment.
- PFS per RECIST version 1.1 according to investigator assessment.
- Duration of response (DOR; CR or PR) per RECIST version 1.1 according to investigator assessment.
- Disease control rate (DCR; CR, PR, or stable disease) per RECIST version 1.1 according to investigator assessment.

3.2.2 Safety Endpoints

- Type, incidence, severity, seriousness, and relatedness of AEs and laboratory abnormalities.
- Vital signs and other relevant safety variables.
- Frequency of dose holds, dose reductions, and discontinuations of tucatinib, trastuzumab, ramucirumab, and paclitaxel.

3.2.3 Pharmacokinetics Endpoints

- The PK parameters to be calculated for tucatinib, paclitaxel, and their respective metabolites (if applicable) may include but are not limited to: area under the plasma concentration-time curve (AUC) to the time of the last quantifiable concentration (AUC_{last}), maximum observed concentration (C_{max}), time of C_{max} (T_{max}), trough concentration (C_{trough}), and metabolic ratio based on AUC (MR_{AUC}).

4 STUDY DESIGN

This was an international, multicenter Phase 2/3 study in subjects with locally-advanced unresectable or metastatic HER2+ GEC who have received prior treatment with a HER2-directed antibody and have received 1 prior line of therapy in the advanced disease setting (overall study design illustrated in Figure 1). After completion of the Phase 2 dose optimization stage, further enrollment to the study was closed by the sponsor.

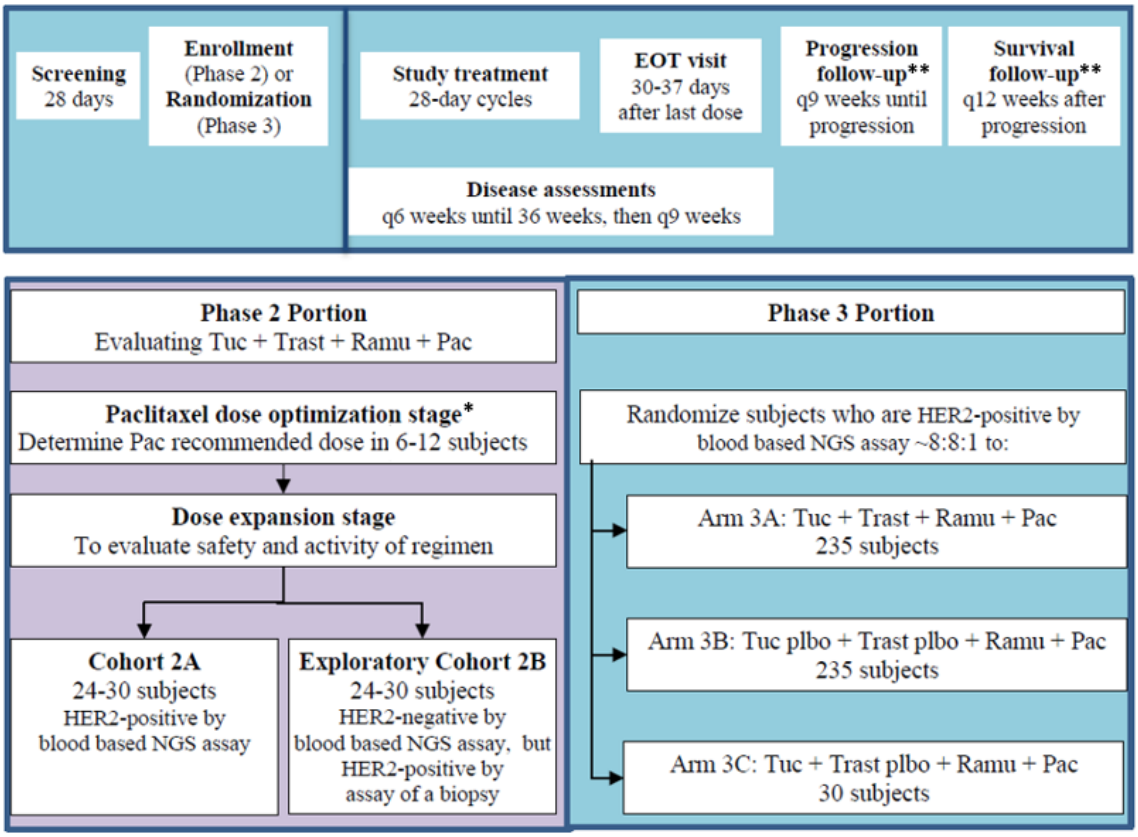
- *Paclitaxel dose optimization stage*

This single-arm stage is to determine the recommended dose of paclitaxel when combined with tucatinib, trastuzumab, and ramucirumab. The initial paclitaxel dose will be 60 or 80 mg/m² intravenous (IV) on Days 1, 8, and 15 of each 28-day cycle, in combination with tucatinib 300 mg orally (PO) twice daily (BID), trastuzumab (6 mg/kg IV loading dose on Cycle 1 Day 1, 4 mg/kg IV on Cycle 1 Day 15 and Days 1 and 15 of each cycle thereafter), and ramucirumab (8 mg/kg IV on Days 1 and 15).

During the study, if any study drug is discontinued, the subject can continue to receive study treatment with the remaining agents. Study treatment (defined as the administration of any of the four study drugs, without initiation of new anti-cancer treatment) will continue until unacceptable toxicity, disease progression, withdrawal of consent, death, or study closure.

Disease response and progression will be assessed using RECIST version 1.1 (Eisenhauer 2009). While on study treatment, radiographic disease evaluations will be done every 6 weeks for the first 36 weeks, and every 9 weeks thereafter, irrespective of dose holds or interruptions. If study treatment is discontinued before documentation of disease progression, radiographic evaluations will be performed at least every 9 weeks until the occurrence of progression, withdrawal of consent, or study closure. After occurrence of disease progression, subjects will continue to be followed for survival every 12 weeks, until death, consent withdrawal, or study closure.

Figure 1: Study visits and overall study design*



Pac=paclitaxel; plbo=placebo; Ramu=ramucirumab; Tuc=tucatinib; Trast=trastuzumab

*Enrollment to study closed after completion of the paclitaxel dose optimization stage

**As of September 30th, 2022, progression follow-up and survival follow-up have been discontinued.

5 ANALYSIS SETS

This section defines each of the analysis sets that will be utilized. The use of each analysis set will be discussed in Section 7.

5.1 Full Analysis Set

The full analysis set will include all subjects who received any amount of any study drug.

5.2 Safety Analysis Set

The safety analysis set is the same as the Full Analysis Set.

5.3 Response Evaluable Analysis Set

The Phase 2 response evaluable analysis set will include all subjects who meet all following criteria:

1. had baseline disease assessment,
2. received study treatment,

3. had post baseline disease assessment or discontinued treatment due to documented disease progression, clinical progression, AEs, or death.

5.4 Pharmacokinetics Analysis Set

The PK analysis set will include subjects in the full analysis set who received at least one dose of tucatinib or paclitaxel and have at least one evaluable PK assessment.

6 STATISTICAL CONSIDERATIONS

6.1 General Principles

In this document, "treatment group" is defined by the paclitaxel dose level each subject initiated treatment with.

In general, descriptive statistics by treatment group will be presented including the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, frequencies, and percentages for categorical variables.

Unless otherwise specified, confidence intervals (CIs) will be calculated at a two-sided 95% level. The two-sided 95% exact CI using Clopper-Pearson method (Clopper 1934) will be calculated for the response rates where applicable (e.g., ORR).

For time-to-event endpoints, the median survival time will be estimated using the Kaplan-Meier method; the associated 95% CI will be calculated based on the complementary log-log transformation (Collett 1994).

Multiplicity adjustment for alpha level is discussed in Section 6.7.

Any analysis not described in this plan will be considered exploratory and will be documented in the Clinical Study Report (CSR) as a post hoc analysis or a change to the planned analysis.

To comply with regulatory electronic submission guidelines, all clinical data will be submitted as electronic data sets. To facilitate data review for the study report, only pertinent data listings will be created and attached to the appendix of the CSR.

All statistical tables, listings, and figures will be produced using SAS, version 9.3 or more recent. Other statistical software, if used, will be described in the CSR.

6.2 Determination of Sample Size

In the paclitaxel dose optimization stage, 6 to 18 subjects will be enrolled to determine the recommended paclitaxel dose. Additional subjects may be enrolled in the paclitaxel dose optimization stage, based on recommendations from the Safety Monitoring Committee (SMC).

6.3 Randomization and Blinding

The Phase 2 portion is open label with no randomization or blinding.

6.4 Data Transformations and Derivations

The following data conventions will be used for the tables, listings, and figures.

Age: Reported age in years will be used.

Baseline: Unless otherwise specified, baseline values used in all analyses will be the most recent non-missing measurement prior to the first dose of any study treatment.

Study Day: Study Day for analyses will be calculated as (Date – Date of First Dose + 1) for dates on or after the first dose date. The date of first dose will be Study Day 1. For dates prior to the first dose date, Study Day will be calculated as (Date – First Dose Date). For all calculations of Study Day, the First Dose Date will be the earliest date of administration of any study treatment.

Other time variables based on two dates, e.g., Start Date and End Date, will be calculated as (End Date – Start Date + 1) (in days) unless otherwise specified in the planned analysis section.

The following unit conversion will be implemented unless otherwise specified:

Months = Days/30.4375

Years = Days/365.25

End-of-Treatment (EOT): The EOT date will be the date the EOT visit is performed or the decision-making date if EOT visit date is not available.

Response assessment date: At each response assessment time point, scans to evaluate tumor lesions can be performed on multiple dates.

- The date of response for CR or PR will be recorded as the date of the last radiographic evaluation included in the series for that assessment.
- The date of response for SD will be recorded as the date of the earliest radiographic evaluation included in the series for that assessment.
- The date of progression (PD) will be recorded as the earliest date that PD has been documented, i.e., the earliest of the following:
    - Date of target lesion assessment when the target lesion response is PD,
    - Date of non-target lesion assessment when the lesion status is unequivocal progression, and
    - Date of documenting new lesion.

  In the cases where a PD occurs due to the fact that an equivocal new lesion was later confirmed to be an unequivocal new lesion, the PD date should be back dated to the visit when the equivocal new lesion was first identified if the equivocal new lesion continued to be present. If an equivocal new lesion was later absent or confirmed to be a benign lesion, then this new lesion is not considered to define a PD. Note: in cases where PD occurs at a date after an equivocal new lesion is identified, but the progression is not due to a change of the equivocal new lesion to an unequivocal lesion, but rather from

progression of other lesions, the PD date will not be back dated, but will be the date when definitive PD is recorded.

6.5 Handling of Dropouts and Missing Data

Except for the scenarios covered in this section, missing data will not be imputed.

Missing disease history date will be imputed for the purpose of calculating the time from diagnosis to the first dose date (Appendix D).

Missing AE dates will be imputed for the purpose of calculating duration of events (Appendix A).

Missing start and end date of subsequent cancer-related therapy, and prior treatment date will be imputed for the purpose of deriving the time-to-event endpoints, and other applicable analysis as applicable (Appendix C).

Unless otherwise specified, lab values which are recorded or provided as being less than the lower limit of quantification (LLOQ), will be included in figures and summaries as LLOQ.

PK values which are recorded as being less than the lower limit of quantification (LLOQ), will be included in summaries as LLOQ/2.

6.6 Multicenter Studies

There are multiple centers in this study, however it is not anticipated that any center will accrue enough subjects to warrant an analysis by center.

6.7 Multiple Comparison/Multiplicity

There is no formal hypothesis testing in the Phase 2 portion.

6.8 Examination of Subgroups

Not applicable due to the small sample size.

6.9 Covariates

There will be no adjustment for covariates in the Phase 2 portion.

6.10 Timing of Analyses

Safety analyses will be undertaken by the sponsor when the first 6 DLT-evaluable subjects in each paclitaxel dose level have been followed for at least one cycle (paclitaxel dose optimization stage). The SMC will review the results of the safety.

The final analysis for the phase 2 portion will be performed after the last patient has completed their last visit in this study.

7 PLANNED ANALYSES

7.1 Disposition

Analysis set: Full Analysis Set or All Screened Subjects

An accounting of study subjects by disposition will be tabulated by treatment group and total. Reasons for discontinuation of treatment and study will be summarized. The number and percentage of subjects who signed informed consent and the number of subjects in each analysis set will be summarized by treatment group and total. Number of screen failures and the percentage relative to the total number of subjects screened will be summarized. A listing of subjects who failed screening will be produced with reasons for screen failure and available demographic information.

The number of subjects enrolled in each country and at each site will be summarized by treatment group and total.

7.2 Demographic and Baseline Characteristics

Analysis set: Full Analysis Set

Demographic and baseline characteristics will be summarized and listed by treatment group and total using counts and percentages for categorical variables and summary statistics (mean, median, standard deviation, and range) for continuous variables.

Characteristics to be summarized include the following:

- Subject demographics: age, sex, race, ethnicity, and ECOG performance status
- Disease history and baseline disease characteristics:
  - Time (months) from diagnosis of GEC to date of first dose of study treatment
  - Disease diagnosis (gastric adenocarcinoma, gastroesophageal junction adenocarcinoma)
  - Histological subtype (diffuse, intestinal, other)
  - Stage at diagnosis
  - History of unresectable locally advanced disease (yes, no, unknown)
  - Time (months) from diagnosis of the earliest diagnosis of locally advanced unresectable disease to the first dose date
  - History of metastatic disease sites at study entry (yes, no, unknown)
  - Time (months) from the earliest diagnosis of distant metastatic disease to the first dose date
  - Locally advanced unresectable or metastatic disease sites at study entry
- Prior disease-related therapies
  - Prior systemic therapy
  - Prior radiation therapy
  - Prior surgical treatment

7.3 Protocol Deviations

Analysis set: Full Analysis Set

Important protocol deviations are those that represent a divergence from the protocol that could have a significant effect on the integrity of the study data, or on the subject's rights, safety, or welfare. Important protocol deviations also include exemptions to the study inclusion/exclusion criteria. Important protocol deviations will be summarized by category and treatment group. A list of subjects with important protocol deviations will be presented.

7.4 Treatment Administration

Analysis set: Full Analysis Set

Exposure will be summarized by treatment group using counts and percentages for categorical variables and summary statistics (mean, median, standard deviation, and range) for continuous variables. The following information will be summarized by dose level and total separately for tucatinib, trastuzumab, ramucirumab, and paclitaxel:

- total number of treatment cycles per subject
- total cumulative dose
- duration of treatment (months)
- dose modification by type (dose reduced, dose interrupted, dose held, drug withdrawn) and by reason
- dose holds by reason
- duration of dose holds
- absolute dose intensity (ADI) and relative dose intensity (RDI) for tucatinib, ramucirumab and paclitaxel.

Duration of treatment (not for calculating dose intensity) is defined as the time from first dose date to the earliest of the following dates:

- the exposure end date:
  - for tucatinib, the last dose date;
  - for trastuzumab,
    - the last infusion date + 6 if planned dose is 2 mg/kg,
    - the last infusion date + 13 if planned dose is 4 mg/kg or 6 mg/kg;
  - for ramucirumab, last infusion date + 13;
  - for paclitaxel,
    - if the last infusion was the first or second paclitaxel infusion in the last cycle, the last infusion date + 6,
    - if the last infusion was the third paclitaxel infusion in the last cycle, the later date of the last infusion date + 13, and the date of paclitaxel discontinuation - 1;
- date of death;

- end of study date;
- analysis data cutoff (DCO) date if the subject is still on treatment at the time of DCO.

Cumulative Dose is defined as the sum of the actual dose amount that a subject received across all cycles. For example, for paclitaxel, it is calculated as the sum of (intended dose (mg) received in each infusion / body surface area at each infusion (m^2)) over all infusions.

Intended dose intensity (IDI) is defined as the intended dose of drug per unit of time.

- Tucatinib IDI = 300 mg BID = 600 (mg/day)
- Ramucirumab IDI = 8 mg/kg twice a cycle = 16/28 mg/kg/days

Paclitaxel IDI = dose three times a cycle = (dose x 3/28) mg/m^2/days. **Absolute dose intensity (ADI) =** cumulative dose / (exposure end date – first dose date + 1)

Relative dose intensity (RDI) = ADI/IDI * 100%

7.5 Efficacy Analyses

Analysis set: Response Evaluable Analysis Set

7.5.1 Primary Endpoints

Not applicable

7.5.2 Key Secondary Endpoints

Not applicable.

7.5.3 Other Secondary Endpoints

7.5.3.1 Objective Response Rate by Investigator Assessment

ORR per investigator assessment is defined as the proportion of subjects achieving a best overall response of CR or PR per RECIST 1.1 by investigator assessment. Only tumor assessments on or before the first documented PD or new anti-cancer therapies will be considered. For a response to be considered as confirmed, the subsequent response needs to be at least 4 weeks after the initial response.

The ORR and confirmed ORR by investigator and the corresponding exact two-sided 95% confidence interval using the Clopper-Pearson method (Collett 1991) will be calculated.

7.5.3.1.1 Progression Free Survival

Progression-free survival (PFS) time is defined as the time from the first dose date to the date of documented disease progression (as determined by investigator assessment using RECIST 1.1) or death due to any cause, whichever occurs first.

Specifically,

PFS=Date of first documented PD or death or censoring – Date of first dose + 1.

PFS event and censoring rules are described in **Error! Reference source not found.Error! Reference source not found.**.

Table 1 PFS analysis censoring rules

Scenario	Progression/Censoring Date	Outcome
No post-baseline baseline assessment	Date of first dose	Censored
No documented progression or death	Date of last tumor assessment of CR, PR, or SD	Censored
New anti-cancer treatment started before PD or death observed	Date of last CR, PR, or SD on or prior to date of new anti-cancer treatment	Censored
Progressive disease (PD)	Date of PD	Event
Death before first PD assessment	Date of death	Event
Death or progression right after two or more consecutively missed tumor assessments	Date of last tumor assessment of CR, PR, or SD	Censored

Note: CT, PET/CT scans are performed every 6 weeks starting at screening through Week 36 and then every 9 weeks until documented PD, death, withdrawal of consent, or study closure.

KM curves depicting PFS will be generated. Additionally, KM estimates of the median and quartiles will be reported for each treatment group. The two-sided 95% CI for the medians and quartiles will be calculated using the complementary log-log transformation method (Collett 1994).

7.5.3.1.2 Duration of Response

DOR is defined as the time from first objective response (CR or PR per investigator) to the date of the first documented PD per RECIST 1.1 or death due to any cause, whichever occurs first. The same derivation of PD date and censoring rules as for primary PFS analysis will apply for DOR.

DOR will only be calculated for the subgroup of subjects achieving a CR or PR. KM curves will be provided. The median DOR and its two-sided 95% CI using the complementary log-log transformation method (Collett 1994) will be calculated.

7.5.3.1.3 Disease Control Rate

DCR is defined as the proportion of subjects with CR, PR, or SD, as best overall response. A subject will have a best overall response of SD if there is at least one SD assessment ≥ 5 weeks after the first dose date and the subject does not qualify for CR or PR. The proportion of subjects with disease control determined by investigator will be calculated, with the exact two-sided 95% confidence interval using the Clopper-Pearson method (Collett 1991).

7.6 Pharmacokinetics Analyses

Analysis set: PK Analysis Set

Blood samples for PK assessments of paclitaxel and tucatinib will be collected at protocol-defined time points. Plasma concentrations of tucatinib, ONT-993, paclitaxel and its metabolites will be analyzed using validated mass spectrometry methods. Remaining PK samples will be archived and may be used for the analysis of administrated compounds or related species with exploratory, non-validated assays.

PK parameters will be calculated using standard non-compartmental methods. PK parameters to be estimated may include, but are not limited to, area under the plasma concentration-time curve to the time of the last quantifiable concentration (AUC_{last}), maximum observed concentration (C_{max}), observed trough concentration in plasma (C_{trough}; tucatinib only), and time of C_{max} (T_{max}).

Descriptive statistics (N, mean, geometric mean, SD, %CV, median, min and max) will be used to summarize the calculated PK parameters for tucatinib and paclitaxel by treatment group. For T_{max}, only N, median, min, and max will be presented.

The effect of tucatinib on the PK of paclitaxel will be assessed using the ratio and 90% confidence intervals (CIs) of the geometric least-squares (LS) means of the paclitaxel plasma PK parameter AUC_{last} and other paclitaxel metabolites PK parameters as appropriate. Estimates on the original scale of measurement will be obtained by exponentiating point estimates on the natural log scale. Geometric LS means will be provided for each treatment group. In all comparisons, paclitaxel administered alone will be used as the reference. No adjustments will be made for multiplicity.

For the calculation of summary statistics, <LLOQ results are imputed to ½ LLOQ value. The summary statistics for a timepoint will not be calculated if more than 50% of the results are <LLOQ.

7.7 Health Economics and Outcomes Analyses

Not applicable.

7.8 Safety Analyses

Analysis set: Safety Analysis Set

Frequency of DLT during the first cycle of treatment will be summarized per treatment group and total. Frequencies and descriptive statistics will be provided for type, incidence, severity, seriousness and relatedness of AEs and laboratory abnormality per treatment group and total. Dose modifications of each component of the treatment will be summarized per treatment group and total.

Adverse event will be coded by standard preferred terms (PT) and system organ classifications (SOC) using Medical Dictionary for Regulatory Activities (MedDRA, version 26.0 or higher).

Concomitant medications will be coded using the World Health Organization Drug Dictionary (version 2023Mar B3 or higher).

7.8.1 Adverse Events

Adverse events (AEs) will be summarized by MedDRA preferred term in descending frequency of occurrence in Arm 3A unless otherwise specified. For incidence reporting, if a subject reports more than one AE that was coded to the same SOC or PT, the subject will be

counted only once for that specific SOC or PT. For summaries by severity, only the worst grade for an AE will be counted for a subject.

A treatment-emergent AE (TEAE) is defined as a newly occurring or worsening AE after the first dose of study treatment (tucatinib, trastuzumab, ramucirumab, or paclitaxel) and up to 30 days after the last dose of study treatment (tucatinib, trastuzumab, ramucirumab, or paclitaxel, whichever is later).

Treatment-related AE is defined as AE assessed by the investigator as 'related' to tucatinib, trastuzumab, ramucirumab, or paclitaxel.

Summary of AEs by treatment group and total will be provided for the following:

- All TEAEs
- TEAEs by PT
- Grade 3 or higher of TEAEs by PT
- Serious TEAEs by PT
- TEAEs leading to dose modification by PT, by types of dose modification and drug discontinuation
- TEAEs leading to death by PT
- TEAEs by SOC and PT
- Treatment-related TEAEs by PT by components of study treatment
- Treatment-related SAEs by PT by components of study treatment
- Treatment-related Grade 3 or higher TEAEs by PT by components of study treatment
- TEAEs by SOC, PT, and maximum severity. At each SOC or PT, multiple occurrences of events within a subject are counted only once at the highest severity

All TEAEs, grade 3 or higher TEAEs, serious TEAEs, TEAEs leading to treatment discontinuation, and TEAEs leading to death will be listed.

7.8.2 Adverse Events of Special Interest

AESI for this study is hepatoxicity, which includes the following types of liver function test elevation:

- AST or ALT elevations that are > 3 x ULN with concurrent elevation (within 21 days of AST and/or ALT elevations) of total bilirubin > 2 x ULN
- AST or ALT elevations > 20 x ULN
- Bilirubin > 10 x ULN

The incidence of treatment emergent AESI will be summarized by lab values and listings.

7.8.3 Other Adverse Events

In addition to the protocol defined AESIs, the incidence of treatment emergent adverse events for additional risks will be summarized by PT and listings will also be produced. Other AEs include:

1. Hepatotoxicity: defined by drug related hepatic disorders – comprehensive search SMQ (Narrow)
2. Diarrhea: defined as a single PT of "Diarrhoea".

   Use of anti-diarrheal medications will also be summarized.

Time to onset or resolution will be analyzed as appropriate.

Time to onset of a specific AE will be calculated as time from the first dose of study drug to the start of first treatment-emergent event that meets the respective search criteria.

Resolution is defined as event outcome of 'recovered/resolved' or 'recovered/resolved with sequelae'. Time to resolution is defined as time from the start of AE to the end date of AE with an outcome of 'recovered/resolved' or 'recovered/resolved with sequelae'.

Time to onset will be summarized at the subject level. Time to resolution will be summarized at the event level.

7.8.4 Clinical Laboratory Results

Clinical laboratory results to be collected during the study are specified in the protocol section of 7.8.3, including serum chemistry and hematology samples. The collection schedules are specified in Appendix A in the study protocol.

Both observed value and changes from baseline will be summarized with descriptive statistics for each scheduled visit by treatment group. Shift from baseline to maximum post-baseline NCI CTCAE grade will be summarized for each lab test by treatment group. Treatment-emergent laboratory abnormalities will also be summarized.

Laboratory results and NCI CTCAE grades for hematology and serum chemistry will be presented in data listings. Normal ranges will be documented, and out-of-range values will be flagged. A separate listing of laboratory results with CTCAE grade 3 or higher will be presented.

7.8.4.1 Incidence of Liver Abnormalities

The incidence of potential drug-induced liver injury will be summarized. In addition to the laboratory abnormalities defined for AESI in Section 7.8.2, (AST and/or ALT) > 3 × ULN + Total Bilirubin > 2 × ULN + Alkaline Phosphatase < 1.5 × ULN and (AST and/or ALT) > 3 × ULN, 5 × ULN, and 10 × ULN will also be summarized.

7.8.4.2 Ejection Fraction

The minimal post baseline cardiac ejection fraction and the maximum decrease from baseline will be summarized for each treatment group. Time to maximum decrease from baseline ejection fraction may also be tabulated.

7.8.5 Vital Signs

Vital signs (weight, body temperature, respiratory rate, heart rate, and systolic and diastolic blood pressure) will be listed by subject and visit for each treatment group.

The frequency and percentage of subjects with post baseline clinically significant vital signs will be summarized. The clinically significant vital signs include: systolic blood pressure >= 120 mmHg or diastolic blood pressure >= 80 mmHg, systolic blood pressure >= 140 mmHg or diastolic blood pressure >= 90 mmHg, systolic blood pressure >= 160 mmHg or diastolic blood pressure >= 100 mmHg, heart rate > 100 bpm, temperature >= 38.0 degrees C (100.4 F) and respiratory rate > 20 breaths per min.;

For weight, the maximum percent decrease from baseline will also be summarized.

7.8.6 Deaths

Death information will be summarized in table and listed by subject.

7.8.7 Pregnancy

Positive pregnancy test will be listed by subject.

8 INTERIM ANALYSIS

No interim analysis is planned.

9 CHANGES FROM PLANNED ANALYSES

9.1 Changes from the Study Protocol

After completion of the Phase 2 dose optimization stage, further enrollment to the study was closed by the sponsor. A recommended paclitaxel dose will not be identified, and the study will be considered terminated upon the last subject completing the last visit. This document only includes statistical analysis plan of the Phase 2 dose optimization portion of the study.

Study protocol specified PK analysis in subgroups of subjects with and without a gastrectomy. Due the small sample size, this analysis will not be conducted.

9.2 Changes from the Original SAP

Not Applicable.

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11 APPENDICES

Appendix A: Imputation of Partially Unknown Adverse Event Dates

For an AE with a partial start or end date, if it can be determined that the event occurred prior to the date of first dose of study treatment, the partial date will not be imputed. Otherwise, the partial date will be imputed using the rules described below. AE start dates should be imputed before imputation of AE condition end date in all cases.

Incomplete AE Start Date:

AE day only is missing.

- If the month/year is the same as the month/year of first dose of any study treatment, then AE start date will be imputed as the first dose date of any study treatment.
- If the month/year is after the month/year of first dose of any study treatment, then AE start date will be imputed as the first day of the month.

AE day and month are missing.

If the year is the same as the year of first dose of any study treatment, then AE start date will be imputed as the first dose date of any study treatment.
If the year is after the year of first dose of any study treatment, then AE start date will be imputed as January 1st.

AE day, month and year are missing.

AE start date will be imputed as the first dose date of any study treatment.

If AE condition end date is known with a full date, and the imputed start date is after the end date, the start date will be set to the AE end date.

Incomplete AE End Date:

If AE outcome is “not recovered/resolved”, “unknown”, or blank, then AE condition end date will not be imputed.

If AE outcome is “recovering/resolving”, “recovered/resolved”, “recovered/resolved with sequelae”, or “fatal”, then apply the following:

AE day only is missing.

AE condition end date will be imputed as the minimum of (death date, DCO date or data extraction date sans DCO, last day of the AE end date month/year, EOS date).

AE day and month are missing.

- If the year is equal to the year of the last dose date, then AE end date will be imputed as the minimum of (last dose date + 30, death date, DCO date or data extraction date sans DCO, December 31st of the end date year, EOS date).

- If the year is not equal to the year of the last dose date, then AE end date will be imputed as the minimum of (death date, DCO date or data extraction date sans DCO, December 31st of the end date year, EOS date).

AE day, month and year are missing.

AE end date will not be imputed.

Within a single record, if the imputed end date is before the start date, then the imputed end date will be set to the start date.

Example

AE Number 4: Condition/Event NAUSEA
First dose date 02APR2012

Prior to imputation

Log Line	Start date	Condition end date	Severity	Outcome
1	25APR2012	UNAPR2012	2	recovering/resolving
2	UNAPR2012	04MAY2012	1	recovered/resolved

Post imputation

Log Line	Start date	Condition end date	Severity	Outcome
1	25APR2012	**30**APR2012	2	recovering/resolving
2	**02**APR2012	04MAY2012	1	recovered/resolved

Appendix B: Definition of the Term "Treatment-Emergent" with Respect to AE Classification

A treatment-emergent adverse event (TEAE) is defined as any AE which is newly occurring or worsening in severity, with starting date on or after the first dose of any study treatment (i.e., tucatinib, trastuzumab, ramucirumab, or paclitaxel) and before the last dose of study treatment + 30 days.

Appendix C: Imputation of Partial Missing Start and End Date of Prior Systemic Therapy and Subsequent Cancer-Related Therapy

Partial missing date will be imputed when both month and year are present and only day is missing.

- Prior therapy start date: first day of the month
- Prior therapy end date: the earlier of
    - Last day of the month and year
    - First dose date of study drug if received any study treatment, enrollment date otherwise
- Subsequent therapy start date: the later of
    - First day of the month and year
    - First dose date of study drug if received any study treatment, enrollment date otherwise
- Subsequent therapy end date: the earlier of
    - Last day of the month
    - End of study date
    - Death date

Appendix D: Imputation of Partial Missing Date for Disease Diagnosis Date

Disease diagnosis date (including initial diagnosis, earliest date disease was considered unresectable locally advanced and earliest date disease was considered distant metastatic) will be imputed as the 1st of the month if both month and year are present and only day is missing, and will be imputed as 01 January if only year is present and both day and month are missing.

Appendix E: Imputation of Partial Missing Death Dates

Death dates are imputed if only the day is missing.

The imputation of partial missing death date depends on the last-know-alive date derived from eCRF.

If the last-known-alive date is in the same month and year of the partial missing death date, then the partial missing death date is imputed as the last-known-alive date.

If the last-known-alive date is not in the same month and year of the partial missing death date, then the partial missing death date is imputed as day fifteen of the month and year.

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