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

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CLINICAL STUDY PROTOCOL

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

TAS-120

Protocol Number: TAS-120-201

Protocol Version Number: 1.0

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Amendment 1 (Version 2.0): 07 June 2019

Sponsor

Taiho Oncology, Inc.
101 Carnegie Center, Suite 101
Princeton, NJ 08540, USA

This clinical study will be conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Good Clinical Practice guidelines and applicable regulatory requirements.

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OVERVIEW OF CHANGES

The primary purpose of this amendment was to incorporate changes based on comments received by the Sponsor from the United States (US) Food and Drug Administration (FDA). Substantive changes are described in the table below. All changes have been incorporated into the study synopsis as appropriate; the Table of Contents and list of abbreviations and terms have also been updated when necessary.

In addition to these substantive changes, minor administrative alterations were made as necessary throughout the protocol, including formatting adjustments and correction of typographical errors. These editorial changes do not affect the rationale or planned conduct of the study or analyses, and therefore are not summarized in the table below.

Affected Section(s)	Description of Change(s)	Brief rationale
Cover Page	Added EudraCT Number to protocol cover.	Administrative change.
Section 1.3 Summary of Study Rationale **Section 2** Objectives and Endpoints **Section 6.1.8** Pharmacokinetic Evaluations **Section 9.2** Population Pharmacokinetic Sample Collection and Analysis **Section 10.3** Analysis Populations **Section 10.5.4** Pharmacokinetic Analysis	Protocol amendment 1 added plasma sample collection for PopPK analyses; this included the addition of a corresponding exploratory objective, the addition of Section 9.2, describing collection and analysis of samples, and additions / amendments to the statistical methods defining the PopPK analysis set and discussing analysis and summarization of data.	This addition is intended to provide additional evidence regarding the pharmacokinetics of TAS-120.
Section 4.1 Inclusion Criteria	Inclusion Criterion #4 was updated with several clarifications related to permitted prior therapies	Clarification of intended practice.
Section 4.1 Inclusion Criteria *And throughout document.*	Increased the required duration of contraception to 1 year after last dose of fulvestrant.	This change was made to ensure consistency with the approved US prescribing information for fulvestrant.
Section 4.3 Screen Failure	Corrected prior text indicating that patients who do not meet entry criteria may be rescreened up to 3 times (patients may be rescreened up to 2 times).	Correction of error.
Section 5.2 Definition of a Dose-Limiting Toxicity (Cohort 4 Only)	The definition of a DLT provided in Table 3 was modified per regulatory feedback.	All changes made per request by the FDA.
Section 5.3.1.1 Dose and Schedule Modifications for TAS-120: General Considerations	Specified that for Cohort 4, in cases where toxicity is not clearly attributable to either study drug, TAS-120 will be modified or discontinued first.	Clarification of intended practice.
Section 6.1.4 Laboratory Assessments	Removed requirement that corrected value for calcium be provided.	Administrative change to reduce risk of calculation errors.

PROTOCOL SYNOPSIS

Name of Sponsor/Company: Taiho Oncology, Inc.	**Name of Investigational Product:** TAS-120
Title of Study: A Phase 2 Study of TAS-120 in Metastatic Breast Cancers Harboring Fibroblast Growth Factor Receptor (*FGFR*) Amplifications	
Phase of Development: Phase 2	

Study Rationale:

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. 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.

Accordingly, this Phase 2 study will include patients with breast cancer harboring *FGFR* gene amplifications. Recent evidence suggests that the addition of an FGFR inhibitor may overcome resistance to hormonal therapy in breast cancer (Turner et al. 2010). Accordingly, patients in this study will receive either single-agent TAS-120 or combination treatment comprising TAS-120 and fulvestrant.

A safety lead-in will be performed for the combination of TAS-120 and fulvestrant to assess any overlapping or exacerbated toxicities with adjustment of the dose of TAS-120 if required.

The maximum tolerated dose (MTD) of TAS-120 is 20 mg QD (continuous daily dosing), based on the results of the Phase 1 dose escalation portion of Study TAS-120-101. Accordingly, the starting dose of TAS-120 in this Phase 2 study will be 20 mg QD.

Objectives and Endpoints:

Primary

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); and
- 6-month progression-free survival (PFS) rate in patients with centrally confirmed high level *FGFR1* amplification and measurable disease (Cohort 4)

Secondary

- 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 1-3.
- To evaluate the duration of response (DOR) among patients with objective response in any cohort.
- 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.

Exploratory

- 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.
- To explore PK of TAS-120 by population pharmacokinetic (PopPK) analysis and exposure-response analyses.

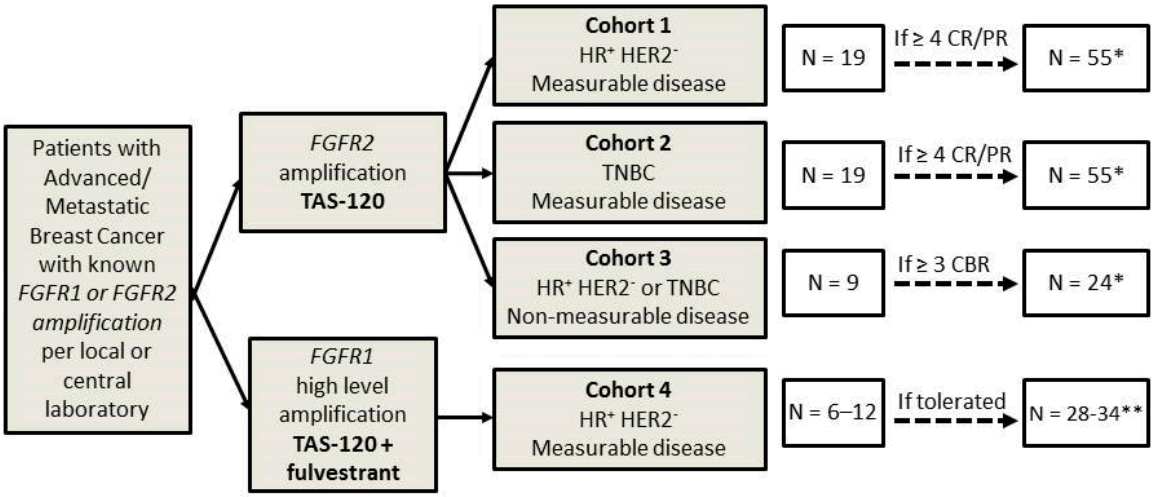
Name of Sponsor/Company:	**Name of Investigational Product:**
Taiho Oncology, Inc.	TAS-120

Title of Study:

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

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



* 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.

In all cohorts, a treatment cycle is defined as 28 days. All patients will receive oral (PO) TAS-120 at a dose of 20 mg QD (continuous daily dosing). Patients in Cohort 4 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 stable disease [SD] ≥24 weeks), 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.

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Patients will be assessed for dose-limiting toxicities (DLTs) and the recommended dose of TAS-120 for this cohort will be determined on the basis of this assessment; a total of 28 patients will ultimately be enrolled and treated at the recommended dose.

Number of Patients:
Up to approximately 168 patients will be enrolled in this study.

Inclusion/Exclusion Criteria:

Inclusion:

A patient must meet all of the following inclusion criteria to be eligible for participation in this study.

1. Patient provides written informed consent.
2. Patient is ≥18 years of age (or meets the country's regulatory definition for legal adult age, whichever is greater)
3. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
4. Histologically or cytologically confirmed recurrent locally advanced or metastatic breast cancer not amenable to treatment with curative intent, meeting all of the criteria for 1 of the following cohorts:
   - **A. Cohort 1**
     - i. Hormone receptor positive (HR+) human epidermal growth factor receptor 2 negative (HER2-) breast cancer harboring an *FGFR2* gene amplification. HR+ HER2- breast cancer is defined per the local pathology report as estrogen receptor (ER) >1% and/or, progesterone receptor (PR) >1%, HER2-negative per the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) guidelines, 2018.
     - ii. Measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1
     - iii. Has received 1-3 prior endocrine-containing therapies and up to 2 prior chemotherapy regimens for advanced/metastatic disease
     - iv. Has received prior treatment with a CDK4/6 inhibitor or is ineligible for such treatment (per Investigator decision)
     - v. Has experienced disease progression/recurrence within 1 month following the completion of any endocrine therapy for advanced/metastatic breast cancer
   - **B. Cohort 2**
     - i. Triple Negative Breast Cancer (TNBC) harboring an *FGFR2* gene amplification. TNBC is defined as negative for ER, PR and HER2. Negative for ER and PR includes the following: local pathology report classifies them as negative, Allred Score of 2 or below or <1% staining. HER2-negative per ASCO / CAP guidelines, 2018.
     - ii. Measurable disease per RECIST 1.1
     - iii. Has received at least 1 prior chemotherapy or chemotherapy/immunotherapy (PD-L1/PD-1 inhibitors) regimen for advanced/metastatic disease
     - iv. Has experienced disease progression/recurrence during or after the most recent prior chemotherapy for advanced/metastatic breast cancer
   - **C. Cohort 3**
     - i. TNBC or HR+ HER2- breast cancer (defined as above) harboring an *FGFR2* gene amplification
     - ii. Nonmeasurable, evaluable disease per RECIST 1.1. Patients with bone-only disease must have lytic or mixed lytic-blastic lesions
     - iii. Other criteria for either HR+ HER2- breast cancer or TNBC should be met as described for Cohort 1 and 2, respectively
   - **D. Cohort 4**
     - i. HR^+ $HER2^-$ breast cancer (defined as above) harboring an *FGFR1* high-level gene amplification as defined in Section 6.1.1.1

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ii. Measurable disease per RECIST 1.1
iii. Has received 1-2 prior endocrine-containing therapies and no more than 1 prior chemotherapy regimen for advanced/metastatic disease. Prior treatment with fulvestrant is not permitted.
iv. Has received prior treatment with a CDK4/6 inhibitor or is ineligible for such treatment (per Investigator decision)
v. Pre/peri-menopausal patients must be on goserelin. Patients must have commenced treatment with goserelin or an alternative GnRH agonist at least 4 weeks prior to the first dose of fulvestrant. If patients have received an alternative GnRH agonist prior to study entry, they must switch to goserelin for the duration of the trial. Postmenopausal is defined as at least one of the following criteria: age ≥60 years; age <60 years and cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and serum estradiol and follicle-stimulating hormone level within the laboratory's reference range for postmenopausal females; or documented bilateral oophorectomy.
vi. Has experienced disease progression/recurrence within 1 month following the completion of any endocrine therapy for advanced/metastatic breast cancer.

5. Archival or (preferably) fresh tumor tissue must be available for central laboratory confirmation of *FGFR* amplification.
6. The patient is able to take medications orally (a feeding tube is not permitted).
7. The patient has adequate organ function as defined by the following criteria:
   a. AST and ALT ≤3.0×ULN; if liver function abnormalities are due to underlying liver metastases, AST and ALT ≤5×ULN.
   b. Total bilirubin ≤1.5×ULN or ≤3×ULN in case of Gilbert's syndrome
   c. Absolute neutrophil count (ANC) $\geq 1.0\times10^9$/L without hematopoietic growth factor support
   d. Platelet count $\geq 75\times10^9$/L without transfusion support (that is, excluding measurements obtained within 3 days after transfusion of platelets)
   e. Hemoglobin ≥9.0 g/dL without transfusion support (that is, excluding measurements within 7 days after transfusion of packed red blood cells or whole blood)
   f. Serum phosphorus ≤ ULN
   g. Creatinine clearance (calculated or measured value): ≥40 mL/min
8. Women of child-bearing potential (WOCBP) must have a negative serum pregnancy test prior to administration of the first dose of TAS-120. Female patients are not considered to be of child-bearing potential if they have a history of hysterectomy or are post-menopausal, defined as no menses for 12 months without an alternative medical cause. Both males and females of reproductive potential must agree to use effective birth control during the study prior to the first dose and for 90 days after the last dose of TAS-120 and 1 year after last dose of fulvestrant (Cohort 4 only).
9. The patient is willing and able to comply with scheduled visits and study procedures.

Exclusion:

A patient must not meet any of the following exclusion criteria to be eligible for participation in this study:

10. History and/or current evidence of any of the following disorders:
    a. Non-tumor related alteration of the calcium-phosphorus homeostasis that is considered clinically significant in the opinion of the Investigator
    b. Ectopic mineralization/calcification, including but not limited to soft tissue, kidneys, intestine, or myocardia and lung, considered clinically significant in the opinion of the Investigator
    c. Retinal or corneal disorder confirmed by retinal/corneal examination and considered clinically significant in the opinion of the Investigator.
11. Corrected QT interval using Fridericia's formula (QTcF) >470 msec. Patients with an atrioventricular pacemaker or other condition (for example, right bundle branch block) that renders the QT measurement

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invalid are an exception and the criterion does not apply.

12. Treatment with any of the following within the specified time frame prior to the first dose of TAS-120:
    a. Major surgery within 4 weeks (the surgical incision should be fully healed)
    b. Radiotherapy for extended field within 4 weeks or limited field radiotherapy within 2 weeks
    c. Any prior systemic therapy regardless of the stop date, but the patient must have recovered to eligibility levels from prior toxicity
    d. Any investigational agent received within 30 days or 5 half-lives (whichever is shorter)
13. Prior treatment with an FGFR inhibitor
14. **Cohort 4 only:** Prior treatment with fulvestrant, or known hypersensitivity to fulvestrant.
15. A serious illness or medical condition(s) including but not limited to the following:
    a. Known acute systemic infection
    b. Myocardial infarction, severe/unstable angina, or symptomatic congestive heart failure within the previous 6 months
    c. History or current evidence of serious uncontrolled ventricular arrhythmia
    d. Chronic diarrhea diseases considered to be clinically significant in the opinion of the Investigator
    e. Congenital long QT syndrome, or any known history of torsade de pointes, or family history of unexplained sudden death
    f. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or TAS-120 administration, or may interfere with the interpretation of study results, and in the judgment of the Investigator would make the patient inappropriate for entry into this study
16. Brain metastases that are untreated or clinically or radiologically unstable (that is, have been stable for <1 month).
17. History of another primary malignancy that is currently clinically significant or currently requires active intervention
18. Pregnant or lactating female

Pharmacokinetics:

Samples will be collected for PopPK analysis, including estimation of steady-state exposure such as area under the plasma-concentration time curve (AUC). PopPK samples will be collected on Cycle 2, Day 1, 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. Details on the collection will be provided in a separate Laboratory manual. Detailed analytical procedures will be described in the SAP.

Pharmacodynamics:

The pharmacodynamic biomarker population will consist of all patients who received TAS-120 and have evaluable pharmacodynamic biomarker data.

A blood sample will be collected to assess *FGF/FGFR* aberrations in ctDNA prior to the first TAS-120 administration on Day 1 of Cycle 1, on Day 1 of each alternative uneven cycle (Cycle 3, 5, 7 and ongoing), at time of disease progression, and at the end-of-treatment (EOT) visit.

Archival or fresh tumor biopsy samples will be collected during the screening period to retrospectively confirm *FGFR* gene status at the Sponsor's designated central laboratories. Optional pre- and post-treatment tumor biopsies for pharmacodynamic assessment will be collected from patients who consent at Baseline, at the end of Cycle 1 (Cycle 1 Day 28 ± 7 days), and at the time of disease progression. These samples are being collected for exploratory analysis to evaluate the changes of downstream protein activation and other markers that may be associated with response and/or development of resistance to TAS-120 in tumor tissues.

Criteria for Evaluation:

Efficacy

Measurements will be performed throughout study treatment using RECIST guidelines (version 1.1, 2009).

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Radiographic tumor assessments (computed tomography [CT] scan with contrast) will be performed at baseline and at the end of every 8 weeks/2 cycles (±1 week) or as clinically indicated until disease progression, death, or withdrawal of consent, and at the end of therapy. Magnetic Resonance Imaging (MRI) scans may be performed if required to assess measurable lesions. The following efficacy endpoints will be evaluated:

- **ORR:** defined as the proportion of patients with a confirmed response of either CR or PR per Investigator assessment.
- **CBR (Cohort 3):** defined as the proportion of patients with a confirmed response of CR, or SD lasting at least 24 weeks, per Investigator assessment.
- **CBR (All Other Cohorts):** defined as the proportion of patients with a confirmed response of CR or PR, or SD lasting at least 24 weeks, per Investigator assessment.
- **6-month PFS rate:** defined as the proportion of patients who are alive and progression-free 6 months after the first dose of study therapy.
- **DOR:** defined as the time from first documentation of objective response to the date of death (any cause) or disease progression per Investigator assessment.
- **PFS:** defined as the time from the first dose of study therapy to the date of death (any cause) or disease progression per Investigator assessment.
- **OS:** defined as the time (in months) from the first dose of study therapy to the date of death (any cause).

Safety

Standard safety monitoring and grading of treatment-emergent adverse events (AEs) will be performed using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (Version 5.0). Other safety evaluations will include vital signs, electrocardiogram (ECG), ophthalmology exams, and laboratory testing (hematology, chemistry, coagulation). Evaluation of DLTs will be performed for Cohort 4 only.

Statistical Methods:

Approximately 168 patients in total may be enrolled in the study. 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 ≥11 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.

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Interim Analyses: Per the study design described above, the Sponsor will review the data at the time a cohort has the required number of patients to determine if that particular cohort should continue.	
Countries: Patients will be enrolled at study sites in the United States (US) and internationally.	
Number of Sites: This study will be conducted at approximately 75 sites globally.	

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									
		1	**4 (±1d)**	**8 (±1d)**	**15 (±1d)**	**22 (±1d)**	**Day 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		See Appendix A.
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 according to this schedule 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.
Sample collection for PopPK Analysis							X				On Cycle 2 Day 1 only, PopPK samples will be collected 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
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.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Term	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the plasma concentration time curve
BCRP	breast cancer resistance protein
CAP	College of American Pathologists
CBR	clinical benefit rate
CCA	cholangiocarcinoma
Ccr	creatinine clearance
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
cPR	confirmed partial response
CR	complete response
CT	computed tomography
ctDNA	circulating tumor DNA
CYP	Cytochrome P450
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOT	end-of-treatment
ER	estrogen receptor
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
FISH	fluorescence in situ hybridization
GCP	Good Clinical Practice
GI_{50}	50% cell growth-inhibitory concentration
GnRH	gonadotropin-releasing hormone
HER2	human epidermal growth factor receptor 2
HR	hormone receptor
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee

Term	Definition
IM	intramuscular
IRB	institutional review board
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
P-gp	P-glycoprotein
PI	prescribing information
PK	pharmacokinetics
PO	oral
PopPK	population pharmacokinetics
PR	partial response OR progesterone receptor
QD	daily
QTcF	corrected QT interval using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SOP	Standard Operating Procedures
TID	three times per day
TNBC	triple negative breast cancer
TOI	Taiho Oncology, Inc.
ULN	upper limit of normal
WOCBP	women of child-bearing potential

1. INTRODUCTION

1.1. Disease Background and Study Population

The fibroblast growth factor/fibroblast growth factor receptor (FGF/FGFR) signaling axis has been well characterized for its role in proliferation, differentiation, migration, and survival of cells, and it is fundamental to embryonic development, regulation of angiogenesis, and wound healing in adults.

Activating *FGFR* genomic aberrations are reported in various cancers including breast cancer, with a reported incidence of 18% (Helsten 2016). *FGFR* gene amplifications are the most frequently observed abnormality, with *FGFR2* gene amplifications observed in approximately 2% of all invasive breast cancers and *FGFR1* gene amplifications observed in approximately 10% of all invasive breast cancers, predominantly in the hormone receptor positive (HR+) breast cancers (Jain and Turner 2012, Turner et al. 2010).

The reported incidence of *FGFR2* gene amplification is approximately 1.5% in HR+ breast cancer, 2%-4% in triple negative breast cancer (TNBC) and 1% in human epidermal growth factor receptor 2 positive (HER2+) breast cancer (Razavi et al. 2018; Jain and Turner 2012, Turner 2013).

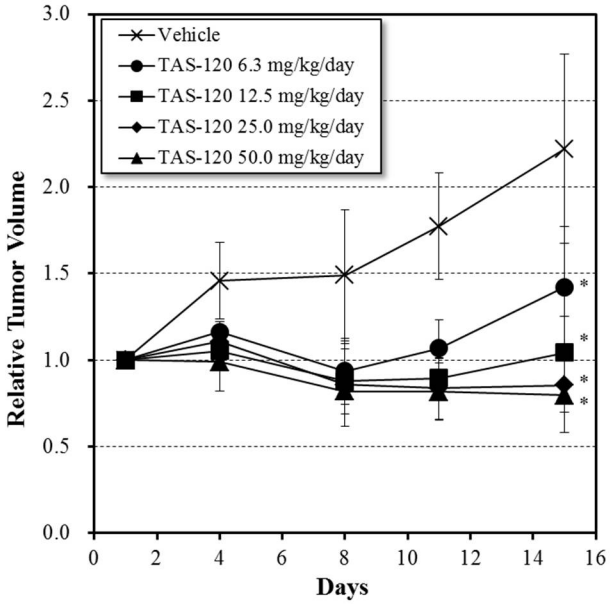
1.2. TAS-120

1.2.1. Background and Nonclinical Overview

TAS-120 is a novel and selective small molecule FGFR inhibitor, which is the first irreversible, covalent inhibitor of FGFR1–4 being tested in humans. TAS-120 selectively and irreversibly binds to FGFR to exert an inhibitory effect on the FGF/FGFR pathway.

The *in vitro* efficacy of TAS-120 against human breast carcinoma cell lines was evaluated in 2 nonclinical studies. In these studies, TAS-120 markedly inhibited the proliferation of breast cancer cell lines with *FGFR1* amplifications; the 50% cell growth-inhibitory concentration (GI_{50}) was 0.00078 ± 0.00012 µmol/L for MFM-223 cells and 0.056 ± 0.029 µmol/L for MDA-MB-134-VI cells. By contrast, the GI_{50} values for breast cancer cell lines not displaying *FGFR1* amplifications (SK-BR-3 and MCF-7) were 6.7 ± 3.3 µmol/L and 9.1 ± 3.4 µmol/L, respectively.

In vivo studies showed that TAS-120 has strong antitumor efficacy in nude mouse or nude rat xenograft models bearing tumors with various *FGFR* gene abnormalities (*FGFR1* or *2* amplification and *FGFR3* translocation). In particular, a multi-dose (range 6.3 – 50 mg/kg/day) study was performed to determine the efficacy of oral (PO) administration of TAS-120 to mice implanted with MFM-223 human breast tumor fragments harboring *FGFR1* gene amplification. In this study, TAS-120 completely suppressed the growth of MFM-223 tumors, especially at doses of 25 and 50 mg/kg/day (Figure 1).



Notes: Each plot and bar indicate the mean and standard deviation, respectively (n = 6).
* $p < 0.05$ in the TAS-120-treated group as compared with the vehicle control group by Dunnett's test.

Figure 1. Antitumor effect of TAS-120 against a human mammary carcinoma MFM-223 xenograft model

1.2.2. Clinical Overview

On the basis of encouraging *in vitro* and *in vivo* data, excerpted above and outlined in full in the Investigator's Brochure, a clinical development program was initiated for TAS-120. To date, 2 clinical studies have been completed: 1 bioequivalence study assessing 2 dosage forms, and 1 food effect study. Two studies assessing the safety, efficacy, and pharmacokinetics (PK) of TAS-120 in advanced cancers are currently ongoing: Study 10059010, a 2-step Phase 1 trial in 45 Japanese patients with advanced solid tumors, and Study TAS-120-101, a Phase 1/2 trial in three parts:

- A Phase 1 Dose Escalation portion (now complete with a total of 86 patients receiving either daily or every-other-day dosing);
- A Phase 1 Dose Expansion portion, which includes additional cohorts in cholangiocarcinoma (CCA), gliomas, urothelial carcinoma, and basket cohorts with *FGF/FGFR* aberrations; and
- A Phase 2 study initiated in April 2018, evaluating TAS-120 at a daily (QD) dose of 20 mg, in patients with CCA harboring *FGFR2* gene fusions.

The Phase 2 portion of this study was initiated based on strong evidence of antitumor activity in CCA in the Phase 1 portions. Forty-five patients with CCA harboring *FGF/FGFR* aberrations were treated at 16 mg, 20 mg, and 24 mg QD. Twenty-eight patients (62%) had *FGFR2* gene fusions; of these 28 patients, 20 (71%) experienced tumor shrinkage and seven achieved confirmed partial response (cPR). The objective response rate (ORR) was 25%, and the overall disease control rate (DCR) was 79%. Of 17 patients with other *FGF/FGFR* aberrations, three had

cPR (two with *FGFR2* re-arrangement and one with co-expression of *FGFR2* re-arrangement and amplification) (Meric-Bernstam et al. 2018).

In addition, durable responses were observed in Studies 10059010 and TAS-120-101 in 2 patients with advanced breast cancer harboring *FGFR2* gene amplifications. Specifically, a patient with TNBC and a patient with HR^+ $HER2^+$ breast cancer both achieved a cPR.

Collectively, safety data from clinical trials suggest that TAS-120 is tolerable to patients with advanced cancers. The most frequently reported treatment-related adverse event (AE) overall has been hyperphosphatemia, mostly of National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grades 1-2 and without clinical complications. Other frequently reported treatment-related AEs included the gastrointestinal system disorders of diarrhea, dry mouth, nausea, and stomatitis. Dry skin and increased liver enzymes were also reported, most of which were mild to moderate in severity.

Safety concerns that have been identified from preclinical studies of TAS-120 include an increase of inorganic phosphorus in plasma, ectopic mineralization in various organs and tissues, lesions in bone/cartilage, and corneal lesions. An embryo-fetal developmental toxicity study conducted in rats showed that TAS-120 inhibited normal development of the rat embryo-fetus and resulted in embryo-fetal lethality. Effective contraception is mandated for any patients receiving TAS-120 who are of child bearing potential and their partners.

1.3. Summary of Study Rationale

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. 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 PRs in patients with treatment-refractory breast cancer.

Accordingly, this Phase 2 study will include patients with breast cancer harboring *FGFR* gene amplifications. Recent evidence suggests that the addition of an FGFR inhibitor may overcome resistance to hormonal therapy in breast cancer (Turner et al. 2010). Accordingly, patients in this study will receive either single-agent TAS-120 or combination treatment comprising TAS-120 and fulvestrant.

A safety lead-in will be performed for the combination of TAS-120 and fulvestrant to assess any overlapping or exacerbated toxicities with adjustment of the dose of TAS-120 if required.

The maximum tolerated dose of TAS-120 is 20 mg QD (continuous daily dosing), based on the results of the Phase 1 dose escalation portion of Study TAS-120-101. Accordingly, the starting dose of TAS-120 in this Phase 2 study will be 20 mg QD.

Population plasma PK samples will be obtained to explore PK of TAS-120 by population pharmacokinetic (PopPK) analysis and exposure-response analyses.

2. OBJECTIVES AND ENDPOINTS

The objectives and endpoints of this study are shown in Table 2.

Table 2: Objectives and Endpoints

Primary	
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:	
• ORR in patients with centrally confirmed *FGFR2* amplification and measurable disease (*Cohorts 1, 2*);	ORR, defined as the proportion of patients with a confirmed response of either complete response (CR) or partial response (PR) per Investigator assessment.
• Clinical benefit rate (CBR) in patients with centrally confirmed *FGFR2* amplification and nonmeasurable, evaluable disease (*Cohort 3*); and	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.
• 6-month progression-free survival (PFS) rate in patients with centrally confirmed high level *FGFR1* amplification and measurable disease (*Cohort 4*).	6-month PFS rate, defined as the proportion of patients who are alive and progression-free 6 months after the first dose of study therapy.
Secondary	
The secondary objectives of this study are:	
• To determine the 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 1-3;	ORR, CR rate, CBR, and 6-month PFS rate, as defined above; CBR will include PR in these cohorts.
• To evaluate the duration of response (DOR) among patients with objective response in any cohort;	DOR, defined as the time from first documentation of objective response to the date of death (any cause) or disease progression per Investigator assessment.
• To evaluate the PFS and overall survival (OS) in all cohorts; and	PFS, defined as the time from first dose of study therapy to the date of death (any cause) or disease progression per Investigator assessment. OS, defined as the time from first dose of study therapy to the date of death (any cause).
• To investigate the safety of TAS-120 as monotherapy and in combination with fulvestrant.	Adverse events, graded according to the NCI-CTCAE, Version 5.0. Evaluation of dose-limiting toxicity (DLT) in Cohort 4 only.

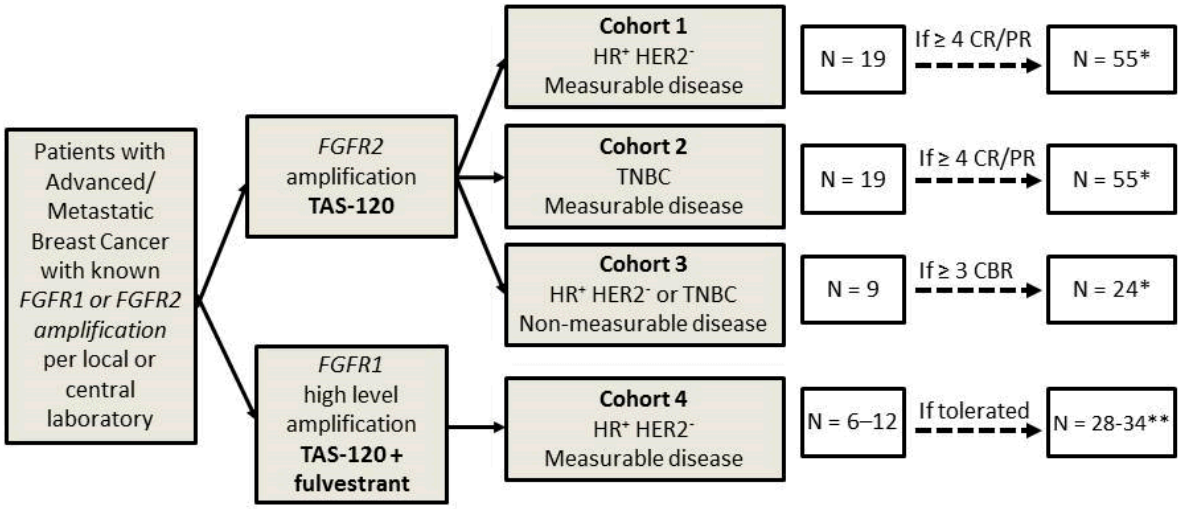
Exploratory	
The exploratory objectives of this study are:	
• To investigate the downstream pharmacodynamic effects of treatment with TAS-120;	Changes in pharmacodynamic markers assessed in fresh tumor tissue biopsies.
• To explore markers of response and mechanisms of resistance in tumor tissue biopsies and/or blood; and	Exploratory association of tissue and/or blood markers with tumor efficacy endpoints and/or tumor resistance to TAS-120.
• To explore PK of TAS-120 by PopPK analysis and exposure-response analyses.	Estimation of individual PK parameters such as AUC and exploratory association of the exposure with clinical parameters.

3. INVESTIGATIONAL PLAN

3.1. Overview 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 2).



* 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 2. 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 (Section 4.4). 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.

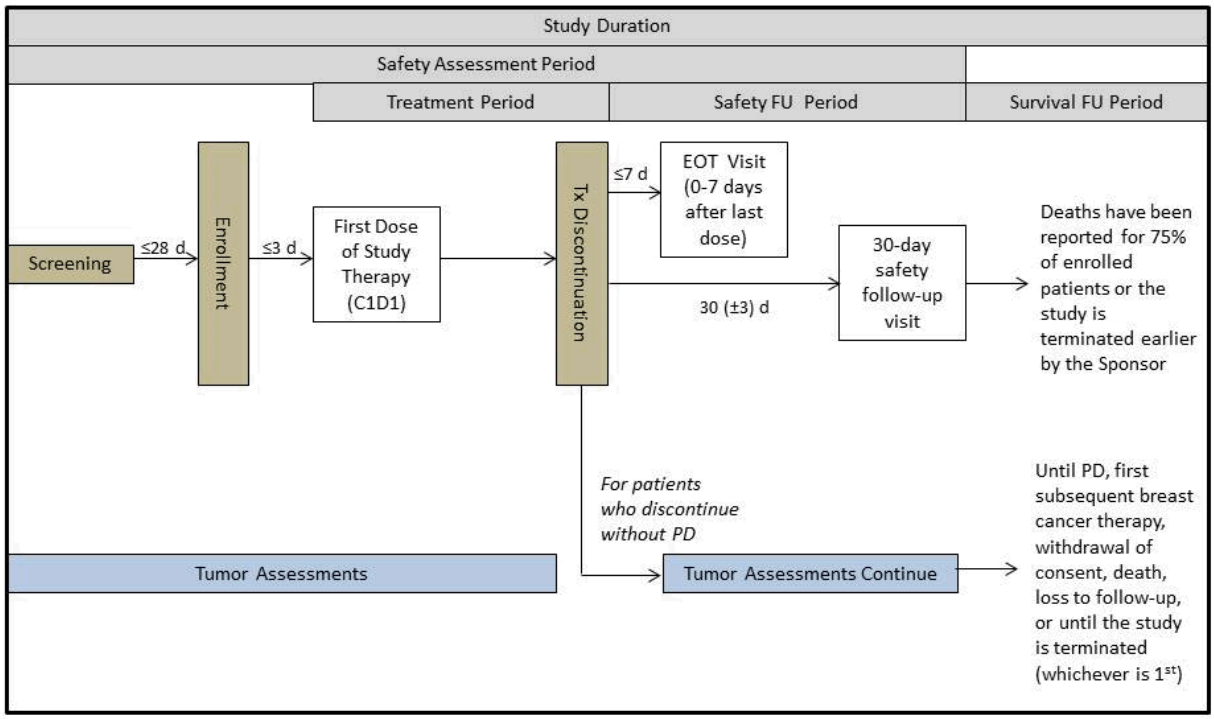
3.2. Study Periods and Visits for Each Patient

The study periods / visits described in this section are defined for all patients, and summarized in Figure 3. Please note:

- For all patients, the Safety Assessment Period begins at the time the informed consent form (ICF) is signed for the study (that is, the beginning of the Screening Period) and continues until at least 30 days after the last day of study therapy (that is, the end of the Safety Follow-up Period). After the 30-day Safety Follow-Up Visit (see below), patients will be assessed for drug-related serious adverse events (SAEs) only.

- For each patient, the Study Duration is defined as the time from day of ICF signature to the last day of Disease Assessment Follow-up / Survival Follow-up (see below).

No protocol-specific procedures or assessments may be performed prior to completion of the ICF, except for those that represent standard-of-care.



Abbreviations: C=Cycle; D=Day; d=days; EOT=end-of-treatment; FU=follow-up; PD=progressive disease; Tx=treatment.

Figure 3. Overview of study periods and visits

3.2.1. Screening Period

The Screening Period is defined as the time from the time the patient completes the ICF form until the date and time of first dose of study therapy. Unless otherwise described in the Schedule of Events (Table 1), all screening assessments must be performed within 28 days prior to the first dose of study therapy.

Determination of eligibility is based on the entry criteria enumerated in Section 4, including determination of *FGFR1* or *FGFR2* amplification status per the methods described in Section 6.1.1 of this protocol.

3.2.2. Patient Enrollment

Once the ICF is signed, the patient will be assigned a unique patient identification number. Once study eligibility is confirmed, the patient will be enrolled into the appropriate treatment cohort.

3.2.3. Treatment Period and End of Treatment Visit

Treatment discontinuation may occur for any of the reasons listed in Section 4.4. The treatment period is the time from the date of first dose of study therapy (Day 1) to the date of last dose of study therapy. An end-of-treatment (EOT) visit must be performed within 7 days after the decision is made to discontinue study treatment; at this visit, every effort should be made to perform the assessments outlined in Table 1. 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.

3.2.4. Safety Follow-Up Period and 30-Day Safety Follow-Up Visit

The safety follow-up period is the time from the date of last dose of study therapy through the 30-day safety follow-up visit, which must be performed 30 days (±3 days) following the last dose of study therapy. If the patient starts new anticancer therapy within 30 days of the last dose of TAS-120, the 30-day safety follow-up visit should be performed before the start of new anticancer therapy. Every effort should be made to perform the assessments outlined in Table 1. If the patient is unable to return to the study site, a follow-up phone call can be made by the study site to collect any new safety information that occurred during the Safety Follow-up Period.

After the 30-day Safety Visit, only AEs that are serious and drug-related will be assessed.

3.2.5. Post-Discontinuation Disease Assessment

Patients who discontinue without documented disease progression should continue to undergo tumor assessments/scans according to the Schedule of Events (that is, every 12 weeks ±7 days until progressive disease (PD) is documented, new anticancer therapy is initiated, the study is terminated, or the patient dies, withdraws consent, or is lost to follow-up).

3.2.6. Survival Follow-Up

Once disease progression is confirmed or the first subsequent new breast cancer therapy is initiated, whichever occurs first, the survival follow-up period begins. During this period, the patient or family should be contacted for survival follow-up every 12 weeks (±2 weeks) until withdrawal of consent, death, or loss to follow up, until survival events (deaths) have been reported for 75% of enrolled patients or the study is terminated earlier by the Sponsor. In addition, all subsequent breast cancer treatments will be recorded.

3.3. Study Completion and Study Extension

The study will be considered complete when:

- Survival events (deaths) have been reported for 75% of enrolled patients; or
- The trial is halted early for any reason.

Following Study Completion, patients still receiving and deriving benefit from study therapy in the opinion of the Investigator and Sponsor will be permitted to continue treatment in a Study Extension phase. During the Study Extension, patients may receive treatment until withdrawal criteria are met. During this period, limited information will be collected as follows (including but not limited to):

- Study drug administration;
- Study drug accountability;
- Serious adverse events;
- Non-serious adverse events that are related to study treatment or result in treatment discontinuation; and
- Any cases of pregnancy, overdose, or medication error.

3.4. Randomization and Blinding

This is an open-label, non-randomized study.

4. SELECTION AND WITHDRAWAL OF PATIENTS

Determination of *FGFR* amplification status should be completed before the patient undergoes any other protocol-specific procedures. Patients must have either HR+ HER2- breast cancer or TNBC harboring an *FGFR2* amplification, or HR+ HER2- breast cancer harboring an *FGFR1* high-level amplification (Section 6.1.1).

Waivers will not be granted for any of the eligibility criteria.

4.1. Inclusion Criteria

A patient must meet all of the following inclusion criteria to be eligible for this study.

1. Patient provides written informed consent.
2. Patient is ≥18 years of age (or meets the country's regulatory definition for legal adult age, whichever is greater)
3. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
4. Histologically or cytologically confirmed recurrent locally advanced or metastatic breast cancer not amenable to treatment with curative intent, meeting all of the criteria for 1 of the following cohorts:

A. Cohort 1

i. HR+ HER2- breast cancer harboring an *FGFR2* gene amplification. HR+ HER2- breast cancer is defined per the local pathology report as estrogen receptor (ER) >1% and/or progesterone receptor (PR) >1%, HER2-negative per American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) guidelines, 2018.
ii. Measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1
iii. Has received 1-3 prior endocrine-containing therapies and up to 2 prior chemotherapy regimens for advanced/metastatic disease
iv. Has received prior treatment with a CDK4/6 inhibitor or is ineligible for such treatment (per Investigator decision)
v. Has experienced disease progression/recurrence within 1 month following the completion of any endocrine therapy for advanced/metastatic breast cancer

B. Cohort 2

i. TNBC harboring an *FGFR2* gene amplification. TNBC is defined as negative for ER, PR and HER2. Negative for ER and PR includes the following: local pathology report classifies them as negative, Allred Score of 2 or below or <1% staining. HER2-negative per ASCO / CAP guidelines, 2018.
ii. Measurable disease per RECIST 1.1
iii. Has received at least 1 prior chemotherapy or chemotherapy/immunotherapy (PD-L1/PD-1 inhibitors) regimen for advanced/metastatic disease
iv. Has experienced disease progression/recurrence during or after the most recent prior chemotherapy for advanced/metastatic breast cancer

C. Cohort 3

i. TNBC or HR+ HER2- breast cancer (defined as above) harboring an *FGFR2* gene amplification
ii. Non-measurable, evaluable disease per RECIST 1.1. Patients with bone-only disease must have lytic or mixed lytic-blastic lesions
iii. Other criteria for either HR+ HER2- breast cancer or TNBC should be met as described for Cohort 1 and 2, respectively

D. Cohort 4

i. HR^+ $HER2^-$ breast cancer (defined as above) harboring an *FGFR1* high-level gene amplification as defined in Section 6.1.1.1
ii. Measurable disease per RECIST 1.1
iii. Has received 1-2 prior endocrine-containing therapies and no more than 1 prior chemotherapy regimen for advanced/metastatic disease. Prior treatment with fulvestrant is not permitted.
iv. Has received prior treatment with a CDK4/6 inhibitor or is ineligible for such treatment (per Investigator decision)
v. Pre/peri-menopausal patients must be on goserelin. Patients must have commenced treatment with goserelin or an alternative GnRH agonist at least 4 weeks prior to the first dose of fulvestrant. If patients have received an alternative GnRH agonist prior to study entry, they must switch to goserelin for the duration of the trial. Postmenopausal is defined as at least one of the following criteria: age ≥60 years; age <60 years and cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and serum estradiol and follicle-stimulating hormone level within the laboratory's reference range for postmenopausal females; or documented bilateral oophorectomy.
vi. Has experienced disease progression/recurrence within 1 month following the completion of any endocrine therapy for advanced/metastatic breast cancer.

5. Archival or (preferably) fresh tumor tissue must be available for central laboratory confirmation of *FGFR* amplification.
6. The patient is able to take medications orally (a feeding tube is not permitted).
7. The patient has adequate organ function as defined by the following criteria:
   a. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3.0 × the upper limit of normal (ULN); if liver function abnormalities are due to underlying liver metastases, AST and ALT ≤5 × ULN
   b. Total bilirubin ≤1.5 × ULN or ≤3 × ULN in case of Gilbert's syndrome
   c. Absolute neutrophil count (ANC) ≥1.0 × 10^9/L without hematopoietic growth factor support
   d. Platelet count ≥75 × 10^9/L without transfusion support (that is, excluding measurements obtained within 3 days after transfusion of platelets)
   e. Hemoglobin ≥9.0 g/dL without transfusion support (that is, excluding measurements within 7 days after transfusion of packed red blood cells or whole blood)
   f. Serum phosphorus ≤ ULN

g. Creatinine clearance (calculated or measured value): ≥40 mL/min

8. Women of child-bearing potential (WOCBP) must have a negative serum pregnancy test prior to administration of the first dose of TAS-120. Female patients are not considered to be of child-bearing potential if they have a history of hysterectomy or are post-menopausal, defined as above. Both males and females of reproductive potential must agree to use effective birth control during the study prior to the first dose and for 90 days after the last dose of TAS-120 and 1 year after last dose of fulvestrant (Cohort 4 only).
9. The patient is willing and able to comply with scheduled visits and study procedures.

4.2. Exclusion Criteria

A patient must not meet any of the following exclusion criteria to be eligible for this study:

10. History and/or current evidence of any of the following disorders:
    a. Non-tumor related alteration of the calcium-phosphorus homeostasis that is considered clinically significant in the opinion of the Investigator
    b. Ectopic mineralization/calcification, including but not limited to soft tissue, kidneys, intestine, or myocardia and lung, considered clinically significant in the opinion of the Investigator
    c. Retinal or corneal disorder confirmed by retinal/corneal examination and considered clinically significant in the opinion of the Investigator.
11. Corrected QT interval using Fridericia's formula (QTcF) >470 msec. Patients with an atrioventricular pacemaker or other condition (for example, right bundle branch block) that renders the QT measurement invalid are an exception and the criterion does not apply.
12. Treatment with any of the following within the specified time frame prior to the first dose of TAS-120:
    a. Major surgery within 4 weeks (the surgical incision should be fully healed)
    b. Radiotherapy for extended field within 4 weeks or limited field radiotherapy within 2 weeks
    c. Any prior systemic therapy regardless of the stop date, but the patient must have recovered to eligibility levels from prior toxicity
    d. Any investigational agent received within 30 days or 5 half-lives (whichever is shorter)
13. Prior treatment with an FGFR inhibitor
14. **Cohort 4 only:** Prior treatment with fulvestrant, or known hypersensitivity to fulvestrant.
15. A serious illness or medical condition(s) including but not limited to the following:
    a. Known acute systemic infection
    b. Myocardial infarction, severe/unstable angina, or symptomatic congestive heart failure within the previous 6 months
    c. History or current evidence of serious uncontrolled ventricular arrhythmia
    d. Chronic diarrhea diseases considered to be clinically significant in the opinion of the Investigator

e. Congenital long QT syndrome, or any known history of torsade de pointes, or family history of unexplained sudden death
f. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or TAS-120 administration, or may interfere with the interpretation of study results, and in the judgment of the Investigator would make the patient inappropriate for entry into this study

16. Brain metastases that are untreated or clinically or radiologically unstable (that is, have been stable for <1 month)
17. History of another primary malignancy that is currently clinically significant or currently requires active intervention
18. Pregnant or lactating female

4.3. Screen Failure

Screen failures are defined as patients who consent to participate in any portion of the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to Regulatory Authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE occurring after completion of the ICF. Patients who do not meet the criteria for participation in this study (screen failure) may be rescreened a maximum of 2 times.

4.4. Discontinuation of Treatment

A patient may be discontinued from all study therapy for any of the following reasons:

1. Disease progression based on RECIST 1.1;
2. Clinical disease progression per Investigator judgement;
3. Unacceptable AEs, or change in underlying condition such that the patient can no longer tolerate therapy, as evidenced by a dose delay > 28 days from the scheduled start date of the next cycle or need for more than the allowable number of dose reductions outlined in this protocol;
4. Physician's decision, including need for other anticancer therapy not specified in the protocol, or surgery or radiotherapy to the only site(s) of disease being followed in the study;
5. Pregnancy;
6. A significant protocol deviation which, in the opinion of the Investigator and/or Sponsor, renders the patient unsuitable for further study treatment;
7. Loss to follow-up;
8. Death;
9. Termination of the study by the Sponsor; or
10. At the patient's request at any time irrespective of the reason.

Patients who withdraw consent for further treatment (treatment discontinuation criterion #10) may choose to remain on study; in such a case, all study evaluations should continue as outlined in this protocol. If the patient withdraws consent to all follow-up, the patient should be considered to have discontinued the study as described in Section 4.5.

The primary reason for discontinuation should be documented in the electronic case report form (eCRF).

If there is strong evidence of clinical benefit and reasons to justify continuation of the study drug, even though treatment discontinuation criteria have been met, this decision must be reviewed with the Sponsor on a case-by-case basis, and continuation of therapy may be allowed assuming all other treatment resumption criteria have been met.

4.5. Discontinuation from the Study

A patient may be discontinued from all study interventions and assessments (that is, discontinued from the study without follow-up) for any of the following reasons:

1. Death;
2. Loss to follow-up / contact despite best effort of investigative site personnel (that is, after at least 2 documented attempts to contact the patient and/or family); or
3. Patient withdrawal of consent to further follow-up, irrespective of the reason.

5. STUDY TREATMENT

5.1. Study Drug Administration

5.1.1. TAS-120

A treatment cycle is defined as 28 days; however, TAS-120 is dosed continuously every day with no planned interruption between cycles.

TAS-120 is supplied as 4-mg tablets and will be taken PO at a dose of 20 mg QD in Cohorts 1, 2, and 3. In Cohort 4, TAS-120 will be taken PO at a dose of 20 or 16 mg QD, depending on the DLT observations in the safety lead-in phase.

TAS-120 should be taken under fasting conditions. It will be taken with a glass of water, on an empty stomach, every 24 hours in the morning or evening at the same time each day, if possible. No food should be consumed for 2 hours prior and 1 hour after the dose of TAS-120, but patients will be permitted to drink water during this period.

In the event of a dosing delay up to 12 hours after the scheduled dosing time, the patient should still take that day's dose. If the dosing delay continues for >12 hours after the scheduled dosing time, or if the patient vomits after a dose, the patient should skip dosing for that day and not make up for it the following day.

Please note: dietary restrictions that limit phosphate intake may reduce the risk of hyperphosphatemia (Appendix B).

5.1.2. Fulvestrant

Fulvestrant (Faslodex®) will be administered to patients in Cohort 4 only according to the approved commercial labeling.

Fulvestrant 500 mg will be administered IM into the buttocks (gluteal area), slowly (1 – 2 minutes per injection), as two 5-mL injections, one in each buttock, on Days 1 and 15 of Cycle 1, then Day 1 every subsequent cycle thereafter (every 28 days ± 3 days).

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 GnRH analogue at least 4 weeks prior to the first dose of fulvestrant.

5.1.3. Treatment Duration

There is no predefined duration of treatment. In all cohorts, study therapy may continue until disease progression, unacceptable toxicity, or any other criteria for treatment discontinuation is met (see Section 4.4).

5.2. Definition of a Dose-Limiting Toxicity (Cohort 4 Only)

For patients in the safety lead-in portion of Cohort 4 only, a DLT is defined as any AE that is not clearly attributable to an extraneous cause, such as an underlying disease, occurring in Cycle 1 and meeting at least one of the following criteria (Table 3).

Table 3: Dose Limiting Toxicity Definition

Hematologic Toxicity	Grade 4 neutropenia lasting >7 consecutive days Grade 4 thrombocytopenia lasting >7 consecutive days ≥ Grade 3 thrombocytopenia with bleeding Febrile neutropenia (ANC <1000/mm^3 with a single body temperature of >38.3°C [101°F] or a sustained temperature of ≥38°C [100.4°F] for more than 1 hour) requiring initiation of antibiotics
Hepatic Toxicity[a]	Grade 3 total bilirubin lasting >7 consecutive days Grade 4 total bilirubin Grade 3 AST and/or ALT lasting >7 consecutive days Grade 4 ALT and/or AST lasting >3 consecutive days For patients with liver metastases, AST or ALT >8 × ULN or AST or ALT >5 × ULN lasting ≥14 consecutive days
	Hy's Law criteria - concurrent observation of the following, with no other reason found to explain the findings (such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed liver injury): • Elevated aminotransferase enzymes of >3 × ULN • Alkaline phosphatase (ALP) <2 × ULN • Associated with an increase in bilirubin ≥2 × ULN
Renal Toxicity	Creatinine clearance <30 mL/min for >3 days despite optimal supportive care
Other Non-Hematologic Toxicity	≥ Grade 3[b]
Other	Any toxicities leading to a TAS-120 Cycle 1 dose intensity of <75% and/or fulvestrant dose intensity of <100% Inability to initiate Day 1 of Cycle 2 within 14 days of schedule due to any continuously ongoing Grade ≥ 2 toxicity Any death not clearly attributed to the underlying disease or extraneous causes

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; ULN=upper limit of normal.

a. For any Grade 3 or 4 hepatic toxicity not resolved within 7 days to Grade 0 – 1 (or Grade 2 if liver metastases), an abdominal computed tomography scan should be performed to assess if it is related to disease progression.

b. The following events will not be considered DLTs:

- Nausea, vomiting and diarrhea (unless they persist to be Grade ≥3 for >3 consecutive days despite optimal supportive care)
- Hyperphosphatemia (unless it persists to be Grade ≥3 for >7 consecutive days despite optimal phosphate-lowering therapy)
- Fatigue (unless it is lasting ≥1 week).
- Asymptomatic Grade ≥3 electrolyte abnormality (unless it is lasting >72 hours). For patients with clinical symptoms, however, all Grade ≥3 electrolyte abnormalities regardless of duration will be considered a DLT.
- Grade ≥3 amylase or lipase elevation not associated with symptoms or clinical manifestations of pancreatitis.

5.3. Dose and Schedule Modifications

5.3.1. Dose and Schedule Modifications for TAS-120

5.3.1.1. General Considerations

This section defines general dose modification guidelines for patients receiving TAS-120 in any cohort. For detailed discussion of TAS-120 dose modification in Cohort 4 in the setting of a DLT, see Section 3.1.

In Cohort 4, in cases where a toxicity cannot be clearly attributed to either drug (TAS-120 or fulvestrant), TAS-120 should be modified or discontinued first.

The starting dose of TAS-120 is

- 20 mg QD for all patients in Cohorts 1 – 3
- 16 or 20 mg QD in Cohort 4, depending on the observations in the safety lead-in (Section 3.1).

Dose reduction to a minimum dose of 12 mg QD is permitted, with available dose levels of 16 mg QD and 12 mg QD.

If dose reduction fails to result in achieving minimal criteria to resume treatment, or if toxicities occur which would necessitate reduction of the dose of TAS-120 below 12 mg QD, the patient should be discontinued from TAS-120.

If the TAS-120 dose is reduced, the dose will not be increased upon resumption. If a benefit/risk assessment favors the increase of dose up to the initial starting dose after dose reduction, an agreement with the Sponsor's Medical Monitor is required prior to the dose increase.

If toxicities requiring dose reduction do not recover based on the criteria defined in Table 4 through Table 6 within 28 days after the last dose of TAS-120, the patient will be discontinued permanently from the study (Section 4.4). If resumption criteria are met within 28 days of the last dose of TAS-120, the patient may resume TAS-120 treatment at the appropriate dose level.

5.3.1.2. Dose Modifications for Nonhematologic Toxicities

Dosing modification guidelines for nonhematologic toxicities are provided in Table 4.

It is highly recommended to follow these guidelines, however, at the discretion of the Investigator, patients may continue on TAS-120 at the same dose without reduction or interruption for AEs (irrespective of grade) if the AE is considered unlikely to become serious or life threatening (including but not limited to fatigue and dry skin).

If there is any uncertainty about continuing therapy or resuming therapy in a patient with Grade ≥3 nonhematologic AEs, the case must be discussed with the Sponsor's Medical Monitor prior to continuing TAS-120.

Table 4: TAS-120 Dosing Modification for Related Nonhematologic Toxicities

Grade	Dose Interruption/Resumption	Dose Adjustment
Grade 1 or 2	Maintain treatment at the same dose level, except for Grade 2 elevations of bilirubin, AST, and ALT, which should be managed as described in Table 7	None
Grade 3	Hold treatment until return to baseline or Grade ≤1	Reduce by 1 dose level from the previous level, except for Grade 3 nausea and/or vomiting controlled by aggressive antiemetic therapy or Grade 3 diarrhea responsive to antidiarrheal medication which does not require a dose hold or reduction.
Grade 4	Discontinue treatment	Permanent discontinuation of TAS-120.
Grade 4 (lab abnormality AE)	Hold treatment	TAS-120 will be permanently discontinued if assessed by the Investigator as life threatening. If it is in the best interest of the patient to continue treatment in the opinion of the Investigator and after discussion with the Sponsor, the patient can continue treatment at a reduced dose level. However, TAS-120 should first be held until toxicity returns to baseline or Grade ≤1.

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase.

Recommendations for hyperphosphatemia management are provided in Table 5. These are suggested guidelines based on emerging data from studies evaluating FGFR inhibitors, and from the experience of Investigators participating in ongoing studies of TAS-120. However, clinical judgment from treating physicians and local standard practices should be followed to decide the best management for each individual patient.

Table 5: Recommendations for Hyperphosphatemia Management

Serum Phosphorus Result[a] (mg/dL and mmol/L)[b]	Grade[c]	TAS-120 Dose Interruption and Modification Recommended Phosphate Binder for Management of Hyperphosphatemia[d]
ULN < P <5.5 (mg/dL) ULN < P <1.78 (mmol/L)	Grade 1	• No interruption, consider phosphate binder once serum phosphorus level is > ULN. • Should serum phosphorus level rapidly increase within 1 week, consider early phosphate-lowering therapy, eg, Sevelamer tablets 800 mg three times per day [TID].
5.5 ≤ P ≤7.0 (mg/dL) 1.78 ≤ P ≤2.26 (mmol/L)	Grade 2	• No interruption, implement phosphate binder (monotherapy or in combination), • Start with Sevelamer monotherapy (range from 800 mg TID to 2400 mg TID). • Re-assess serum phosphate within 7 days, and plan to escalate Sevelamer or add treatment with acetazolamide 250 mg QD or TID and/or lanthanum carbonate (Fosrenol®) 1.0 g QD or TID, and further titration[e], if phosphate level continues to increase.
7.0 < P ≤10.0 (mg/dL) 2.26< P ≤3.23 (mmol/L)	Grade 3	• Dose reduce TAS-120 to the next lower dose level and intensify phosphate lowering therapy • If the serum phosphorus level has resolved to ≤ Grade 2 within 14 days after dose reduction, continue TAS-120 at the reduced dose level. • If the serum phosphorus level has not resolved to ≤ Grade 2 after 14 days, further reduce TAS-120 from the last reduced dose level (or no lower than 12 mg QD). • If the serum phosphorus level has not resolved to ≤ Grade 2 after 14 days of the second dose reduction of TAS-120 (or no lower than 12 mg QD), interrupt dosing with TAS-120 until it is resolved to ≤ Grade 2 before resuming TAS-120 at the reduced dose prior to dose interruption.
P >10.0 (mg/dL) P >3.23 (mmol/L)	Grade 4	• Interrupt TAS-120 until it's resolved to ≤ Grade 2, then resume TAS-120 at the next lower dose level and intensify phosphate lowering therapy. If after 2 dose interruptions and 2 dose reductions the serum phosphorus level has not resolved to ≤ Grade 2 after 14 days, permanently discontinue TAS-120.

Abbreviations: P=phosphorus; QD=once a day; TID=three times a day; ULN=upper limit of normal

a. Serum phosphorus will be tested 4 days (± 24 hours) after Day 1 of Cycle 1 to initiate early intervention for hyperphosphatemia if indicated.
b. mmol/L = mg/dL × 0.3229 (conversion factor).
c. This grading for the range of serum phosphorus levels will be used for the protocol.
d. Phosphate binders can be used as monotherapy or in combination. Please consult the drug package insert. Sevelamer should be preferably taken in the middle of meals, both tablets and powder, in order to improve gastrointestinal tolerance and compliance. If Sevelamer cannot be used, other phosphate binders or hyperphosphatemia treatment drugs can be used. Lanthanum carbonate should be taken instead just after meals – tablets of Fosrenol® are quite big, but can be cut if required. No dose adjustments are needed in patients with renal or hepatic impairment.
e. Titrate the dose every 2-3 weeks until an acceptable serum phosphate level is reached.

5.3.1.3. Dose Modifications for Hematologic Toxicities

Criteria for dose interruption and resumption for hematologic toxicities are presented in Table 6.

Table 6: TAS-120 Dose Interruption and Modification Criteria for Related Hematologic Toxicities

Worst toxicity CTCAE Grade (value)	Recommended dose modification any time during a cycle of TAS-120
Anemia (Hgb)	
Grade 1 (Hgb < LLN - 10.0 g/dL)	Maintain dose level
Grade 2 (Hgb < 10 – 8.0 g/dL)	Maintain dose level
Grade 3 (Hgb < 8.0 - 6.5 g/dL)	Withhold dose until resolved to ≤ Grade 1 or baseline, • If resolved ≤7 days, then maintain dose level • If resolved >7 days, then reduce 1 dose level
Grade 4 (life threatening consequences; urgent intervention indicated)	Withhold dose until resolved to ≤ Grade 1 or baseline, then reduce 1 dose level
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1500/mm^3)	Maintain dose level
Grade 2 (ANC < 1500 - 1000/mm^3)	Maintain dose level
Grade 3 (ANC < 1000 - 500/mm^3)	Maintain dose level
Grade 4 (ANC < 500/mm^3)	Withhold dose until resolved to ≤ Grade 2 or baseline, • If resolved ≤7 days, then maintain dose level • If resolved >7 days, then reduce 1 dose level
Febrile neutropenia (ANC < 1000/mm^3, fever ≥ 38.5°C)	Withhold dose until resolved, then reduce 1 dose level
Thrombocytopenia	
Grade 1 (PLT < LLN - 75,000/mm^3)	Maintain dose level
Grade 2 (PLT < 75,000 - 50,000/mm^3)	Maintain dose level
Grade 3 (PLT < 50,000 - 25,000/mm^3)	Withhold dose until resolved to ≤ Grade 1 or baseline, • If resolved ≤7 days, then maintain dose level • If resolved >7 days, then reduce 1 dose level
Grade 4 (PLT < 25,000/mm^3)	Withhold dose until resolved to ≤ Grade 1 or baseline, then reduce 1 dose level

Abbreviations: ANC=absolute neutrophil count; CTCAE=Common Terminology Criteria for Adverse Events; Hgb=hemoglobin; LLN=lower limit of normal; PLT=platelets.

5.3.1.4. Adverse Event Follow-Up

All treatment-emergent AEs should be followed until resolution/stabilization or initiation of new anticancer therapy according to Table 7.

Table 7: Required Follow-up for Adverse Events

Toxicity	Follow-up Evaluation
Hematology	If ≥ CTCAE Grade 3 neutropenia or ≥ CTCAE Grade 3 thrombocytopenia have been demonstrated, these parameters must be repeated at least twice a week until resolution to ≤ CTCAE Grade 1 or baseline to allow for initiation of re-treatment, and then at least weekly until either initiation of re-treatment or until stabilization.
Renal	If creatinine clearance (calculated or measured value) <30 mL/min has been demonstrated, this parameter must be repeated at least twice a week until resolution to baseline to allow for initiation of re-treatment, and then at least weekly until either initiation of re-treatment or until stabilization.
Hepatic	If bilirubin ≥2×ULN or ≥ CTCAE grade 3 ALT or AST or the combination of ≥ CTCAE Grade 2 bilirubin and ≥ CTCAE Grade 2 ALT or AST elevation has been demonstrated, assessment of these parameters must be repeated at least twice a week until resolution to ≤ CTCAE Grade 1 or baseline to allow for initiation of re-treatment, and then at least weekly until either initiation of re-treatment or until stabilization. Patients with total bilirubin >1.5 × ULN, or >3.0 × ULN for patients with Gilbert's syndrome (any duration) should have fractionation of bilirubin into total/direct or indirect/direct components and any additional work-up as clinically indicated by these results. Follow-up of hyperbilirubinemia should proceed as per the guidelines above, irrespective of the results of fractionation.
Cardiac	If at any time a QTcF >480 ms and ≤500 ms is observed, a cardiology consultation must be sought to re-evaluate both baseline and abnormal electrocardiogram (ECG) finding to confirm the occurrence, severity, and causality of the AE. If at any time a QTcF >500 ms is observed, 1) Triplicate ECGs (2-3 minutes apart) need to be taken approximately 1 hour after the initial ECG. 2) If the mean QTcF is >500 ms, the patient must postpone study treatment until a cardiologist has re-evaluated the ECG. 3) The re-evaluation of ECG needs to be done as soon as practical but within 7 days of the initial abnormal ECG. 4) If the cardiologist confirms a mean QTcF >500 ms, the patient must be discontinued permanently from study.
Nonlaboratory	Patients who experience non-laboratory Grade 3 or 4 AEs must be evaluated at least once a week following demonstration of the resolution of the toxicity to allow for re-treatment, until stabilization of the toxicity, or until study completion.

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; ECG=electrocardiogram; ULN=upper limit of normal

5.3.2. Dose and Schedule Modifications for Fulvestrant

The only dose modification for fulvestrant in the prescribing information (PI) is the recommendation for a reduction to 250 mg per IM injection for patients with moderate hepatic impairment (Child-Pugh Class B). A Child-Pugh score of 7 – 9 is deemed Class B, and is a composite of scores for total bilirubin, serum albumin, prothrombin time, ascites and hepatic encephalopathy (Appendix C).

5.4. Treatment Compliance

Each patient will be instructed to comply with the dosage and dosing regimen of TAS-120. Fulvestrant will be administered to patients in Cohort 4 only in the clinic under the supervision of clinic staff; all details of administration will be recorded in the eCRF.

Compliance with all study medication administration should be documented in the patient's source documents.

5.5. Concomitant Medications and Therapies

The following therapies are permitted:

- Bisphosphonates;
- Denosumab;
- Non enzyme-inducing anticonvulsants such as gabapentin, lamotrigine, and levetiracetam;
- Steroids for patients with brain metastases; and/or
- Local or regional palliative cryotherapy or radiation, such as for bone pain or palliative surgery (non-anti-neoplastic intent), provided this is not a site of measurable disease and is not indicative of disease progression.

If, after assessment by the Investigator, radiation for brain metastasis, therapy for bone metastasis, or locoregional therapy should be initiated for the best benefit of the patient, the patient may begin such therapy a minimum of 2 days after discontinuation of TAS-120. Consequently, the patient will be censored for the primary endpoint analysis. TAS-120 may be restarted 2 weeks after completion of such treatment or when the patient has recovered from the side effects of such treatment.

The following medications/therapies may be given concomitantly under the following guidelines:

Hematologic Support: may be administered as medically indicated (that is, blood transfusions, granulocyte colony-stimulating factor, erythropoietin stimulating agents) according to the institutional site standards or ASCO guidelines (Smith et al. 2015).

Management of Diarrhea: Prophylactic treatment for diarrhea is permitted during the study if clinically indicated according to the institutional or published guidelines (Benson et al. 2004).

Management of Nausea/Vomiting: Antiemetics may be administered as clinically indicated according to institutional standards or ASCO guidelines (Hesketh et al. 2017).

5.5.1. Drug Interactions

Drug interaction studies with TAS-120 have not been conducted in humans. The following information is based on results from *in vitro* studies. Caution is advised if these drugs are given concomitantly (see Appendix D, Classification of Substrates, Inhibitors, and Inducers of CYP Enzymes and Transporters).

Cytochrome P450 (CYP) 3A inhibitors and inducers: CYP3A is involved in the metabolism of TAS-120. CYP3A inhibitors and inducers may alter the concentration and activity of TAS-120.

CYP3A substrates: TAS-120 is a potential time-dependent inhibitor of CYP3A. TAS-120 may increase the concentration and activity of CYP3A substrates.

P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) substrates and inhibitors: TAS-120 is a substrate of P-gp and BCRP, and a potential inhibitor of P-gp and BCRP. TAS-120 may alter the PK and activity of P-gp and BCRP substrates. P-gp and BCRP inhibitors may alter the concentration and activity of TAS-120.

There are no known drug-drug interactions reported for fulvestrant (Fulvestrant PI).

5.5.2. Prohibited Medications and Therapies

Patients are not permitted to receive any other investigational or any other anticancer therapy, including chemotherapy, immunotherapy, biological response modifiers, or antineoplastic endocrine therapy during the study treatment period.

Extended-field radiation therapy or palliative radiation to a focal site of measurable disease is also prohibited. If it is deemed in the best interest of the patient and after discussion between the Investigator and Sponsor, it can be administered, but the patient will be censored for the primary endpoint analysis.

5.6. Effective Contraception During Study

Female patients considered not to be of childbearing potential must have a history of being postmenopausal (no menses for 12 months without an alternative medical cause), or hysterectomy that is clearly documented in the patient's source documents.

For WOCBP, including female study participants and partners of male participants, effective contraception is required during the study and for 90 days after the last dose of TAS-120 and 1 year after last dose of fulvestrant (Cohort 4 only). Effective contraception is defined as follows:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - oral
    - intravaginal
    - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
    - oral
    - injectable
    - implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner with documentation of the success of the vasectomy
- Complete abstinence from heterosexual intercourse (periodic abstinence is not a safe method)

Male patients with partners who are WOCBP should use a male condom in combination with at least one of the effective contraception methods for WOCBP during the study and for 90 days after the last dose of TAS-120 and 1 year after last dose of fulvestrant (Cohort 4 only).

Donation of sperm or ova is not allowed during the study and for 90 days following the last dose of TAS-120 and 1 year after last dose of fulvestrant (Cohort 4 only).

5.7. Study Drug Materials and Management

TAS-120 will be supplied by the Sponsor; fulvestrant will be supplied by the Sponsor or procured by investigative sites. Detailed information, including requirements for accountability, and disposal of study drug will be provided in a separate Pharmacy Manual.

5.7.1. Description of Study Drug

5.7.1.1. TAS-120

A description of the TAS-120 study drug and packaging information are provided in Table 8.

Table 8: TAS-120 Product Description and Packaging Information

Product Description and Dosage Form	Potency/ Strength	Appearance	Primary Packaging
TAS-120 Tablet	4 mg	Round, white, film-coated tablet	Aluminum/Aclar blister

5.7.1.2. Fulvestrant

Please refer to the PI for the description of fulvestrant.

5.7.2. Packaging and Labeling

TAS-120 tablets will be packaged in child-resistant Dosepak® cards. Labeling will identify tablet counts in each card. The Dosepak® cards will be labeled with at least the following:

a. Protocol number
b. Sponsor name
c. Storage conditions
d. Study drug name
e. Tablet strength
f. Lot number
g. Number of tablets in each container
h. Investigational caution statement

Additional clinical labeling will be added as required by local regulations.

Fulvestrant will follow the packaging and labeling specified on the PI and will receive additional clinical labeling as required by local regulations.

5.7.3. Study Drug Storage

TAS-120 tablets should be stored at room temperature (according to the country's regulatory definition for room temperature) in accordance with the label.

Fulvestrant should be stored per the storage conditions specified on the PI. All study medication must be kept in a locked area with access restricted to specific study personnel.

5.7.4. Drug Accountability

The Investigator is responsible for ensuring that all TAS-120 received at the site is inventoried and accounted for throughout the study. TAS-120 will be stored and disposed of according to the Sponsor's instructions. The dispensing of TAS-120 to the patient and the return of TAS-120 from the patient must be documented in the patient's source documents/the drug accountability form. Patients must be instructed to return all original containers, whether empty or containing study drug. Dose reductions, interruptions, and reason for these actions must be recorded in the patient's source documents and eCRF.

The Investigator is responsible for ensuring that all fulvestrant received at the site is inventoried and accounted for throughout the study.

At the conclusion of the study, all study drugs supplied by the Sponsor must be destroyed or returned to the designated depot, per the instructions provided in the Pharmacy Manual.

TAS-120 is not to be used outside of this study.

6. STUDY ASSESSMENTS

6.1. Study Assessments and Procedures

The Schedule of Events (Table 1) summarizes the frequency and timing of all applicable study assessments, including allowable windows for study visits and assessments / procedures. Written informed consent must be provided before any study-related procedures are performed.

6.1.1. Determination of *FGFR1* or *FGFR2* Amplification Status

Determination of eligibility is based in part on the determination of *FGFR1* or *FGFR2* amplification status per the following methods:

6.1.1.1. High-Level *FGFR1* Amplification

- The patient must have an *FGFR1*/CEN8 ratio of ≥5 or an *FGFR1* copy number ≥10 signals per cell determined in tumor tissue using next-generation sequencing (NGS), fluorescence in situ hybridization (FISH), or other assays that can determine gene amplifications in tumor tissues.
- May be based on local Clinical Laboratory Improvement Amendments (CLIA) or other similarly certified laboratory testing on tumor tissue using NGS, FISH, or another assay that can determine gene amplifications in tumor tissues.
- Archival or (preferably) fresh tumor tissue must be available for central laboratory confirmation of *FGFR1* amplification.

6.1.1.2. *FGFR2* amplification

- May be based on local CLIA or other similarly-certified laboratory testing using NGS, FISH, or other assays that can determine gene amplifications in tumor tissues or circulating tumor DNA (ctDNA).
- Archival or (preferably) fresh tumor tissue must be available for central laboratory confirmation of *FGFR2* amplification.

6.1.2. General Assessments

The following general assessments are performed as indicated in the Schedule of Events.

- **Demographics / medical history:** Includes sex, age, race, clinical diagnosis, date and method of diagnosis, prior cancer therapy, and relevant medical history (past and concurrent).
- **Review eligibility criteria:** Eligibility is assessed during the screening period and should be confirmed on Day 1 of Cycle 1, prior to first dose of study therapy.
- **Physical examination**

- **Vital signs:** Pulse rate, systolic and diastolic blood pressure, body temperature, and respiration rate. Any abnormal reading should be repeatedly immediately.
- **Height and body weight:** Height is collected for the purpose of body mass index calculations at baseline only.
- **ECOG performance status:** See Appendix A.
- **Pregnancy test:** Serum β-human chorionic gonadotrophin (human chorionic stimulating hormone) test required for WOCBP at screening and end of treatment; serum or urine test required at all other timepoints listed in the Schedule of Events.
- **Concomitant medication:** Including all medications / therapies administered 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.
- **12-Lead electrocardiogram (ECG)**: Single, resting, semirecumbent 12-lead ECG will be performed locally. Data collection includes RR interval (heart rate), QT interval, QTcF interval and abnormal findings; the Investigator is responsible for interpreting and measuring ECG data.

6.1.3. Ophthalmological Examination

The cornea and conjunctiva are readily visible tissues, and therefore, abnormalities of the cornea and conjunctiva can usually be recognized via external ocular examination and routine slit lamp biomicroscopy. The retina is visible through fundoscopy after dilation of the pupil. Ophthalmologic examination will be performed 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.

Each evaluation will encompass:

1. External ocular examination
2. Routine slit lamp biomicroscopy of anterior ocular structures, including the anterior and posterior chambers (Fluorescein or rose Bengal or other dyes used to evaluate the ocular surface can be used according to institutional guidelines and local clinical practice)
3. Dilation of the pupil with direct/indirect fundoscopy per institutional guidelines and local clinical practice

6.1.4. Laboratory Assessments

All laboratory assessments will be performed locally. The laboratory must provide normal reference ranges for hematology, chemistry and coagulation tests. Laboratory results for hematology, chemistry, and coagulation assessments must be reviewed for clinically significant events. Any clinically significant events must be followed and reported as required by the protocol (see Section 8.4.1).

- **Hematology assessments include:** Red blood cell count, hemoglobin, hematocrit, platelets, white blood cell count with differential (ANC, lymphocytes, monocytes, eosinophils, basophils)

- **Coagulation assessments include:** Prothrombin time-international normalized ratio, activated partial thromboplastin time, fibrinogen
- **Chemistry (serum or plasma) assessments include:** 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, magnesium, blood glucose, creatinine clearance (if there is a measured value, use the measured value) or estimated glomerular filtration rate.

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

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

  Female Ccr (mL/min) = male Ccr×0.85

6.1.5. Tumor Assessments/Scans

On-site tumor assessments (including computed tomography [CT]/magnetic resonance imaging [MRI]) will be performed by the Investigator/local radiologist according to RECIST 1.1 guidelines (Eisenhauer et al. 2009). Results of these assessments, including response for target and non-target lesions and appearance of new lesions, will be the basis for the continuation or discontinuation of study therapy. Response definitions are provided in Section 7.2.1.

If the Investigator determines that a patient has developed clinical disease progression manifested by symptomatic deterioration but not supported by radiologic evidence of progression, the patient may stop treatment. Symptoms of clinical disease progression must be documented in the patient's source documents and must be reported as AEs. Every effort should be made to document objective disease progression even after discontinuation of treatment.

The same method of assessment and the same technique must be used to characterize each identified and reported lesion at screening, throughout the study, and during the follow-up period. Please see Section 7 for more detailed discussion of efficacy evaluations.

Note that patients who discontinue without documented disease progression should continue to undergo tumor assessments/scans according to the Schedule of Events until PD is documented, new anticancer therapy is initiated, the study is terminated, or consent is withdrawn.

6.1.6. Safety Evaluations

For a detailed description of safety data collection, please refer to Section 8.

6.1.7. Pharmacodynamic Evaluations

For discussion of pharmacodynamic evaluations planned in this study, including collection of blood samples for ctDNA assessment and optional fresh tumor biopsies, please refer to Section 9.

6.1.8. Pharmacokinetic Evaluations

For discussion of PK evaluations planned in this study, including collection of blood samples, please refer to Section 9.

6.1.9. Survival Follow-Up

Please refer to Section 3.2.6.

7. EFFICACY EVALUATIONS

7.1. Efficacy Criteria

The determination of antitumor efficacy will be based on the results of objective tumor assessments/scans interpreted by the Investigator, according to RECIST 1.1.

7.1.1. Method of Imaging

All patients with and without measurable disease will be eligible for assessment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at each assessment timepoint. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of treatment. All measurements should be recorded in metric notation using a ruler or calipers.

Contrast-enhanced CT scans or MRIs are the preferred methods for tumor assessments. If a contrast agent is contraindicated in a patient, obtain a non-contrast chest CT and enhanced MRI of the abdomen (and pelvis if clinically indicated). A spiral CT should be performed using a ≤5 mm contiguous reconstruction algorithm. Images must be acquired of the chest and abdomen (and pelvis if clinically indicated or obtained at Baseline) at each time point. Only CT scans and MRI may be used for tumor measurement.

Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules, palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Ultrasound should not be used to measure tumor lesions that are clinically not easily accessible for overall response evaluation (eg, visceral lesions). Ultrasound is a possible alternative to clinical measurements of superficial palpable nodes, subcutaneous lesions, and thyroid nodules. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

For additional guidance, refer to RECIST 1.1 specifications for standard anatomical radiological imaging.

7.1.2. Tumor Definitions

Measurable Lesions: Only measurable lesions can be selected as target lesions.

- Measurable visceral lesions: Lesions that can be accurately measured in at least 1 dimension with the longest diameter (to be recorded) ≥10 mm by CT scan if using slice thickness of ≤5 mm, or at least double the slice thickness of the CT or MRI scan if the slice thickness is >5 mm.
- Measurable pathological lymph nodes: A malignant lymph node must be considered pathologically enlarged with high suspicion of metastasis and measure ≥15 mm in the short axis when assessed by CT scan. The short axis is defined as the longest linear dimension perpendicular to the node's longest diameter as assessed within the same plane that the scan was acquired.

Non-measurable Lesions: All non-measurable lesions can only be selected as non-target lesions.

- Small visceral metastatic lesions that have a longest dimension <10 mm, or if slice thickness is >5 mm, less than twice the slice thickness
- Abnormal and suspected metastatic lymph nodes that are ≥10 mm to <15 mm in the short axis
- Truly non-measurable lesions (eg, ascites and peritoneal carcinomatosis)

Target Lesions:

- All measurable lesions up to a maximum of 2 lesions/organ and 5 lesions in total, representative of all involved organs/tissues should be identified as target lesions
- Target lesions should be selected on the basis of their size (visceral lesion with the longest diameter and lymph node with the measurement of short axis), be representative of all involved organs/tissues, but in addition should be those that lend themselves to reproducible repeated measurements
- When recording tumor measurements, the longest diameter will be measured for each non-nodal target lesion. For measurable pathological lymph nodes that may be identified as target lesions, the short axis measurement will be combined with the measurements of non-nodal (ie, visceral lesion) target lesions. Therefore, in cases of CR when abnormal nodes have been used as target lesions, the sum of diameters will not reduce to a null value.
- Target lesions will be followed up and measured at each subsequent timepoint.
- The sum of the diameters for all target lesions will be calculated and recorded. The baseline sum will be used as a reference to further characterize any objective tumor assessment in the measurable dimension of the disease.
- Assign a measurement to all target lesions regardless of size. An option of "too small to measure" will be provided if a measurement cannot be assigned. A value of zero should only be assigned in the case of a CR.
- An option of "not assessable" for a lesion will only apply to lesions that cannot be read due to technical reasons including:
  - CT artifact
  - Patient positioning where the lesions are obstructed or cannot be seen
  - Lesions that may not be seen in their entirety due to CT slice thickness
- In cases where a lesion divides into 2 lesions, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum.
- In cases where 2 lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion."

Non-target Lesions:

- Non-target lesions include all non-measurable lesions and measurable lesions that have not been selected as target lesions.
- The primary lesion should always be classified as a non-target lesion irrespective of its size and whether or not it can be accurately measured.
- Lymph nodes that have a short axis <1 mm are considered non-pathological and should not be recorded.
- Any equivocal lesion without clear diagnosis (eg, uncharacteristic solitary lung nodule without biopsy, uncharacteristic thyroid mass lesion without fine needle aspiration) may be considered a non-target lesion if it cannot be differentiated from a benign lesion.
- All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at Baseline. Measurements are not required, but their presence, absence, or unequivocal progression should be followed throughout the study.
- It is possible to record multiple non-target lesions involving the same organ as a single item on the eCRF (eg, multiple enlarged pelvic lymph nodes or multiple liver metastases).

7.2. Efficacy Endpoints

The efficacy evaluation criteria described in Section 7.1 will be used to derive the following primary and secondary efficacy endpoints (Table 9). Definitions of each endpoint are provided in Section Section 10.5.2.

Table 9: Efficacy Endpoints

Primary	Secondary
ORR (Cohorts 1 and 2)	CR rate (Cohort 3); ORR (Cohort 4)
CBR (Cohort 3)	DOR (All)
6-month PFS (Cohort 4)	CBR (Cohorts 1, 2, and 4)
	PFS (All)
	6-month PFS (Cohorts 1, 2, and 3)
	OS (All)

Abbreviations: CBR=clinical benefit rate; DOR=duration of response; ORR=objective response rate; OS=overall survival; PFS=progression-free survival

7.2.1. Response Criteria

Efficacy evaluation will include the assessment of target and non-target tumor responses as well as objective responses. Responses will be assessed as defined in the statistical analysis plan (SAP).

7.2.1.1. Target and Non-Target Response Assessments

Assessments will be based on the definitions for target and non-target lesions described in Table 10.

Table 10: Target and Non-target Lesions

TARGET LESIONS	
Lesions Response:	**Definition:**
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph node must have reduction in short axis to <10 mm
Partial Response (PR)	At least a 30% decrease in the sum of diameters of the target lesions, taking as a reference the baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of the target lesions, taking as a reference the smallest sum on study, including the baseline sum. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Definitive new lesion presence also indicates progression.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, referencing the smallest sum diameters while on study.
NON-TARGET LESIONS	
Lesions Response:	**Definition:**
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10-mm short axis)
Partial Response (PR)	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions (see following definition).

Abbreviations: CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease

Progression in Non-target Disease: There must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

7.2.1.1.1. Additional Criteria to Consider When Making Tumor Response Assessments

Because worsening in non-target disease cannot be easily quantified, a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease (ie, an increase in tumor burden representing an additional 73% increase in “volume” [which is equivalent to a 20% increase in the diameter of a measurable lesion]).

When effusions are known to be a potential adverse effect of treatment, cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or SD is not mandatory, but might be performed to differentiate between response (or SD) and PD when substantial change of effusion and or ascites is noted.

If a patient is discontinued from the study before PD occurs and receives local or regional palliative radiotherapy during the follow-up period, the irradiation site must be omitted from the response assessment of the patient; however, if the site is observed to demonstrate disease progression, this case should be judged as PD.

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

7.2.1.2. Objective Response Assessment

Assessments will be based on the definitions provided in Table 11 and Table 12.

Since this is a non-randomized study, all responses (CR/PR) must be confirmed.

Table 11: Time Point Response for Patients with Target (±Non-target) Disease

Target Lesions	Non-Target Lesions	New Lesions	Objective 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	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR=complete response; NE=not evaluable; PD=progressive disease; PR=partial response; SD=stable disease

Table 12: Time Point Response for Patients with Only Non-target Disease

Non-Target Lesions	New Lesions	Objective Response
CR	No	CR
Non-CR/Non-PD	No	SD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR=complete response; NE=not evaluable; PD=progressive disease; PR=partial response; SD=stable disease

8. SAFETY INFORMATION

8.1. Adverse Events

8.1.1. Definitions of Adverse Events

An AE is any untoward medical occurrence in a clinical study patient and does not necessarily have a causal relationship with the study drug. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a study drug, whether or not related to the study drug. This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

All AEs will be collected from the time the main ICF is signed through 30 days after the last dose of study therapy (safety follow-up) or until the start of new antitumor therapy, whichever is earlier. For AEs that occur between signing the pre-screening consent and main study ICF, there is no need to record those that are unrelated unless it is mandatory by local regulations. All AEs will be documented in the eCRF. Any untoward medical event that occurs after the safety follow-up is not considered an AE, unless the Investigator considers that the AE is related to the study drug. Serious AEs related to study therapy will be collected through the survival follow-up.

All AEs will be documented in the eCRF. Documentation should include onset and resolution/stabilization dates, severity/grade, relationship to study drug, and outcome of the event.

Signs and symptoms of a pre-existing disease should not be considered an AE, but should rather be considered baseline signs and symptoms. Worsening of pre-existing signs and symptoms is considered an AE.

For definitions and reporting of pregnancies, overdoses, and medication errors, refer to Section 8.5.1, Section 8.5.2, and Section 8.5.3, respectively.

8.1.2. Reporting of Adverse Events

8.1.2.1. Terms of Reported Adverse Events

All AEs will be documented in the eCRF according to the eCRF Completion Guidelines.

When a diagnosis for the reported signs or symptoms is known, the Investigator should report the diagnosis, not the symptoms, as the AE.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a patient in order to prevent reporting bias, patients should not be questioned regarding the specific occurrence of 1 or more AEs.

8.1.2.2. Severity of Adverse Events

The NCI-CTCAE Version 5.0 will be used to grade the severity of AEs.

8.1.2.3. Causal Relationship with Study Drug

The causal relationship between an AE and study drug will be assessed using the following 2-point scale, taking into account the patient's condition, medical history, concomitant medications, and the temporal relationship between study drug administration and onset of the event.

1. An AE is considered to be "**Related**" if the event follows a reasonable temporal sequence from administration of study drug and there is a **reasonable possibility** that at least one of the following conditions is true:
    - A positive dechallenge: This means that the event improves or resolves after the drug is stopped (temporarily or permanently).
    - A positive rechallenge: This means that the event reappears after the drug is restarted.
    - The event cannot be reasonably explained by the patient's clinical state and/or other therapies administered.
    - A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (eg, angioedema, Stevens-Johnson syndrome).
2. An AE is considered to be "**Not related**" if there is **no reasonable possibility** that:
    - The event occurred prior to study drug administration.
    - There is no reasonable possibility that the study drug caused the event.
    - The event does not follow a reasonable temporal sequence from administration of study drug and could have been produced by a documented pre-existing condition, concomitant medication or patient's clinical state.
    - For the purposes of safety reporting, "no reasonable possibility" means there is no evidence to suggest a causal relationship between the study drug and the AE.

8.1.2.4. Outcome of Adverse Events

Record the outcome of AEs as follows:

1. Resolved
2. Not resolved
3. Fatal

The AE reporting process is provided in the eCRF Completion Guidelines.

8.1.2.5. Follow-up of Adverse Events

Any ongoing AEs should be followed until the earliest occurrence of one of the following:

- The AE has resolved or stabilized
- Completion of Safety Follow-up visit
- Start of new antitumor therapy

- Withdrawal of consent
- Death
- Other (eg, transfer to another hospital)

8.2. Serious Adverse Events

8.2.1. Definitions of Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
    - The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization to treat the AE
    - The following are not considered hospitalizations for the purposes of assessing seriousness:
        - Emergency room visits <24 hours;
        - Hospitalizations for preplanned procedures;
        - Hospitalization for study-related treatment and procedures.
- Results in persistent or significant disability/incapacity, where disability is defined as a substantial disruption of a person's ability to conduct normal life functions, either reported or defined as per clinical judgment.
- Is a congenital anomaly/birth defect (if exposure to product just before conception or during pregnancy resulted in an adverse outcome in the child).
- Is any other important medical event that based upon appropriate medical judgement may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above. (eg, may not result in death, be life-threatening, or require hospitalization). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, and blood dyscrasias, or convulsions that do not result in inpatient hospitalization, or development of drug dependency or drug abuse.

8.2.2. Reporting of Serious Adverse Events (within 24 hours)

SAEs must be reported to the Sponsor's Pharmacovigilance group or its designee **within 24 hours** from the time the Investigator first becomes aware of the SAE. Comprehensive information available at the time of initial reporting (including narrative description, medical history, and concomitant medications) needs to be provided with careful consideration regarding causality and

serious criterion. The SAE reporting process and contact information are provided on the paper SAE Form Completion Guidelines.

All SAEs occurring from the time the ICF is signed through the Safety Follow-up Period (30 days after the last dose of study drug or discontinuation, whichever is earlier) must be reported to the Sponsor's Pharmacovigilance group or its designee. Any untoward medical event that occurs after the Safety Follow-up Period or discontinuation (whichever is earlier) is not considered an SAE, unless the Investigator considerers that the SAE is related to the study drug.

After the initial SAE notification to the Sponsor's Pharmacovigilance group or its designee, all follow-up SAE information will be submitted each time they become available (for example, clinical diagnosis, outcome, causality assessment, results of specific investigations) on a follow-up paper SAE form.

The Investigator also must submit further information if it is required by the Sponsor, the director of the study site, or an institutional review board (IRB)/independent ethics committee (IEC).

8.2.3. Reporting of Deaths

All deaths, including death due to disease progression, occurring from the time the ICF is signed through the Safety Follow-up Period (30 days after the last dose of study drug or discontinuation, whichever is earlier) must be reported as an SAE on a paper SAE form **within 24 hours** from the time the Investigator first becomes aware of the death.

Death is not an acceptable AE/SAE term; death is an outcome of an SAE. When reporting a death, site personnel will be required to identify which of the following best describes the category for cause of death:

- Toxicity caused by study drug
- Disease progression
- Clinical disease progression
- Other causes

8.2.4. Follow-up of Serious Adverse Events

When an SAE occurs, the Investigator will promptly take appropriate measures and follow up with the patient until the earliest occurrence of one of the following:

- The SAE has resolved
- The SAE has stabilized; an SAE can only be considered "stabilized" if the clinical manifestation or laboratory results being followed/assessed has remained constant (is not worsening) based on the Investigator's medical judgement.
- Start of new antitumor therapy
- Death

8.3. Disease Progression

Disease progression is not an acceptable AE term. In cases of non-fatal disease progression, the relevant symptom(s), sign(s), and complication(s) that led to the diagnosis of clinical disease progression should be reported as AE(s). If the relevant symptom(s), sign(s), and complication(s) meet any of the serious criteria, they should be reported as SAE(s). In both cases it should be indicated whether the symptom(s), sign(s), and complication(s) are related to clinical disease progression.

In cases of death due to clinical disease progression, the relevant major symptom(s), sign(s), and complication(s) that led to the death should be reported as SAE term(s). Clinical disease progression may only be reported as an SAE term if none of the relevant symptoms, signs, or complications supports a fatal outcome.

8.4. Laboratory Assessments

8.4.1. Reporting and Evaluation of Laboratory Test Results

All laboratory results must be reviewed by the Investigator. A new laboratory or instrumental abnormality that has a clinical impact on a patient (including eg, resulting in study drug dose reduction, treatment delay, treatment discontinuation or requirement of intervention) is considered an AE, unless it is considered part of clinical manifestations to a clinical diagnosis that is already reported as an AE.

All laboratory values that are out of the normal range are to be evaluated for their clinical impact before exposing the patient to the next dose of TAS-120. The laboratory must provide normal reference ranges.

The NCI-CTCAE Version 5.0 will be used to grade the severity of laboratory data.

8.4.2. Repeat Testing

Evaluation of any clinically significant laboratory test will be repeated, as clinically indicated, until the value returns to the baseline level or clinically stabilizes, or until another treatment is given.

8.5. Other Safety Information

8.5.1. Pregnancy

If a patient becomes pregnant while on study treatment or within 30 days following the last dose of study therapy, the study treatment must be immediately discontinued if ongoing. Pregnancy information in a female patient (or for the female partner of a male patient) should be reported **within 24 hours** from the time the Investigator first becomes aware of a pregnancy or its outcome. This should be performed by completing a paper Pregnancy Form and faxing or e-mailing it to Sponsor's Pharmacovigilance group or its designee.

New and/or corrected information regarding the pregnancy obtained after submitting the Pregnancy Form must be submitted on an updated Pregnancy Form to the Sponsor's Pharmacovigilance group or its designee.

If the outcome of the pregnancy is a stillbirth, congenital anomaly/birth defect, or a serious event in the mother, it should be reported as a SAE to the Sponsor's Pharmacovigilance group or its designee. Live births will be followed up by the Investigator. Any information that may be associated with the study drug should be reported even after study completion.

8.5.2. Overdose

An overdose for this clinical study is defined as taking an intentional or unintentional dose of TAS-120 or fulvestrant beyond the recommended dose for 1 day or beyond the recommended total dose in each cycle.

An overdose of TAS-120 or fulvestrant should be reported as an AE, and must be recorded on the SAE form and/or eCRF (or other specified report form) and reported to the Sponsor's Pharmacovigilance group or its designee **within 24 hours** from the time the Investigator first becomes aware of the overdose, whether or not it was accidental or intentional, and whether or not the patient developed an AE (even if not fulfilling a seriousness criterion).

An accidental or intentional overdose of concomitant medication should only be reported if it is associated with an AE.

There is no known antidote available in case of TAS-120 or fulvestrant overdose. Overdose should be managed with close monitoring and administration of prophylactic and symptomatic therapies to prevent or correct potential side effects.

8.5.3. Medication Errors

A medication error for this clinical study is defined as any unintentional error in prescribing, dispensing, or administering the study drug while the study drug is in the control of the healthcare professional or patient.

Please refer to the current eCRF Completion Guidelines for the details regarding reporting of medication errors to the Sponsor's Pharmacovigilance or designee.

The following types of medication errors, regardless of whether it is associated with an AE or SAE, should be reported to the Sponsor's Pharmacovigilance or designee **within 24 hours of first awareness** from the time the Investigator first becomes aware of its occurrence, using the SAE form and/or eCRF (or other specified report form):

- Medication errors with study medication or concomitant medication resulting in an AE
- Medication errors with study medication resulting in an overdose
- Incorrect route of study medication administration
- Administration of the incorrect study medication

Note: Medication errors with the study medication that result in the omission of an administration, an incorrect dose, or the administration of more than the prescribed dose (but does not meet the overdose criteria), will not be reported as a SAE, but will be identified through the recording of study drug accountability data in the eCRFs.

9. PHARMACODYNAMIC AND PHARMACOKINETIC EVALUATION

9.1. Pharmacodynamic and Biomarker Assessments

9.1.1. Objectives and Background

Exploratory objectives of this study are to assess the downstream pharmacodynamic effect of TAS-120 in single-agent and/or combination therapy and to explore markers of response and mechanisms of resistance to TAS-120 in tumor tissue biopsies and/or in ctDNA. These exploratory assessments of biomarkers include but are not limited to:

- Any *FGFR* aberrations
- p-AKT
- p-MAPK
- Ki67

All biomarker assessments described in this section will be performed at the timepoints shown in the Schedule of Events (Table 1); methods of sample collection and preparation will be described in a separate Laboratory Manual.

The pharmacodynamic biomarker population will consist of all patients who received TAS-120 and have evaluable pharmacodynamic biomarker data. Detailed analytical procedures will be described in the SAP.

9.1.2. Assessment of *FGF/FGFR* Aberrations in Blood

A blood sample will be collected to assess *FGF/FGFR* aberrations in ctDNA prior to the first TAS-120 administration on Day 1 of Cycle 1, on Day 1 of each alternative uneven cycle (Cycle 3, 5, 7 and ongoing), at time of disease progression, and at the EOT visit. Blood will be collected at each time point. This sample is being collected for exploratory analysis to evaluate *FGF/FGFR* aberrations in circulating blood and for future clinical development.

9.1.3. Tumor Biopsy

Archival or fresh tumor biopsy samples will be collected during the screening period to retrospectively confirm *FGFR* gene status at the Sponsor's designated central laboratories. The remaining samples may be stored at the Sponsor's designated central laboratories for up to 10 years for future testing.

Optional pre- and post-treatment tumor biopsies for pharmacodynamic assessment will be collected from patients who consent at Baseline, at the end of Cycle 1 (Cycle 1 Day 28 ± 7 days), and at the time of disease progression. These samples are being collected for exploratory analysis to evaluate the changes of downstream protein activation and other markers that may be associated with response and/or development of resistance to TAS-120 in tumor tissues.

9.2. Population Pharmacokinetic Sample Collection and Analysis

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. Dates and times of each sample collection must be recorded.

Details on the collection and preparation of plasma samples will be provided in a separate Laboratory Manual. Detailed analytical procedures will be described in the independent SAP for PopPK.

10. STATISTICS

The statistical analysis methods will be documented in detail in the SAP.

10.1. Estimation of Sample Size

Up to 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 (Table 13). 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 ≥11 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.

10.2. Planned Interim Analysis

The Sponsor will review the data at the time a cohort has the required number of patients to determine if that particular cohort should continue.

10.3. Analysis Populations

The analysis study populations in this study are defined in Table 13.

Table 13: Analysis Populations

Analysis Population	Definition
All Enrolled Population:	All patients enrolled in this study
All Treated Population/Full Analysis Set:	All enrolled patients who received at least 1 dose of study drug
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% and/or the cumulative dose of fulvestrant was <100% 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, 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.
PopPK Evaluable Set:	All patients in the All Treated Population who have evaluable plasma TAS-120 concentration data for analyses
Pharmacodynamic/Biomarker Evaluable Set:	All patients in the All Treated Population who have evaluable pharmacodynamic/biomarker data for analyses

Abbreviations: DLT=dose-limiting toxicity.

10.4. Criteria for Handling of Patient Data

Criteria for handling of patient data in the study are provided in the SAP.

10.5. Statistical Analyses

10.5.1. Demographic and Baseline Characteristics

The number of patients in each study population and the reasons for exclusion will be summarized. In each analysis population, the distribution of main patient background, disease characteristics, and baseline laboratory values and clinical findings will be summarized. These patient attributes will be summarized using frequency distribution or descriptive statistics as appropriate.

10.5.2. Efficacy Analyses

A description of each efficacy endpoint is provided in Table 14. Tumor assessments will be performed as per Section 6.1.5. Response assessments will be made based on RECIST 1.1. See the SAP for more detailed information on the efficacy analyses.

The evaluation of endpoints will be based on Investigator assessment and central independent radiology review.

Table 14: 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 PR or CR 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.

Efficacy data for the primary and secondary endpoints will be summarized descriptively.

The primary endpoint of ORR will be determined for patients in the Response Evaluable Set. At the analysis stage, the best objective response will be assigned for each patient as the best response recorded after initiation of study treatment and confirmed at least 4 weeks later. If applicable, responses recorded after disease progression or initiation of new anticancer treatment will be excluded. The exact 2-sided CI based on Clopper-Pearson methodology will be derived for ORR.

Duration of response will only be evaluated in patients with objective response of CR or PR. Patients who are alive and progression-free as of the analysis 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.

Progression-free survival will be estimated using the Kaplan-Meier method. Patients who die without a reported disease progression will be considered to have progressed on the date of their death. Patients who did not progress or die will be censored on the date of their last tumor assessment. Patients who did not have any on-study assessments and did not die will be censored on the first dosing date. Patients who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last tumor assessment prior to initiation of the subsequent anti-cancer therapy.

Overall survival will be analyzed similar to PFS. In the absence of death confirmation or for patients alive as of the OS cut-off date, survival time will be censored at the date of last known alive date.

10.5.3. Safety Analyses

The safety analysis will be performed using the All-Treated Population.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities terminology and the severity of the toxicities will be graded according to the NCI-CTCAE (Version 5.0), where applicable.

Concomitant medications will be coded according to the World Health Organization Drug Dictionary for Concomitant Medication.

All AEs will be summarized (by incidence) and listed by the System Organ Class, Preferred Term, toxicity/severity grade, and causal relationship to TAS-120. In addition, separate summaries of SAEs and Grade 3 or 4 AEs will be presented.

For all AEs that occurred between the signing of the ICF and the last day of the Safety Follow-up Period, lists of preferred AE terms, grade, onset date, actions, outcome of AE, date of outcome confirmed, causalities with the study drug, and comments on AEs will be listed by patient.

Hematological and chemistry laboratory parameters will be graded according to the NCI-CTCAE (Version 5.0) where applicable. The worst severity grade, time to maximum Grade 3 or 4 value, and time to resolution (return to baseline grade or below) will be summarized.

Safety data (AEs and clinical laboratory results) will be summarized descriptively. A list of 12-lead ECG findings will be presented by patient.

10.5.4. Pharmacokinetic Analysis

PopPK is described in Section 9.2. Analyses will include all patients in the All Treated Population who have evaluable plasma TAS-120 concentration data for PK analyses, unless any key information such as dosing records was missed. The data will be integrated with other studies and analyzed by the nonlinear mixed effect modeling. Individual PK parameters will be estimated for

the subsequent exposure-response analysis if the estimation is feasible. The results will be summarized and reported separately.

10.5.5. Pharmacodynamic/Biomarker Analysis

The exploratory pharmacodynamic/biomarker endpoints are described in Section 9.1. Analyses will be performed using all patients in the All Treated Population who have evaluable data for pharmacodynamic/biomarker analyses.

Pharmacodynamic and biomarker data will be summarized descriptively.

11. ADMINISTRATIVE CONSIDERATIONS

11.1. Protocol Compliance

The Investigator will agree to comply with the protocol by signing the Declaration of Investigator. In the event that the Investigator is unable to continue the study and another suitable person is designated as the Investigator, the Sponsor must be notified in advance (30 days prior notice is requested). The new Investigator must accept the responsibility in writing and be approved by the Sponsor and the IRB/IEC.

11.2. Protocol Deviations

The Investigator may implement a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to study patients without prior IRB/IEC approval/favorable opinion. As soon as possible, the implemented deviation or change and the reasons for it should be documented and submitted to the IRB/IEC and Sponsor.

The Investigator is to record any deviation from the protocol in the source documents, describing this departure and the circumstances under which it was required.

11.3. Protocol Amendments

All protocol amendments must be issued by the Sponsor, and signed and dated by the Investigator. Documentation of amendment approval by the Investigator and IRB/IEC must be provided to the Sponsor.

If the changes involve only logistic or administrative aspects of the study, these changes will be notified in writing by the Sponsor.

11.4. Study Termination

If the Sponsor and/or the Investigator should discover conditions arising during the study that indicate it should be terminated, an appropriate schedule for termination will be instituted. The Sponsor also reserves the right to discontinue this study for administrative or discretionary reasons at any time.

In this case, the Sponsor will promptly notify study site personnel with the reasons for study termination. Study site personnel will promptly inform the IRB/IEC and the Investigator in writing. The Investigator will immediately advise the patients of the termination of the study and discuss other healthcare options with the patient. The Sponsor will promptly notify the Regulatory Authorities of the premature termination of the study.

11.5. Post-trial Provisions

Please see Section 3.3 for discussion of Study Completion and Study Extension.

11.6. Case Report Forms

The Investigator should complete all eCRFs in accordance with the eCRF Completion Guidelines. Data in the eCRFs shall be consistent with source documents.

In this study, the Investigator and assigned personnel will be given access to the electronic data capture (EDC) system; passwords should not be shared. Data managers and Monitors will have the right to access the EDC system for performing source data verification. Data managers will have the right to access the EDC system as appropriate for their roles. Other relevant personnel may receive access to view EDC data.

An eCRF should be completed for each screened and enrolled patient.

After verification of the eCRFs, the Sponsor or designee may query discrepancies or request additional information. The Investigator, or assigned personnel, should verify the data and correct as necessary prior to approval of the eCRFs.

11.7. Access to Source Data/Documents

The Investigator or designated study personnel must make all study-related records available for study-related monitoring, audit, IRB/IEC review, and regulatory inspection.

11.7.1. Source Data/Documents

Source documents are original documents, data, and records such as hospital records, clinical and office charts, laboratory notes, memoranda, patient's evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, microfilm or magnetic media, X-ray, patient files, and records kept at the pharmacy, laboratories, and medical-technical departments involved in the study.

Specific details regarding source documents and source data to be recorded directly on the eCRFs for the study should be identified with the Investigator prior to and during the study.

11.7.2. Source Data Verification

The Sponsor's study monitor, or other representatives, should verify the entries in the eCRF and source documents to confirm the completeness and accuracy of the data. If there are any discrepancies between the entries in eCRFs and source documents, the monitor will query the site.

11.8. Data Handling

All study information is confidential. The patient's and Investigator's personal data which may be included in the Sponsor's database shall be treated in compliance with all applicable laws and regulations.

When processing and archiving personal data pertaining to the Investigator and to the patients, the Sponsor or its representatives shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

11.9. Responsibilities of Recordkeeping

11.9.1. Investigator and Study Site

The Investigator and the study site are responsible for the retention of all study documents according to institutional policies, local laws, and International Council for Harmonisation (ICH) E6 Guideline.

The Investigator and the study site agree to inform the Sponsor in writing of the intention to remove or destroy any study-related records. Prior to contacting the Sponsor, the Investigator and study site must ensure that the applicable regulatory requirements have been satisfied. The Sponsor will evaluate the requests from the Investigator and the study site and will provide authorization for destruction of such records in writing.

In the event that all retention of records requirements have been fulfilled, but the Sponsor requests that the Investigator and study site maintain the records for a longer period of time, additional arrangements will be made.

11.9.2. Sponsor

The Sponsor must retain all Sponsor-specific essential documents in conformance with the applicable regulatory requirements of the countries where the product is approved, and where the Sponsor intends to apply for approvals.

If the Sponsor discontinues the clinical development of the study drug, the Sponsor must maintain all Sponsor-specific essential documents in conformance with the applicable regulatory requirements.

11.10. Monitoring

The Sponsor and designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and study source documents, and other records relative to study conduct.

11.11. Financial Disclosure

Financial disclosure for Investigators will be obtained and record keeping of financial records will be in accordance with local regulatory requirements. Investigators will provide the Sponsor with sufficient, accurate financial information upon the Sponsor’s request.

11.12. Compensation for Health Injury

The clinical study is insured according to applicable regulatory requirements. A copy of the Compensation Policy Document will be provided to the study site by the Sponsor. In the case of a compensation claim, excluding claims that have arisen due to medical malpractice or negligence, the legally responsible person is clearly identified. Sponsor should address the policies and payment procedures of compensation for the event of study-related injuries as the Compensation Policy Document. When patients receive compensation, the policies and payment procedure of compensation should comply with the Compensation Policy Document.

12. QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor will perform quality control and quality assurance procedures in accordance with the Sponsor's SOPs to ensure the quality of the clinical study.

12.1. Quality Control

The Sponsor is responsible for controlling the quality of the clinical study according to the SOPs regarding eg, study operation, monitoring, data collection and management, statistical analysis, and handling of safety information to verify that the study-related activities have been fulfilled.

12.2. Quality Assurance

To ensure compliance with Good Clinical Practice (GCP) and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. Authorized representatives of the Sponsor, a Regulatory Authority, or an IRB/IEC may visit the site to perform audits or inspections, including source data verification. The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data and documents pertaining to the clinical study.

The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to ensure that these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH GCP E6 guidelines, and any applicable local regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a Regulatory Agency regarding an inspection.

Any results arising from such inspections will be immediately communicated by the Investigator to the Sponsor. The Investigator and the Sponsor will take corrective actions for all findings and observations found during audits and/or inspections. The auditors and inspectors will not disclose private information unless required by law.

13. ETHICS

13.1. Ethical Conduct of the Study

It is mandatory that all considerations regarding the protection of patients be carried out in accordance with the latest versions of the protocol, ICH GCP Guidelines, the ethical principles that have their origin in the Declaration of Helsinki, and all applicable regulatory requirements.

13.2. Written Informed Consent

The ICF must be approved by the IRB/IEC before patients sign consent for any study-related activity. It must be in a language that the patient can read and understand. The process for obtaining consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, and applicable regulatory requirements. Each patient (or a legally acceptable representative) must give written consent according to local requirements.

The Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient.

There must be documentation in each patient's case history/medical record that informed consent was obtained prior to any study procedure being performed. Patients must be re-consented to the most current version of the ICF(s) throughout their participation in the study (including during survival follow-up).

13.3. Institutional Review Board/Independent Ethics Committee

The study must be approved by an appropriately constituted IRB/IEC, as required in the applicable local regulation such as ICH E6 Guidelines (Part 3), Code of Federal Regulations Title 21, part 56, and Ordinance of the Ministry of Health and Welfare No. 28, Chapter IV, Section 1 before the study is initiated. At the end of the study, the Investigator will notify the IRB/IEC of the conclusion of the study and its outcome.

14. PUBLICATION POLICY

14.1. Publication Policy

The Sponsor maintains the right to use the results of this study in their original form and/or in a global report for submission to governmental and regulatory authorities of any country or region.

The results of the study may be presented during scientific symposia and/or published in a scientific journal only after review by the Sponsor in accordance with the guidelines set forth in the applicable publication or financial agreement.

The Investigators and the Sponsor will discuss and determine the presenter(s) or author(s) and timing of any presentation or publication related to this study and/or its results. Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

15. LIST OF REFERENCES

Benson AB, Ajani JA, Catalano RB, Engelking C, Kornblau SM, Martenson JA, et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. *J Clin Oncol.* 2004;22:2918-2926.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45:228-247.

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Helsten T, Elkin S, Arthur E, Tomson BN, Carter J, Kurzrock R. The FGFR landscape in cancer: analysis of 4,853 tumors by next-generation sequencing. *Clin Cancer Res.* 2016;22:259-267.

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Razavi P, Chang MT, Xu G, Bandlamudi C, Ross DS, Vasan N, et al. The genomic landscape of endocrine-resistant advanced breast cancers. *Cancer Cell.* 2018;34:427-438.

Smith TJ, Bohlke K, Lyman GH, Carson KR, Crawford J, Cross SJ, et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol.* 2015;33:3199-3121.

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Turner N. (2013) FGFR2 in breast cancer. *My Cancer Genome*. Available at URL: https://www.mycancergenome.org/content/disease/breast-cancer/fgfr2/. Last accessed: 08 March 2019.

16. SIGNATURES OF SPONSOR AND PRINCIPAL INVESTIGATOR

16.1. Declaration of the Sponsor

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

This study protocol was subject to critical review and has been approved by Taiho Oncology Inc. The information it contains is consistent with:

- The current risk-benefit evaluation of the investigational product
- The moral, ethical, and scientific principles governing clinical research as set out in the protocol, GCP, ICH Guidelines, and all applicable regulatory requirements

The Investigator will be supplied with details of any significant or new findings, including AEs, relating to treatment with the investigational product.

Sponsor's Medical Officer

[redacted], MD, [redacted]

Taiho Oncology, Inc.
101 Carnegie Center, Suite 101
Princeton, NJ 08540 USA

Signature: [redacted]

Date: 07 June 2019

16.2. Declaration of the Investigator

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

I have read the above protocol, appendices, and referenced documents. I understand the contents and intend to fully comply with all requirements. No changes will be made without formal authorization by Taiho Oncology, Inc. in the form of a protocol amendment. I will work according to the moral, ethical, and scientific principles governing clinical research as set out in the protocol, GCP, ICH Guidelines and all applicable regulatory requirements.

I confirm that I am not banned from conducting clinical research and I will immediately contact Taiho Oncology, Inc. if I cannot fulfill my obligations to complete this protocol.

Investigator

Signature: _____

Name (block letters): _____

Date: _____

APPENDIX A. ECOG PERFORMANCE STATUS

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
From: Oken MM, Creech, RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-55.	

APPENDIX B. DIETARY GUIDELINES FOR TREATMENT OF HYPERPHOSPHATEMIA

The best way to limit phosphorus in the diet is to limit foods highest in phosphorus, including:

- Fast food, convenience foods, and processed foods, which may be full of phosphorus additives
- Beverages that contain phosphorus (look for the letters "phos" in the ingredient list)

Also, look for any ingredient that contains "phos" in the term such as:

- Calcium phosphate
- Disodium phosphate
- Phosphoric acid
- Monopotassium phosphate
- Sodium acid pyrophosphate
- Sodium tripolyphosphate

Listing of Some Lower and Higher Phosphorus Foods	
Higher Phosphorus Foods	**Lower Phosphorus Foods**
Milk, pudding, yogurt, soy milk, nondairy creamers and enriched rice milk	Unenriched rice milk
Processed cheeses and cheese spreads	A small amount of Brie or Swiss cheese
Hard cheeses, ricotta or cottage cheese, fat-free cream cheese	Regular or low-fat cream cheese
Ice cream or frozen yogurt	Sherbet, sorbet or frozen fruit pops
Soups made with higher phosphorus ingredients (milk, dried peas, beans, lentils)	Soups made with lower phosphorus ingredients (broth- or water-based with other lower phosphorus ingredients)
Whole grains, including whole-grain breads, crackers, cereal, rice and pasta	White bread, crackers, cereals, rice and pasta
Quick breads, biscuits, cornbread, muffins, pancakes or waffles	White dinner rolls, bread, bagels or English muffins
Dried peas (split, black-eyed), beans (black, garbanzo, lima, kidney, navy, pinto) or lentils	Green peas, green beans or wax beans
Processed meats (ie, bologna, ham and hot dogs), and meat, poultry or seafood with "phos" in the ingredients	All-natural lean beef, pork, lamb, poultry, seafood or other fish without "phos" in the ingredients
Organ meats, walleye, pollock or sardines	All-natural lean beef, pork, lamb, poultry, seafood or other fish without "phos" in the ingredients
Nuts and seeds	Popcorn or pretzels
Peanut butter and other nut butters	Jam, jelly or honey
Chocolate, including chocolate drinks	Jelly beans, hard candy, fruit snacks or gumdrops
Colas and pepper-type sodas, some flavored waters, bottled teas, some drink mixes (any with "phos" in the ingredients)	Lemon-lime soda, ginger ale, root beer, plain water or some drink mixes (any without "phos" in the ingredients)
Although a food or drink may be low in phosphorus, limitation of portion size and the number of servings you eat or drink each day may still be recommended.	

From: Rachael Majorowicz, R.D.N., L.D. (Feb, 2016). Why is a low-phosphorus diet useful in managing kidney disease? What foods contain phosphorus? https://www.mayoclinic.org/food-and-nutrition/expert-answers/faq-20058408.

APPENDIX C. CHILD-PUGH SCORE

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin	<2 mg/dL (<34.2 µmol/L)	2 to 3 mg/dL (34.2 to 51.3 µmol/L)	>3 mg/dL (>51.3 µmol/L)
Albumin	>3.5 g/dL (35 g/L)	2.8 to 3.5 g/dL (28 to 35 g/L)	<2.8 g/dL (<28 g/L)
Prothrombin time: - Seconds over control - INR	 <4 <1.7	 4 to 6 1.7 to 2.3	 >6 >2.3
Encephalopathy	None	Grade 1 to 2	Grade 3 to 4

Modified Child-Pugh classification of the severity of liver disease according to the degree of ascites, the serum concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy. A total Child-Turcotte-Pugh score of 5 to 6 is considered Child-Pugh Class A (well-compensated disease); 7 to 9 is class B (significant functional compromise); and 10 to 15 is class C (decompensated disease).

APPENDIX D. CLASSIFICATION OF SUBSTRATES, INHIBITORS, AND INDUCERS OF CYP ENZYMES AND TRANSPORTERS

The classification below is based on the FDA Draft Guidance for Industry, Clinical Drug Interaction Studies —Study Design, Data Analysis, and Clinical Implications, October 2017. (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf)

CYP3A inhibitors and inducers: CYP3A is involved in the metabolism of TAS-120. CYP3A inhibitors and inducers may alter the concentration and activity of TAS-120.

CYP3A substrates: TAS-120 is a potential time-dependent inhibitor of CYP3A. TAS-120 may increase the concentration and activity of CYP3A substrates.

P-gp substrates and BCRP substrates: TAS-120 is a potential inhibitor of P-gp and BCRP. TAS-120 may alter the PK and activity of P-gp and BCRP substrates.

P-gp inhibitors and BCRP inhibitors: TAS-120 is a substrate of P-gp and BCRP. P-gp and BCRP inhibitors may alter the concentration and activity of TAS-120.

Examples of CYP3A Inhibitors		
CYP Enzyme	**Strong Inhibitors:[1] ≥ 5-fold increase in AUC or ≥ 80% decrease in CL**	**Moderate Inhibitors:[2] ≥ 2 but < 5□fold increase in AUC or 50 – 80% decrease in CL**
CYP3A	Boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir and ritonavir, diltiazem, elvitegravir and ritonavir, grapefruit juice[3], indinavir and ritonavir, idelalisib, itraconazole, ketoconazole, lopinavir and ritonavir, nefazodone, nelfinavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, voriconazole	Aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil

[1] A strong inhibitor for a specific CYP is defined as an inhibitor that increases the area under concentration-time curve (AUC) of a substrate for that CYP by equal to or more than 5-fold.

[2] A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 5-fold but equal to more than 2-fold.

[3] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation□dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (eg, low dose, single strength).

Abbreviations: AUC = area under the concentration-time curve; CL = oral clearance.

Example of CYP3A Inducers		
CYP Enzyme	**Strong inducers[1] or ≥ 80% decrease in AUC**	**Moderate Inducers[2] 50 – 80% decrease in AUC**
CYP3A	Carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort[3]	Bosentan, efavirenz, etravirine, modafinil

[1] A strong inducer is a drug that decreases the AUC of sensitive index substrates of a given metabolic pathway by ≥80%.
[2] A moderate inducer is a drug that decreases the AUC of sensitive index substrates of a given metabolic pathway by ≥50% to <80%.
[3] The effect of St. John's wort varied widely and is preparation-dependent.
Abbreviation: AUC = area under the concentration-time curve.

Example of CYP3A Substrates		
CYP Enzymes	**Sensitive Substrates[1]**	**Moderate Sensitive Substrates[2]**
CYP3A	Alfentanil, avanafil, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, eplerenone, everolimus, felodipine, ibrutinib, indinavir, lomitapide, lovastatin, lurasidone, maraviroc, midazolam, naloxegol, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tacrolimus, ticagrelor, tipranavir, tolvaptan, triazolam, vardenafil	Alprazolam, aprepitant, atorvastatin, colchicine, eliglustat, pimozide, rilpivirine, rivaroxaban, tadalafil

[1] Sensitive substrates are drugs that demonstrate an increase in area under the concentration-time curve (AUC) of ≥ 5-fold with strong index inhibitors of a given metabolic pathway in clinical drug-drug interaction studies.
[2] Moderate sensitive substrates are drugs that demonstrate an increase in AUC of ≥ 2 to < 5□fold with strong index inhibitors of a given metabolic pathway in clinical drug-drug interaction studies.

Example of Inhibitors for P-gp and BCRP		
Transporters	**Gene**	**Inhibitor**
P-gp[1]	*ABCB1*	Amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil
BCRP[2]	*ABCG2*	Curcumin, cyclosporine A, eltrombopag

[1] P-gp: (1) AUC fold-increase of digoxin ≥2 with co-administration and (2) *in vitro* inhibitor.
[2] BCRP: (1) AUC fold-increase of sulfasalazine ≥1.5 with co-administration and (2) *in vitro* inhibitor. Cyclosporine A and eltrombopag were also included, although the available DDI information was with rosuvastatin, where inhibition of both BCRP and OATPs may have contributed to the observed interaction.
Abbreviations: AUC = area under the concentration-time curve; BCRP = breast cancer resistance protein; P-gp = p-glycoprotein.

Example of Substrates for P-gp and BCRP		
Transporters	**Gene**	**Substrate**
P-gp[1]	*ABCB1*	Dabigatran, digoxin, fexofenadine
BCRP[2]	*ABCG2*	Rosuvastatin, sulfasalazine

[1] P-gp: (1) AUC fold-increase ≥2 with verapamil or quinidine co-administration and (2) in vitro transport by P-gp expression systems, but not extensively metabolized.
[2] BCRP: (1) AUC fold-increase ≥2 with pharmacogenetic alteration of ABCG2 (421C>A) and (2) in vitro transport by BCRP expression systems.
Abbreviations: AUC = area under the concentration-time curve; BCRP = breast cancer resistance protein; P-gp = p-glycoprotein.