Official Title: A Phase 2 Study of TAS-120 in Metastatic Breast Cancers Harboring Fibroblast Growth Factor Receptor (FGFR) Amplifications

NCT ID: NCT04024436

Document Date: Statistical Analysis Plan Version 1.0, 04 February 2020

STATISTICAL ANALYSIS PLAN

VERSION: 1.0

DATE OF PLAN: 04 Feb 2020

STUDY DRUG: TAS-120

PROTOCOL NUMBER: TAS-120-201

STUDY TITLE:

A Phase 2 Study of TAS-120 in Metastatic Breast Cancers Harboring Fibroblast Growth Factor Receptor (FGFR) Amplifications

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This trial was conducted in accordance with the ethical principles of Good Clinical Practice (GCP), according to the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline.

STATISTICAL ANALYSIS PLAN
Version 1.0

APPROVAL PAGE

A Phase 2 Study of TAS-120 in Metastatic Breast Cancers Harboring Fibroblast Growth Factor Receptor (FGFR) Amplifications

Protocol TAS-120-201

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1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	Adverse event
ALT	Alanine aminotransferase
ANC	absolute neutrophil count
AST	Aspartate aminotransferase
Ccr	Calculated creatinine clearance
CI	Confidence interval
CBR	Clinical benefit rate
CR	Complete response
ctDNA	Circulating tumor DNA
DLT	Dose-limiting toxicity
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FGF	Fibroblast growth factor
FGFR	Fibroblast growth factor receptor
HER2	Human epidermal growth factor receptor 2
HR	Hormone receptor
ICF	Informed consent form
IM	Intramuscular
ms	Milliseconds
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PO	Oral
PR	Partial response
PT	Preferred term
QD	Once daily (continuous) dosing
QTcF	Fridericia's corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical Analysis Plan

SD	Stable disease
SI	The International System of Units
SOC	System Organ Class
WHO	World Health Organization

2. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and data displays to be included in the Clinical Study Report (CSR) for Protocol TAS-120-201.

FGFR gene mutations, particularly amplifications, play an important role in the development of breast cancer; FGFR1 and FGFR2 gene amplifications are present in approximately 10% and 2%, respectively, of all invasive breast cancers (1). TAS-120, an inhibitor of FGFR1-4, has shown promising preclinical activity in the treatment of breast cancers and other cancer types; in a Phase 1 clinical study, TAS-120 monotherapy was associated with 2 durable partial responses (PRs) in patients with treatment-refractory breast cancer (2).

This Phase 2 study will include patients with breast cancer harboring FGFR gene amplifications. Patients in this study will receive either single-agent TAS-120 or combination treatment comprising TAS-120 and fulvestrant. The primary goal of this study is to assess the antitumor activity of TAS-120 as monotherapy or in combination with fulvestrant in the treatment of patients with metastatic breast cancer harboring FGFR amplifications.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objective(s)

The primary objective of this study is to assess the antitumor activity of TAS-120 as monotherapy or in combination with fulvestrant in the treatment of patients with metastatic breast cancer harboring FGFR amplifications, as measured by:

- Objective response rate (ORR) in patients with centrally confirmed FGFR2 amplification and measurable disease (Cohorts 1, 2).
- Clinical benefit rate (CBR) in patients with centrally confirmed FGFR2 amplification and nonmeasurable, evaluable disease (Cohort 3).
- 6-month progression-free survival (PFS) rate in patients with centrally confirmed high level FGFR1 amplification and measurable disease (Cohort 4).

3.1.2. Secondary Objectives

- To determine the complete response (CR) rate in Cohort 3, the ORR in Cohort 4, the CBR in Cohorts 1, 2, and 4, and the 6-month PFS rate in Cohorts 1, 2 and 3.
- To evaluate the duration of response (DOR) among patients with objective response in all cohorts.
- To evaluate the PFS and overall survival (OS) in all cohorts.
- To investigate the safety of TAS-120 as monotherapy and in combination with fulvestrant.

3.1.3. Exploratory Objectives

- To investigate the downstream pharmacodynamic effects of treatment with TAS-120.
- To explore markers of response and mechanisms of resistance in tumor tissue biopsies and/or blood

3.2. Study Endpoints

3.2.1. Primary Endpoint(s)

- ORR, defined as the proportion of patients with a confirmed response of either complete response (CR) or partial response (PR) per Investigator assessment (Cohorts 1, 2).
- CBR, defined as the proportion of patients with a confirmed response of CR, or stable disease (SD) lasting at least 24 weeks, per Investigator assessment (Cohort 3).
- 6-month PFS rate, defined as the proportion of patients who are alive and progression-free 6 months after the first dose of study drug (Cohort 4).

3.2.2. Secondary Endpoints

- ORR (Cohort 4), CR rate (Cohort 3), CBR (Cohorts 1, 2, 4), and 6-month PFS rate (Cohorts 1, 2, 3), as defined above; CBR will include PR in these cohorts.
- DOR, defined as the time from first documentation of objective response to the date of death (any cause) or disease progression per Investigator assessment (Cohorts 1, 2, 3 ,4).

- PFS, defined as the time from first dose of study drug to the date of death (any cause) or disease progression per Investigator assessment (Cohorts 1, 2, 3 ,4).
- OS, defined as the time from first dose of study drug to the date of death (any cause) (Cohorts 1, 2, 3 ,4).
- Adverse events in all cohorts, graded according to the National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 5.0 or most up-to-date version at the time of analysis.
- Evaluation of dose-limiting toxicity (DLT) in Cohort 4 only.

3.2.3. Exploratory Endpoints

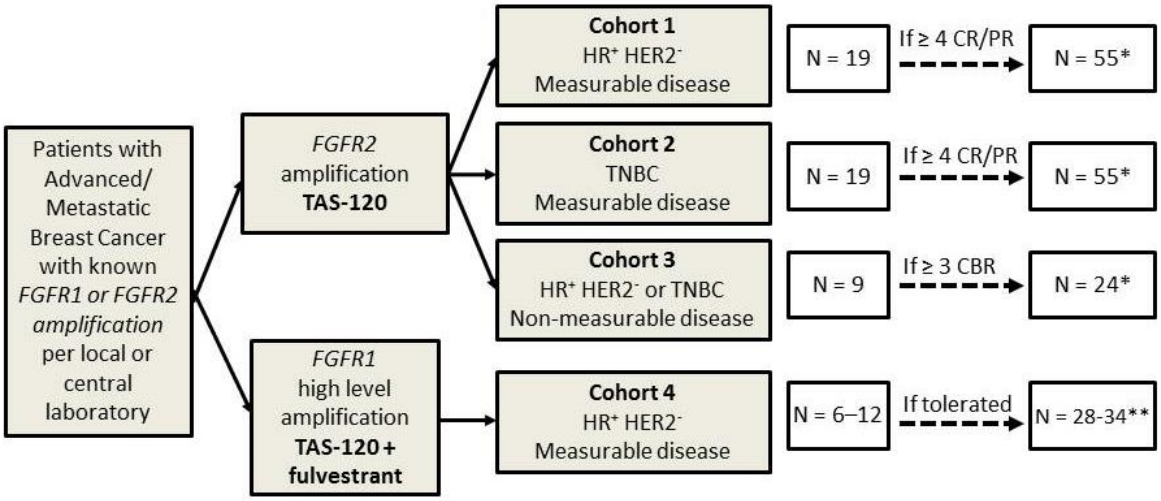
- Changes in pharmacodynamic markers assessed in fresh tumor tissue biopsies.
- Exploratory association of tissue and/or blood markers with tumor efficacy endpoints and/or tumor resistance to TAS-120.

4. STUDY DESCRIPTION

4.1. Summary of Study Design

This is a Phase 2, open-label, non-randomized, multicenter study designed to evaluate the efficacy and safety of TAS-120 and TAS-120 + fulvestrant in adult patients with locally advanced/metastatic breast cancer harboring FGFR gene amplifications. Up to approximately 168 patients will be enrolled in this study, which will be conducted at approximately 75 sites globally.

Patients will be enrolled to 1 of 4 treatment cohorts based on diagnosis and *FGFR* gene amplification status, and will receive either single agent TAS-120 in Cohorts 1-3 or TAS-120 plus fulvestrant in Cohort 4 (Figure 1).



* Total number of enrolled patients including patients enrolled in Stage 1.

** In the safety lead-in period of Cohort 4, 6 patients will initially be treated at a TAS-120 dose of 20 mg QD, with the possibility of 6 additional patients treated at 16 mg QD if 20 mg QD is not tolerated. After the safety lead-in, additional patients will be enrolled to ensure a total of 28 patients are treated at the recommended dose (including patients treated at the recommended dose in the safety lead-in.

Figure 1. Study design flow chart

In all cohorts, a treatment cycle is defined as 28 days. All patients will receive PO TAS-120 at a dose of 20 mg QD (continuous daily dosing). Patients in Cohort 4 only will also receive intramuscular (IM) fulvestrant 500 mg on Days 1 and 15 of Cycle 1 and Day 1 of every subsequent cycle. Pre/peri-menopausal patients in Cohort 4 are required to also have ovarian suppression with goserelin as part of standard of care, having started a gonadotropin-releasing hormone (GnRH) analogue at least 4 weeks prior to the first dose of fulvestrant.

Treatment will continue until disease progression, unacceptable toxicity, or any other of the criteria for treatment discontinuation is met. For patients who discontinue treatment for reasons other than disease progression, tumor assessments should be continued until radiologic disease progression is documented or until initiation of subsequent new anticancer therapy (whichever occurs first). Patients will be followed for survival every 12 weeks (±2 weeks) until survival events (deaths) have been reported for 75% of enrolled patients or the study is terminated early by the Sponsor.

Cohorts 1 and 2 will initially enroll a total of approximately 19 response-evaluable patients per cohort. If ≥4 responses (PR or CR) are observed in a cohort, that cohort will be further expanded to a total of approximately 55 response-evaluable patients.

Cohort 3 will initially enroll a total of approximately 9 response-evaluable patients. If ≥3 patients experience clinical benefit (CR, or SD ≥24 weeks) are observed, the cohort will be further expanded to a total of approximately 24 response-evaluable patients.

Because the combination of TAS-120 and fulvestrant has not been assessed in patients, **Cohort 4** will begin with a safety lead-in period. During the safety lead-in, 3 patients will initially be enrolled and will receive TAS-120 (20 mg QD) and fulvestrant (500 mg) according to the study schedule, with safety follow-up of at least 1 cycle. Patients will be assessed for DLTs and the recommended dose of TAS-120 for this cohort will be determined as follows.

- Of the initial 3 patients, if 0/3 or 1/3 patients present with a DLT, another 3 patients will be enrolled.
    - If 0/6 or 1/6 patients present with a DLT, the safety lead-in phase will conclude and enrollment will continue to a total of 28 patients treated with TAS-120 (20 mg QD) plus fulvestrant.
- If ≥2/3 or ≥2/6 patients present with a DLT, TAS-120 20 mg QD plus fulvestrant will be defined as a non-tolerated dose level for the combination. Subsequent patients will be treated at a dose of TAS-120 of 16 mg QD plus fulvestrant, and the sequence will be repeated. Initially, 3 patients will be enrolled:
    - If 0/3 or 1/3 patients present with a DLT, another 3 patients will be enrolled.
        - If 0/6 or 1/6 patients present with a DLT, the safety lead-in phase will conclude and enrollment will continue to a total of 28 patients treated with TAS-120 (16 mg QD) plus fulvestrant.

If ≥2/3 or ≥2/6 patients present with a DLT at the dose of TAS-120 at 16 mg QD plus fulvestrant, the assessment of the combination and further enrollment to Cohort 4 will be discontinued.

The detailed study schedule is shown in Table 1.

Table 1: Schedule of Events

Written informed consent will be obtained prior to any study evaluations. Evaluations on Day 1 (D1) of a cycle should be performed within 24 hours prior to dosing, unless otherwise noted. Procedures already performed during the screening period within 96 hours prior to dosing do not need to be repeated on Cycle 1 Day 1 (C1D1).

The EOT visit must be performed 0-7 days after the decision is made to discontinue study treatment (for patients who discontinue at a planned study visit, that visit may be considered the EOT visit if all assessments required at EOT are performed).

	Screening Period (Within 28 Days Prior to First Dose)	Treatment Period (1 cycle = 28 days)						Safety Follow-up		Follow-up Period	Notes
		Cycle 1					Cycles ≥2	End of Tx (+0-7 days)	30 (±3) days After Last Dose		
		Day					Day				
		1	4 (±1d)	8 (±1d)	15 (±1d)	22 (±1d)	1 (±3d)				
Demographics / medical history	X										Includes sex, age, clinical diagnosis, date and method of diagnosis, prior cancer therapy, and relevant medical history (past and concurrent).
Review eligibility criteria	X	X									Eligibility should be confirmed on C1D1 prior to first dose of study therapy.
Collect tumor tissue	X										Archival or fresh (preferred) tumor tissue biopsy samples must be made available during the screening period.
Submit tumor tissue to central laboratory		X									Tumor samples must be submitted to a designated central laboratory for testing as soon as possible after the patient is enrolled. Tumor samples may be stored at the Sponsor's designated central laboratory for up to 10 years for future testing.
Physical examination	X	X					X	X	X		
Vital signs	X	X					X	X	X		Pulse rate, systolic and diastolic blood pressure, body temperature, and respiration rate. Any abnormal reading should be repeated immediately.
Height and body weight	X	X					X	X	X		Height at baseline only.

	Screening Period (Within 28 Days Prior to First Dose)	Treatment Period (1 cycle = 28 days)						Safety Follow-up		Follow-up Period	Notes
		Cycle 1					Cycles ≥2	End of Tx (+0-7 days)	30 (±3) days After Last Dose		
		Day 1	4 (±1d)	8 (±1d)	15 (±1d)	22 (±1d)	Day 1 (±3d)				
Ophthalmological examination	X						(X)	X	X		At screening and 4-6 weeks after first dose; additional on-study evaluation as needed due to local requirements, physician judgment, and/or symptoms or signs of mineral deposits.
ECOG performance status	X	X					X	X	X		
12-Lead Electrocardiogram	X	X					X	X	X		At screening and 2 hours (±15 minutes) after dosing on D1 of each cycle.
Hematology	X	X		X	X	X	X	X	X		Within 24 hours prior to treatment.
Coagulation	X	X					X	X	X		Within 24 hours prior to treatment at each timepoint, and as clinically indicated.
Chemistry (Serum or plasma)	X	X	(X)	X	X	X	X	X	X		Within 24 hours prior to treatment, on D1 of each cycle and on D8, D15, and D22 of Cycle 1 only. Additional collection to verify phosphorus levels on C1D4 (±24 hours). More frequent assessments may be performed if clinically indicated.
Pregnancy test	X	X					X	X	X		Serum pregnancy test required for women of child-bearing potential (WOCBP) at screening and end of treatment; serum or urine pregnancy test required at all other timepoints.
Tumor Assessments/Scans	X						see notes	X		(X)	At screening and at the end of every 8 weeks/2 cycles (± 1 week). Note that patients who discontinue without PD should continue to undergo tumor assessments/scans every 12 weeks ±7 days until PD is documented, new anticancer therapy is initiated, the study is terminated, or consent is withdrawn. Note that scans obtained prior to completion of the ICF may be used as the screening tumor scan if completed within 28 days of first dose.

	Screening Period (Within 28 Days Prior to First Dose)	Treatment Period (1 cycle = 28 days)						Safety Follow-up		Follow-up Period	Notes
		Cycle 1					Cycles ≥2	End of Tx (+0-7 days)	30 (±3) days After Last Dose		
		Day 1	4 (±1d)	8 (±1d)	15 (±1d)	22 (±1d)	Day 1 (±3d)				
ctDNA blood samples		X					see notes	X		(X)	Collected prior to the first TAS-120 administration on C1D1, on D1 of each alternative uneven cycle (Cycle 3, 5, 7 and ongoing), at time of PD, and at the EOT visit.
Prior & concomitant medications, AE assessments	X	→						X	X	X	Collect from the time ICF is signed through 30 days after administration of the last dose of study therapy or until the start of new anticancer therapy. Thereafter, only SAEs considered related to study therapy will be collected.
Survival status and subsequent therapy										X	After discontinuation of treatment, survival follow-up should occur every 12 weeks (±2 weeks) until survival events (deaths) have been reported for 75% of enrolled patients or the study is terminated earlier by the Sponsor.
OPTIONAL: fresh tumor biopsy for pharmacodynamic assessment	X						see notes	(X)		(X)	Baseline and at the end of Cycle 1 (C1 D28 ± 7 days). It is strongly recommended to also obtain a fresh tumor sample at the time of disease progression.
TAS-120 Dosing		→									Patients are required to fast for at least 2 hours before and 1 hour after each administration of TAS-120; patients are permitted to drink water during this period. TAS-120 should be administered in the morning or evening, at the same time (if possible) each day.
Fulvestrant Dosing **(Cohort 4 ONLY)**		X			X		X				Days 1 and 15 of Cycle 1 and Day 1 of all subsequent cycles, for patients in Cohort 4 only.

4.2. Treatment Assignment and Blinding/Unblinding

After the patient's initial eligibility is established and informed consent has been obtained, TAS-120 (futibatinib) will be administered orally at a dose of 20 mg QD in Cohorts 1, 2, and 3. In Cohort 4, TAS-120 will be administered orally at a dose of 20 or 16 mg QD, depending on the DLT observations in the safety lead-in phase. Fulvestrant 500 mg will be administered IM on Days 1 and 15 of Cycle 1, then Day 1 every subsequent cycle thereafter (every 28 days ± 3 days) to patients in Cohort 4 only.

This is an open-label, non-randomized study. Blinding/unbinding is not applicable.

4.3. Determination of Sample Size

Approximately 168 patients in total may be enrolled in the study.

Please note: the patient numbers given for efficacy analysis are for the response-evaluable population, defined as the subset of treated patients who have measurable disease (or evaluable disease in Cohort 3), who have at least 1 post-baseline disease/tumor assessment, and who have centrally confirmed *FGFR* amplification. If a treated patient is not eligible for the response-evaluable population (for example, because *FGFR* amplification cannot be centrally confirmed or no post-baseline tumor assessment is available), additional patients will be enrolled to ensure the correct number of response-evaluable patients for analysis as described below.

Sample size considerations for **Cohorts 1 and 2** (primary endpoint ORR) are based on a 2-stage Optimal Simon design, comparing a poor response of ≤15% versus a promising response of ≥30%, at an approximate 5% 1-sided significance level and 80% power.

- In Stage 1 (futility assessment), enrollment will include 19 patients in each cohort and accrual will continue to Stage 2, if at least 4 (21%) of 19 patients respond (CR or PR).
- In Stage 2, if the Stage 1 futility boundary is exceeded, an additional 36 patients will be enrolled, for a total of at least 55 patients per cohort. In Cohorts 1 or 2, with a total of 55 patients, if the observed ORR is 30.9%, the 95% exact confidence interval (CI) is (19.1%, 44.8%).

Sample size considerations for **Cohort 3** (primary endpoint CBR) are also based on a 2-stage Optimal Simon design. The null hypothesis that the true CBR is 25% will be tested against a 1-sided alternative, which yields a type I error rate of 5% and power of 80% when the true CBR rate is 50%. In the first stage, 9 patients will be treated. If there are ≤2 patients with clinical benefit (ie, CR or SD ≥24 weeks) in these 9 patients, the cohort will be discontinued. Otherwise, 15 additional patients will be treated for a total of 24 patients. The null hypothesis will be rejected if ≥10 patients with clinical benefit are observed in 24 patients.

Sample size considerations for **Cohort 4** (primary endpoint 6-month PFS) are based on a proof-of-concept Phase 2 design, differentiating a null 6-month 25% PFS rate with a target rate of 50%. Approximately 28 patients will be treated. It has approximately 80% power to reject the null hypothesis that the true 6-month PFS rate is ≤25%, considering a 1-sided alpha (type 1 error rate) of 5%. In addition, 6-12 patients will be enrolled as a safety lead-in. The patients in the safety lead-in who are treated at the recommended Phase 2 dose will be included in the main cohort of 28 patients. Thus up to 34 patients may be enrolled for this cohort.

5. STUDY PERIODS, TREATMENT REGIMENS, AND POPULATIONS FOR ANALYSIS

5.1. Study Periods for Analyses

Study periods are defined in Table 2.

Table 2: Definition of Study Periods for Analysis

Period	Definition
Baseline / Screening	From the day of Informed consent form (ICF) signature (up to 28 days before first dose) to the day and time of the first dose of study drug.
On-treatment	From the date of first dose of study drug through 30 days after the last dose of study drug. Unless otherwise specified, the on-treatment period will be the basis for the summaries of safety.

5.2. Treatment Groups/Cohorts

There are 4 groups (cohorts) in this study as described in Section 4.1. 20mg QD of TAS-120 will be administered to the patients in Cohort 1, 2 and 3. In Cohort 4, TAS-120 will be administered at a dose of 20 or 16 mg QD, depending on the DLT observations in the safety lead-in phase. Fulvestrant 500 mg will also be administered to patients in Cohort 4 on Days 1 and 15 of cycle 1, then Day 1 every subsequent cycle thereafter.

This is an open-label, non-randomized study. Blinding/unblinding is not applicable.

5.3. Populations for Analysis

- **All Enrolled Population:** All patients enrolled in this study
- **All Treated Population:** All enrolled patients who received at least 1 dose of TAS-120
- **DLT Evaluable Set:** All patients in the All Treated Population in Cohort 4, excluding those for whom the cumulative dose of TAS-120 was <75% of planned TAS-120 dose or the cumulative dose of fulvestrant was <100% of planned fulvestrant dose for reasons other than DLTs in Cycle 1, or who received prohibited concomitant medications or therapies
- **Response Evaluable Set:** All patients in the All Treated Population who meet Inclusion Criterion #4 (section 4.1 of protocol), have measurable disease (or evaluable disease in Cohort 3), who have at least 1 post-baseline disease/tumor assessment, and have centrally confirmed FGFR amplification. Patients who discontinue due to intolerable toxicity or death prior to the first post-baseline tumor assessment will also be considered evaluable and will be classified as non-responders
- **Pharmacodynamic Population:** All patients in the All Treated Population who have evaluable pharmacodynamic biomarker data.

5.4. Timing of Analysis

The interim analysis will be performed at the time a cohort (Cohort 1, 2, 3) has the required number of patients to determine if that particular cohort should continue.

The final analysis will be performed when all patients have at least 6 months follow-up. The clinical cut-off date for the final analysis is defined as the date at which all patients either discontinue from the study or have sufficient follow-up (at least 6 months) from the first dosing date of TAS-120 of the last enrolled patient, whichever comes first.

6. STATISTICAL ANALYSIS

6.1. General Methods

All recorded data will be presented in listings.

The categorical data will be summarized using frequency counts and percentages of patients. The continuous data will be summarized using number of non-missing observation (n), mean, standard deviation (SD), median, minimum and maximum unless otherwise specified.

Summary tables will be presented by cohort. Data listings will be presented with patient ID and cohort.

For concomitant medications/therapy and adverse events, the cycle number is determined based on their start/onset dates. For other collected data, the cycle number is determined based on their visit dates. These data include Lab test, Physical exam, Vital signs, Height and Weight, Ophthalmological exam, ECOG, ECG, Pregnancy test, Circulating tumor DNA (ctDNA), tumor biopsies, Scheduled tumor assessment.

When there are multiple laboratory records for a scheduled visit, the one closest to the target date will be used for analysis. If there are two or more records with the same time period to the target date, the record with the latest database entry date will be used for analysis.

Time to event distribution (e.g. progression free survival, overall survival, duration of response, time to onset of AESI in a specific category, time to resolution of AESI in a specific category) will be estimated using Kaplan Meier techniques. The number of events and censorings will be reported. When appropriate, the median along with the corresponding log-log transformed 95% CI will be estimated. Rates at fixed time points will be derived from the Kaplan Meier estimate and corresponding confidence interval will be derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function S(t). Confidence intervals for binomial proportions, ORR, CRB, CR rate and 6-month PFS rate, will be derived using the Clopper-Pearson method.

All the analyses of efficacy, safety, and pharmacodynamics data for this study will be performed using SAS® statistical software package, Version 9.3 or a higher version.

6.2. Study Conduct

6.2.1. Accrual

The number of patients accrued will be summarized by country and investigational site on All Enrolled Population. A by-patient listing of accrual with cohort, first dosing date, country and investigational site will also be presented.

6.2.2. Protocol Deviations

Important protocol deviation (ICH E3 Q&A (R1)) is defined as a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect the subject's rights, safety or well-being. These include: Important ICF issues, inclusion/exclusion criteria not met, withdrawal criteria not followed; wrong treatment, incorrect dose/overdose based on protocol definitions, important deviations based on protocol design, and other important GCP deviations.

Important protocol deviations will be summarized by category and listed as well.

6.3. Study Population

6.3.1. Patient Disposition

The number of patients in each study population (All Enrolled Population, All Treated Population, Response Evaluable Set, Pharmacodynamic Evaluable Set) will be summarized by cohort. Patient disposition table will include number of patients treated at data cutoff, number of subjects with treatment ongoing at data cutoff, number of discontinued patients along with the reason for study discontinuation.

For Cohort 4 only, the number and percentage of patients in DLT Evaluable Set will be presented by different dosage levels of TAS-120. The reasons for exclusion will be summarized as well.

6.3.2. Demographic and Other Baseline Characteristics

The following baseline characteristics will be summarized by cohort. Listings will also be provided.

- Age (descriptive statistics)
- Age category (< 65, ≥65)
- Sex (Male, Female)
- Ethnicity (Hispanic/Latino, Not Hispanic/Latino)
- Race (Caucasian/white, Black, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Region (North America, Europe)
- ECOG PS (0, 1)
- Baseline height
- Baseline weight
- Prior surgery (Yes/No)
- Prior radiotherapy (Yes/No)
- Prior systemic anticancer therapy (Yes/No)
- Number of prior lines of systemic therapy
- Breast cancer type (HR^+HER^-, TNBC) (for Cohort 3)
- FGFR amplification status by local lab and/or central lab

All collected information for cancer diagnosis will be summarized and listed.

6.3.3. Medical History

Medical history will be coded according to the Medical Dictionary for Regulatory Activities (the most up-to-date version at the time of analysis). Medical history will be summarized by system organ class and preferred term for each cohort and for all patients and will be listed as well.

6.3.4. Prior/Concomitant Therapy

6.3.4.1. Prior Anticancer Therapy

Prior anticancer surgery and prior radiation therapy will be summarized for each cohort and for all patients based on All Treated Population. For prior surgery, the number and percentage of patients with at least one anticancer surgery for primary disease will be presented. The type of surgery will be summarized. The time from prior surgery to the first dosing date will be summarized. For prior radiation therapy, the number and percentage of patients with at least one radiation therapy for primary disease will be presented. The intention of radiotherapy, radiation therapy site location, duration of radiation therapy and time from end date of radiation therapy to first dosing date will be summarized.

For prior anticancer therapy, the number and percentage of patients with at least one prior anticancer therapy for primary disease will be presented. The treatment type and therapy type will be summarized. Patients' best response (CR, PR, SD, PD, NE) to the therapy will be summarized. The duration of anticancer therapy and time from end date of anticancer therapy to first dosing date will be summarized. The reason for therapy discontinuation will also be summarized. The above analysis will be repeated for each treatment type (adjuvant therapies, neoadjuvant therapies, therapies for advanced/metastatic disease) in separate tables.

Prior anticancer therapy will be coded with World Health Organization (WHO) Drug Dictionary (most up-to-date version at the time of analysis) and will be summarized by ATC level 2 (Therapeutic Main Group) and ATC level 4 (Chemical/Therapeutic Subgroup) for each cohort and for all patients based on All Treated Population. Medications and therapies will be sorted in descending order of frequency of ATC level 2 and ATC level 4 within ATC level 2 in the total column. A patient will be counted only once within each level of summarization if the patient has taken a medication more than once.

All collected information for prior surgery, prior-radiation therapy, and prior anticancer therapy will be listed.

6.3.4.2. Concomitant Medication and Therapy

Medications started prior to the first dose of study drug and continued into the treatment period are considered as concomitant medications and therapies. Medications taken on or after the first dose of study drug through 30 days after the last dose of study drug are considered as concomitant medications and therapies.

Concomitant medications will be coded with World Health Organization (WHO) Drug Dictionary (most up-to-date version at the time of analysis). Concomitant medications will be summarized by ATC level 2 (Therapeutic Main Group) and ATC level 4 (Chemical/Therapeutic Subgroup) for each cohort and for all patients based on All Treated Population. Medications will be sorted in

descending order of frequency of ATC level 2 and ATC level 4 within ATC level 2 in the total column. A patient will be counted only once within each level of summarization if the patient has taken a medication more than once. Agents and medications will be reported using the generic name. All concomitant medications will be listed.

In addition, the number and percentage of patients who received concomitant medications for management of hyperphosphatemia will be summarized by medication class and generic term for each cohort and for all patients. Total duration of medications (excluding overlaps) for management of hyperphosphatemia will be also summarized.

6.4. Efficacy Analyses

Unless otherwise specified, all efficacy analyses will be performed based on patients in All Treated Population with centrally confirmed FGFR amplification. For Cohort 4 only, patients treated with recommended dose of TAS-120 in All Treated Population with centrally confirmed FGFR amplification will be used for efficacy analyses.

6.4.1. Primary Efficacy Analyses

The primary endpoints are ORR (Cohorts 1 and 2), CBR (Cohort 3) and 6-month PFS (Cohort 4). The description of each efficacy endpoint is provided in Table 3. Tumor assessments will be performed as per Table 1. Response assessments will be made based on Response Evaluation Criteria in Solid Tumors (RECIST 1.1) (3). The evaluation of endpoints will be based on central independent radiology review and the investigator or local radiologist.

Table 3: Efficacy Endpoint Definitions

Endpoint	Definition
ORR	The percentage of patients with a confirmed response of either CR or PR
CBR	The percentage of patients with a confirmed response of CR or PR or SD lasting at least 24 weeks (Cohorts 1, 2 and 4) The percentage of patients with a confirmed response of CR or SD lasting at least 24 weeks (Cohort 3)
PFS	The time from the day of first dose to the date of first objectively documented disease progression or death (any cause), whichever occurs first
6-month PFS	The percentage of patients who remain alive and progression free at 6 months
DOR	The time from the first documentation of response (CR or PR) to the first documentation of objective tumor progression or death due to any cause, whichever occurs first
OS	The time from the date of first dose to the death date

Abbreviations: CBR=clinical benefit rate; CR=complete response; DOR=duration of response; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PR=partial response; SD=stable disease.

ORR (Cohorts 1 and 2) will be summarized by a binomial response rate for each cohort. ORR will be calculated based on the best overall response recorded from the start of treatment until

progression disease or start of subsequent new anticancer treatment. The overall response can be derived based on target lesion response, non-target lesion response and the emergence of new lesion for patients with measurable disease at baseline. Table 4 presents the rules to derive the overall response.

The best overall response, CR and PR, will be confirmed with at least 4 weeks intervals of two consecutive time points. A minimum of 6-week interval between initial treatment (first dosing date) and tumor measurement is required for SD. The confirmation rule of the best overall response is shown in Table 5.

The exact 2-sided 95% CI based on Clopper-Pearson methodology will be derived for ORR. The null hypothesis will be rejected if at least 15 responders observed out of 55 patients. If 17 responders observed out of 55 patients, the ORR is 30.9% and the 95% exact CI is (19.1%, 44.8%).

CBR (Cohort 3) will be calculated based on the best overall response. Because patients in Cohort 3 have non-measurable disease at baseline, the overall response will be derived based on non-target lesion response and/or the emergence of new lesion(s). The exact 2-sided 95% CI based on Clopper-Pearson methodology will be derived for CBR. The null hypothesis will be rejected if at least 10 patients with clinical benefit are observed out of 24 patients in Cohort 3.

The exact 2-sided 95% CI based on Clopper-Pearson methodology will be derived for 6-month PFS rate (Cohort 4). The null hypothesis will be rejected if at least 14 patients observed to remain alive and progression free at 6 months after the start of treatment out of 28 patients who are treated at recommended dose in Cohort 4.

Table 4. Overall Response Assessment with Target/Non-target Lesion and New Lesions

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD or Not all evaluated	No	PR
PR	Non-PD or Not all evaluated	No	PR
SD	Non-PD or Not all evaluated	No	SD
Not all evaluated	Non-PD	No	Not evaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Table 5. Confirmation Rules for Overall Response of PR and CR

Earlier Response (to be confirmed)	Later Response (confirmation)	Confirmed Response
CR	CR	CR
CR	Not CR or missing	SD
PR	CR or PR	PR
PR	SD or PD or missing	SD
PR	SD and then PR (only one SD in between)	PR
SD	n/a – no confirmation needed	SD
PD	n/a – no confirmation needed	PD

6.4.1.1. Sensitivity Analyses

The primary efficacy endpoints, ORR (Cohorts 1 and 2), CBR (Cohort 3) and 6-month PFS (Cohort 4), will be analyzed based on the Response Evaluable Set using the same method as that used in the primary efficacy analysis.

6.4.2. Secondary Efficacy Analyses

The secondary efficacy endpoints are CBR (Cohorts 1, 2, 4), CR rate (Cohort 3), ORR (Cohort 4), 6-month PFS rate (Cohorts 1, 2, 3), DOR (all cohorts), PFS (all cohorts) and OS (all cohorts). The description of each efficacy endpoint is provided in Table 3. Tumor assessments will be performed as per Table 1. Response assessments will be made based on RECIST 1.1. The evaluation of endpoints will be based on central independent radiology review and the investigator or local radiologist.

CBR, CR rate and ORR will be calculated based on the best overall response. The exact 2-sided 95% CI based on Clopper-Pearson methodology will be derived for CBR, CR rate, ORR and 6-month PFS rate.

DOR, PFS, and OS will be analyzed using Kaplan–Meier product-limit estimates for each cohort. Median DOR, PFS and OS will be presented with 2-sided 95% CI if estimable. Censoring rules for PFS and OS (Table 6, Table 7) are based on the Food and Drug Administration Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007). The cumulative PFS and OS will be plotted over time by cohort.

DOR will only be evaluated in patients with objective response of CR or PR. Patients who are alive and progression-free as of the data cut-off date will be censored at their last evaluable tumor response assessment prior to initiation of any new anticancer treatment. Patients who start subsequent anticancer therapy without a prior reported progression will be censored at the last tumor assessments prior to initiation of the subsequent anticancer therapy. The censoring rule for DOR is in Table 8.

Table 6. Censoring Rules for Progression-Free Survival (PFS)

No.	Situation	End Date	Outcome
1	Documented PD between scheduled visits	Date of the first assessment that determined PD	PFS event
2	Death during the study with no prior PD	Date of death	PFS event
3	Patients still on treatment without PD as of data cut-off [a]	Date of the last tumor assessment [b]	Censored
4	Treatment discontinuation for reasons other than PD or death, and no post baseline tumor assessments	Date of the first dose	Censored
5	Treatment discontinuation for reasons other than PD or death with post baseline tumor assessments	Date of the last tumor assessment	Censored
6	New anticancer treatment started	Date of the last tumor assessment before start of new treatment	Censored
7	Death or PD after two or more missed tumor assessments [c]	Date of the last tumor assessment before missed assessments	Censored

8	No baseline or unreadable baseline assessment but readable post baseline assessments	Date of the first dose	Censored

a. For PFS analysis, the date of last tumor assessment refers to the date of last adequate tumor assessment.
b. This refers to patients who were still receiving study treatment at time of data cutoff.
c. Two or more missed tumor assessments is defined as having either one of the following two durations being longer than 4 cycles:
- Duration between two consecutive tumor assessments
- Duration between the last tumor assessment and death or PD

Table 7. Censoring Rules for Overall Survival (OS)

Situation	End Date	Outcome
Death before cut-off	Date of death	Death
Death after data cut-off	Date of data cut-off	Censored event
Patient still alive at data cut-off	Date of data cut-off	Censored event
Patient discontinued treatment due to any reason before data cut-off	Date last known to be alive	Censored event

Table 8. Censoring Rules for Duration of Response (DOR)

No.	Situation	End Date	Outcome
1	Documented PD between scheduled visits	Date of the first assessment that determined PD	DOR event
2	Death during the study with no prior PD	Date of death	DOR event
3	Patients still on treatment without PD as of data cut-off [a]	Date of the last tumor assessment [b]	Censored
4	Treatment discontinuation for reasons other than PD or death	Date of the last tumor assessment	Censored
5	New anticancer treatment started	Date of the last tumor assessment before start of new treatment	Censored
6	Death or PD after two or more missed tumor assessments [c]	Date of the last tumor assessment before missed assessments	Censored

a. For DOR, the date of last tumor assessment refers to the date of last adequate tumor assessment.
b. This refers to patients who were still receiving study treatment at time of data cutoff.
c. Two or more missed tumor assessments is defined as having either one of the following two durations being longer than 4 cycles:
- Duration between two consecutive tumor assessments
- Duration between the last tumor assessment and death or PD

6.5. Safety Analyses

Unless otherwise specified, all safety analyses will be performed based on All Treated Population. Tables and figures will be generated by cohort (Cohort 1, 2, 3, 4) and generated for Cohort 4 separately by different dosage levels of TAS-120.

6.5.1. Extent of Exposure

6.5.1.1. Administration of Study Drug

The following parameters will be summarized:

- Duration of treatment
- Number of cycles treated
- Number of doses received
- Cumulative dose
- Relative dose intensity

Duration of treatment (days) will be calculated as: 1) calculate Date of last dose – Date of first dose + 1 for each treated cycle; 2) sum up across all treated cycles.

Cumulative dose is sum of the doses administered to a subject during the treatment period.

Relative dose intensity will be calculated as cumulative dose (dose received) divided by dose planned (taking the dosing cycle into consideration)

A by-patient listing of dosing of study drug and listing of batch number will be also provided.

6.5.1.2. Modification of Study Drug

The number and percentage of patients with at least one dose interruption along with reason for the interruptions will be summarized.

The number and percentage of subjects with at least one dose reduction and reason for the dose reduction will be summarized.

The number and percentage of subjects with at least one dose discontinuation and reason for the dose discontinuation will be summarized.

By-patient listings of dose interruption, dose reduction and dose discontinuation will be also provided.

6.5.2. Adverse Events

6.5.2.1. Deaths

On-treatment deaths and reasons for death will be summarized.

A by-patient listing of all deaths occurring during screening, on treatment, 30-day safety follow-up, or survival follow-up periods will be provided.

6.5.2.2. Adverse Events

An adverse event (AE) is any untoward medical condition that occurs in patients while participating in this clinical study. Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (the most up-to-date version at the time of analysis) terminology and the severity of the toxicities will be graded according to NCI CTCAE (Version 5.0 or most up-to-date version at the time of analysis), where applicable.

A treatment-emergent AE (TEAE) is defined as an AE that is starting or worsening at the time of or after the first dose of study drug administration and within 30 days after the last dose of study drug, and do not necessarily have a causal relationship to the use of the study drug. All AEs captured in the database will be listed; however, only TEAEs will be summarized.

The following AE summary tables will be generated:

1) Summary of AEs with the number and percentage of patients reporting AEs, serious AEs, grade ≥ 3 AEs, AEs leading to study drug discontinuation, interruption and dose reduction, and AEs with outcome of deaths.

2) Summary of treatment-related AEs with the number and percentage of patients reporting AEs, serious AEs, grade ≥ 3 AEs, AEs leading to study drug discontinuation, interruption and dose reduction, and AEs with outcome of deaths.

3) Summary of AEs by worst CTC Grade (grade 1, 2, 3, 4, 5, any grade, Grade ≥ 3) presented by System Organ Class (SOC) and Preferred Term (PT).

4) Summary of treatment-related AEs by worst CTC grade (Grade 1, 2, 3, 4, 5, any grade, Grade ≥ 3) presented by SOC and PT.

5) Grade ≥ 3 AEs by worst CTC Grade (grade 3, 4, 5, 3-5) presented by SOC and PT.

6) Grade ≥ 3 treatment-related AEs by worst CTC Grade (grade 3, 4, 5, 3-5) presented by SOC and PT.

7) Summary of AEs leading to death by SOC and PT.

8) Summary of the most common AEs (≥10% incidence) and median time to first AE by SOC and PT.

6.5.2.3. Adverse Events Leading to Discontinuation of Study Drug

AEs leading to discontinuation will be summarized:

- Summary of AEs leading to discontinuation of study drug by worst CTC Grade (grade 1, 2, 3, 4, 5, any grade, Grade ≥ 3) presented by SOC and PT
- Summary of treatment-related AEs leading to discontinuation of study drug by worst CTC grade (Grade 1, 2, 3, 4, 5, any grade, Grade ≥ 3) presented by SOC and PT

A by-patient listing of AEs leading to discontinuation of study drug will also be provided.

6.5.2.4. Adverse Events Leading to Dose Modification of Study Drug

AEs leading to dose modification (including dose interruption and reduction) of study drug will be summarized:

- Summary of AEs leading to dose modification of study drug by worst CTC Grade (grade 1, 2, 3, 4, 5, any grade, Grade ≥ 3) presented by SOC and PT
- Summary of treatment-related AEs leading to dose modification of study drug by worst CTC grade (Grade 1, 2, 3, 4, 5, any grade, Grade ≥ 3) presented by SOC and PT

A by-patient listing of AEs leading to dose modification of study drug will also be provided.

6.5.2.5. Serious Adverse Events

Serious adverse event (SAE) will be summarized:

- Summary of SAEs by worst CTC Grade (grade 1, 2, 3, 4, 5, any grade, Grade ≥ 3) presented by SOC and PT
- Summary of treatment-related SAEs by worst CTC Grade (grade 1, 2, 3, 4, 5, any grade, Grade ≥ 3) presented by SOC and PT

A by-patient listing of SAEs will also be provided.

6.5.2.6. Adverse Events of Special Interest

Incidence

Adverse event of special interest (AESI) will be summarized:

- Summary of AESI with the number and percentage of patients reporting AESI, serious AESI, grade ≥ 3 AESI, AESI leading to study drug discontinuation, interruption and dose reduction, and AESI with outcome of deaths.
- Summary of AESI by worst CTC grade (grade 1, 2, 3, 4, 5, any grade, Grade ≥ 3) presented by category or subcategory / PT

A by-patient listing of AESI will also be provided.

Time to Onset

Time-to-onset of selected AESI (e.g. hyperphosphatemia) will be graphically displayed using the Kaplan-Meier technique.

- Time-to-onset of any grade AESI
- Time-to-onset of Grade ≥3 AESI

The derivation of time-to-onset of AESI is detailed in Section 8.4.

Time to Resolution

Time-to-resolution of selected AESI (e.g. hyperphosphatemia) will be summarized.

- Time-to-resolution of Grade ≥3 AESI

The following summary statistics will be reported: percentage of subjects who experienced the specific events, percentage of subjects with resolution of the AESI (clustered), median, 1st quartile and 2nd quartile of time-to-resolution along with 95% CI (derived from Kaplan-Meier estimation) and ranges.

Time-to-resolution of Grade ≥3 AESI (e.g. hyperphosphatemia) will be graphically displayed using the Kaplan-Meier technique.

Time-to-resolution analyses are restricted to patients who experienced the specific events. Collapsing selected AE and derivation of time-to-resolution of AESI is detailed in Section 8.5.

6.5.2.7. Dose Limiting Toxicity (Cohort 4 only)

The number and percentage of patients with dose limiting toxicity (DLT) will be presented by different dose levels of TAS-120. The patients with DLT will also be listed.

6.5.2.8. Multiple Events

The following summary tables will be provided:

- A table showing the total number and rate (exposure adjusted) of occurrences for all AEs by SOC and PT
- A table showing the total number and rate (exposure adjusted) of occurrences for AESI by category / subcategory

The exposure adjusted incidence rate per X patient time is calculated as X×Y× (total number of unique AEs) / (total exposure time), where:

X = user-specified time factor, X= 1000 or 100

Y = 365.25 for years or Y = 30.4375 for months

For example, Incidence rate per 100 person-years of exposure (IR/100 P-Y) is calculated as 100 x 362.5 x (total number of unique AE count) / (total exposure time in days).

Unique instances of all AEs (that is, after duplicates have been eliminated and overlapping and contiguous occurrences of the same event (same PT) have been collapsed) will be summarized (0 event, 1 event, 2-3 events, ≥ 4 events) by PT. Unique instances of AESI will be summarized (0 event, 1 event, 2-3 events, ≥ 4 events) by category/subcategory.

Unique instances of all AEs will be listed.

The algorithm of collapsing selected AE records is detailed in Section 8.5.

6.5.3. Clinical Laboratory Evaluations

Clinical laboratory results will be summarized using SI units. Laboratory measurements will be summarized for each parameter. Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be presented for clinical chemistry, hematology and coagulation parameters at each scheduled visit. Change from baseline will be summarized in a similar manner.

Laboratory test results will be graded by NCI CTCAE (Version 5.0 or most up-to-date version at the time of analysis). Shift tables will be presented for each laboratory parameter to display the shift from baseline grade to the worst post-baseline grade. Summary tables will be provided presenting the number and percentage of patients for each laboratory test by baseline grade and worst post-baseline grade. All post-baseline assessments (including unscheduled visits) will be used to determine the worst post-baseline grade. Time to maximum Grade 3/4 and time to resolution (return to grade <=2 or baseline grade or below) may be summarized as appropriate.

All clinical laboratory data will be presented in by-patient listings.

The laboratory tests of Hematology, Coagulation, Serum chemistry are listed in Table 9.

Table 9. Laboratory Tests

Assessment	Test Items
Hematology and Coagulation	Red blood cell count, hemoglobin, hematocrit, platelets, white blood cell count with differential (absolute neutrophil count (ANC), lymphocytes, monocytes, eosinophils, basophils), Prothrombin time-international normalized ratio (INR), Activated partial thromboplastin time (APTT), fibrinogen
Chemistry (Serum or plasma)	AST, ALT, alkaline phosphatase (ALP), total bilirubin, direct bilirubin, albumin, lactate dehydrogenase, inorganic phosphorus, triglyceride, total cholesterol, creatinine, urea or blood urea nitrogen, sodium, potassium, chloride, calcium (corrected value), magnesium, blood glucose, creatinine clearance (if there is a measured value, use the measured value) or estimated glomerular filtration rate (eGFR)

For a calculated creatinine clearance (Ccr) value, use the Cockcroft-Gault formula:

Male Ccr (mL/min) = weight (kg)×(140-age(years))/[72×serum creatinine (mg/dL)]

Female Ccr (mL/min) = male Ccr×0.85

6.5.3.1 Ophthalmological Examination

Ophthalmological examination is performed at screening (within 28 days prior to TAS-120 administration on Day 1 of Cycle 1), 4-6 weeks after starting treatment with TAS-120, end of treatment visit and 30 days after last dose of study drug. Ophthalmological examination encompasses external ocular examination, slit lamp biomicroscopy and dilated ophthalmoscopy. The results of each test will be summarized by scheduled time point. All ophthalmological examination results will be listed in by-patient listing.

6.5.4. Vital Signs

Vital sign measurements include systolic blood pressure, diastolic blood pressure, pulse rate, respiration rate, and body temperature. Each vital sign parameter will be summarized with descriptive statistics by scheduled time point. Change from baseline will be summarized in a similar manner.

Weight at each scheduled time point and change from baseline will be summarized with descriptive statistics by scheduled time point. Weight will be displayed in kilograms. Height, collected only at baseline, will be displayed in centimeters. Body temperature will be displayed in Celsius.

All vital sign data will be presented in by-patient listings.

6.5.5. Electrocardiograms

ECG measurements include HR, RR interval, QT interval and its Fridericia's correction and Bazett's correction, and clinically abnormal findings. QTcF (Fridericia's correction) is calculated as $QT/RR^{0.33}$. QTcB (Bazett's correction) is calculated as $QT/RR^{0.5}$. Each ECG parameter will be summarized with descriptive statistics by scheduled time point. Change from baseline will be summarized in a similar manner.

Shift tables will present changes from baseline in ECG interpretation (categorized as normal, abnormal not clinically significant, abnormal clinically significant) to the worst post-baseline result.

In addition, the number and percentage of patients with at least one post-baseline abnormal ECG result in QTcF during on-treatment period will be summarized. Clinically abnormal ECG results in QTcF will be categorized as follows:

Absolute QTcF interval prolongation:

- QTc interval <= 470 ms
- QTc interval >470 - 480 ms (with baseline QTc interval ≤ 470)
- QTc interval > 480 - 500 ms (with baseline QTc interval ≤ 480)
- QTc interval > 500 ms (with baseline QTc interval ≤ 500)

Change from baseline in QTcF interval:

- QTC interval increases from baseline <= 30 ms
- QTC interval increases from baseline 30 - 60 ms
- QTC interval increases from baseline > 60 ms

All ECG data will be presented in by-patient listings.

6.5.6. Physical Examination

The physical examination will be performed during screening period, on day 1 of each cycle of treatment period, at the End of Treatment, and at 30-day safety follow-up.

The physical examination data will be presented in by-patient listing.

6.5.7. ECOG Performance Status

The ECOG performance status score will be obtained during screening period, on day 1 of each cycle of treatment period, at the End of Treatment, and at 30-day safety follow-up. The ECOG performance status scores and the grades from 0 to 5 are described in Table 10:

Table 10. Grade Categories of Eastern Cooperative Oncology Group Score

GRADE	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

The ECOG performance status score will be summarized with descriptive statistics by scheduled time point. A shift table will be presented to display the shift from baseline grade to the worst post-baseline grade.

6.5.8. Pregnancy Test

If the patient is female and of child bearing potential, a serum or urine β-HCG pregnancy test will be performed during screening period, on day 1 of each cycle of treatment period, at the End of Treatment, and at 30-day safety follow-up. Pregnancy test result will be presented in by-patient listing.

6.5.9. Tumor Tissue Biopsy Sample Collection

The archived tumor tissue biopsy samples will be collected during screening period from patients who signed the ICF if available. A patient level listing will be produced to display the tumor tissue sample collection and the results of tumor tissue sample analysis.

6.6. Exploratory Analyses

The exploratory pharmacodynamic/biomarker analyses will be performed using all patients in Pharmacodynamic Evaluable Set. The exploratory biomarkers may include but are not limited to: Any *FGFR* aberrations, p-AKT, p-MAPK and Ki67. Other than FGFR 1 and 2 amplifications, biomarkers data will be interpreted on exploratory basis.

6.7. Pharmacokinetic Analyses

Blood samples will be collected for PopPK analysis including estimation of steady-state exposure such as AUC. The samples will be used to determine concentrations of TAS-120 in plasma.

Total of three PK samples will be collected on Cycle 2 Day 1 (C2D1), within 1 hour prior to dosing and at 2 hours (±1 hour) and 5 hours (at least 3 hours apart from sampling at 2 hours) post-dose. The 3 samples should be collected on the same day. A pre-dose sample may be collected again in case the patient interrupted medication after the pre-dose sample was collected and had C2D1 at a later date. The second pre-dose sample will be recorded as pre-dose sample for C2D1. Detailed analytical procedures will be described in the independent SAP for PopPK.

The listing of TAS-120 plasma concentration will be provided.

6.8. Interim Analyses

The interim analyses will be performed to determine if the futility criterion was met in Cohort 1, 2 and 3, and if the particular cohort should continue. The interim analysis on Cohort 1 will be performed at the time when there are 19 response evaluable patients in Cohort 1. The interim analysis on Cohort 2 will be performed at the time when there are 19 response evaluable patients in Cohort 2. The interim analysis on Cohort 3 will be performed at the time when there are 9 response evaluable patients in Cohort 3.

During interim analyses, the sponsor will review the data and perform statistical analysis to determine if the particular cohort should continue. The interim analyses will be performed on primary efficacy endpoints only.

Because the study is powered for two-stage design (Cohort 1, 2, 3), the overall type I error is controlled for interim analysis. There is no need for type I error adjustment or sample size adjustment. Because this is open label study, there is no blinding/unblinding. Therefore there is no need for maintaining blinding during interim analysis.

7. CHANGES IN PLANNED ANALYSIS

There have been no changes to the initially planned analyses as of the finalization of this SAP.

8. DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

8.1. Baseline Period

Baseline evaluations or events will be defined as evaluations or events that occur before the date and time of the first dose of study drug.

If the onset time of event or evaluation time or dosing time is missing or not collected, the following definitions will apply:

- Pre-treatment AEs will be defined as AEs with an onset date prior to but not including the day of the first dose of study drug
- Baseline evaluations (laboratory tests, ECOG performance status and vital signs) will be defined as evaluations with a date on or prior to the day of first dose of study drug (for ECG, assessments on the day of first dose of study drug will not be included in baseline evaluation)

If there are multiple valid assessments, the assessment that is closest to day (and time if collected) of the first dose of study drug will be used as the baseline in the analyses. If multiple assessments are collected on the same date (and time, if collected), the assessment with the latest database entry date (and time, if collected) will be considered as baseline.

8.2. Post-Baseline Period

To allow differentiation as to which study period an Adverse Event occurred, three categories are defined based upon onset date. Adverse Events that had onset dates prior to the first dose of study drug are considered "prior". Adverse events with onset dates on or after the first dose of study drug and within 30 days following the last dose of study drug are considered "**on-treatment**" or equivalently "**treatment emergent**". Events with onset dates more than 30 days after the last dose of study drug are considered as "post-treatment". No "subtracting rule" will be applied when an AE occurs both pre-treatment and post-treatment with the same preferred term and grade. AE summary tables will be based on on-treatment AEs only. Adverse events with onset dates prior to the first dose of study drug as well as those after the last dose of study drug +30 days will be identified in the data listings.

8.3. AESI Definition and Conventions

The AESI consist of a list of preferred terms grouped by specific category (for example, pulmonary events, gastrointestinal events categories) and/or by subcategory (for example, diabetes). These categories and subcategories are defined based on MedDRA, and the list that is most current at the time of analysis will be used. Also, changes may be made to this list with each new version of MedDRA.

8.4. Time-to-Onset Definition

Time-to-onset of AESI (any grade) for a specific category (for example, pulmonary events, gastrointestinal events) is defined as the time between the day of the first dose of study drug and the onset date of the earliest AESI (of any grade) in this category.

If the subject did not experience an AESI (of any grade) in the category, time-to-onset will be censored at the maximum follow-up time of that subject (that is, for subjects without an event, time-to-onset will be censored at last dosing date +30 days if subjects are off treatment and followed for at least 30 days, otherwise it will be censored at the last known alive date.). If subjects experience AESI for a specific category but with event start date after the last dosing date +30 days, time-to-onset will be censored at last dosing date +30 days. The resulting Kaplan-Meier plot will represent the cumulative rate of the AESI (any grade) in the category over time.

Time-to-onset of AESI (Grade 3-5) for a specific category is defined similarly but restricted to Grade 3-5 AESI.

Time-to-onset of drug-related (Grade 3-5 or any grade) AESI for a specific category is defined similarly but restricted to drug-related AESI.

Time-to-onset for a specific subcategory is defined similarly but restricted to events in this subcategory.

8.5. Time-to-Resolution Definition

In order to derive the time-to-resolution, overlapping or contiguous AESI within a specific category will be collapsed into what will be termed “clustered” AESI. For example, if a subject (without pre-treatment AE) experienced an AE from 01 January to 05 January, another AE (with different PT but within same category) from 06 January to 11 January, and the same AE from 10 January to 12 January, these will be collapsed into one clustered AESI from 01 January (onset date) to 12 January (resolution date). Table 11 summarizes key derivation steps for each type of clustered select AEs.

Time-to-resolution of AESI (any grade) for a specific category is defined as the longest time from onset to complete resolution or improvement to the grade at baseline among all AESI clusters in this category experienced by patients. Events which worsened into Grade 5 events (death) or have a resolution date equal to the date of death are considered unresolved. If a clustered AESI is considered to be unresolved, the resolution date will be censored to the last known alive date. Improvement to the grade at baseline implies that all different AE events in the clustered AESI should at least have improved to the corresponding (that is, with same preferred term) baseline grade (or improve to lower grade). Time-to-resolution is defined only for subjects who experienced at least one AESI in the specific category.

The time-to-resolution of AESI (Grade 3-5) for a specific category is defined similarly with an onset date corresponding to a Grade 3-5 AESI.

Time-to-resolution of drug-related AESI (any grade or Grade 3-5) is defined similarly but restricted to drug-related AESI.

Time-to-resolution for a specific subcategory is defined similarly but restricted to events of this subcategory.

Table 11: Derivation of Clustered AESI

Type of clustered select AE	Derivation
Any grade	Collapse any on-treatment AESI from the same category
Drug-related of any grade	Collapse any on-treatment drug-related AESI from the same category
Grade 3-5	Collapse any on-treatment AESI from the same category. Resolution will be based on the onset date of the earliest Grade 3-5 records (clusters with only Grade 1-2 should not be selected)
Drug-related of Grade 3-5	Collapse any on-treatment drug-related AESI from the same category. Resolution will be based on the onset date of the earliest Grade 3-5 record (clusters with only Grade 1-2 should not be selected)

Abbreviations: AE=adverse event; AESI=adverse event of special interest.

The algorithm for collapsing selected AE records is using the following conventions. For each patient and specified category, the corresponding AE records will be collapsed when:

- Multiple AE records have the same onset date.
- The onset date of an event record is either the same day or 1 day later than the resolution date of a preceding event record (contiguous events).
- The onset date of an event record is after the onset date and prior to or on the resolution date of a preceding event record (overlapping events).

8.6. Other Data Handling Rules

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

If an AE has a completely missing onset date, then the AE will be considered a TEAE. A medication with a completely missing start date is considered a prior medication. A medication with a completely missing stop date is considered a concomitant medication.

If an adverse event or a medication has a partial missing start date or stop date, the following rules will be used to determine whether it is a TEAE, or a prior or concomitant medication.

Table 12. Partial Date Imputation Rule for TEAE or Medication

Partial Missing Start or Stop Date	Derived Start Date	Imputed Stop Date
Missing month and day, and the year is present	January 1 of that year or first dose date if the year is the same as the year of first dose date	December 31 of that year
Missing day, but year and month are present	First day of that month or first dose date if the year and month are the same as the year and month of first dose date	Last day of that month
Missing month, but year and day are present	Missing month derived as January or same as first dose month if the year is same as the year of first dose.	Missing month imputed as December

A date with missing year will be considered as completely missing date, no imputation rule will be applied.
The rule in Table 12 is also used for determining the cycle of adverse event and concomitant medication. The derived date is used for determining TEAEs, the cycle of adverse event and concomitant medication.

For medical history, pre-study surgery, prior radiotherapy, and prior systemic anticancer therapies, a partial missing start date will be imputed as below:

- Missing year - no imputation, date left missing
- Missing day and month - January 1 will be assigned to the missing fields.
- Missing month only - Treat day as missing and replace both month and day with January 1.
- Missing day only - Assign the first day of the month to the missing day.

Note: additional rules for prior systemic anticancer therapies may apply as they pertain to checking for protocol violations

For medical history, pre-study surgery, prior radiotherapy, and prior systemic anticancer therapies,

a partially missing stop dates will be imputed as below:

- Missing year - no imputation, date left missing
- Month is missing and year is prior to year of first dose of study drug- impute 'December'.
- Month is missing and year is the same as the year of the first dose of study drug - impute same month as in first dose date of study drug.

- Day is missing - impute 'last day of that month'. If results in a date ≥ the date of the first dose of study drug impute day as the day prior to date of first dose of study drug.

9. REFERENCES

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