PHASE 1/2 STUDY OF TAS-120 IN PATIENTS WITH ADVANCED SOLID TUMORS HARBORING FGF/FGFR ABERRATIONS

TAS-120

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PROTOCOL AMENDMENT 1: 31 January 2014
PROTOCOL AMENDMENT 2: 22 September 2014
PROTOCOL AMENDMENT 3: 19 February 2016
PROTOCOL AMENDMENT 4: 15 May 2017
PROTOCOL AMENDMENT 5: 29 August 2017
PROTOCOL AMENDMENT 6: 31 January 2018
PROTOCOL AMENDMENT 7: 28 September 2018
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PROTOCOL AMENDMENT 9: 01 August 2019

This multinational study will be conducted under the sponsorship of Taiho Pharmaceutical Co., Ltd. for sites in Japan and Taiho Oncology, Inc. for sites in the rest of the world:

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This clinical study will be conducted in accordance with International Council for Harmonisation Good Clinical Practice Guidelines.

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SUMMARY OF CHANGES

The following table summarizes substantive changes made to the protocol in Amendment 9; all changes shown here were also incorporated into the Study Synopsis as appropriate. In addition, minor administrative changes (not summarized in this table) were made throughout the document, including updating of the headers and cover page and correction of minor typographical or formatting errors.

Section	Description of Change	Brief Rationale
Section 7.2.1 *Inclusion Criteria* **Section 9.1** *Pre-screening of Tumor Tissue Sample for FGFR2 Gene Fusions or Other FGFR2 Rearrangements in Patients with iCCA (Phase 2 Only)*	Criterion #3 (b) was amended as follows: i. Patient has histologically or cytologically confirmed, locally advanced, metastatic, unresectable iCCA harboring FGFR2 gene fusions or other FGFR2 rearrangements based on results from either of the following (see Section 9.1 for details): a. Testing by Foundation Medicine: i. As part of study pre-screening; or ii. Previously tested by Foundation Medicine; in this case, it is requested that tumor tissue ~~should~~ be provided to Foundation Medicine if available. b. Local laboratory testing using next generation sequencing [NGS], fluorescence in situ hybridization [FISH], or other assays that can determine FGFR2 gene fusions or other FGFR2 rearrangements on tumor tissues or from ctDNA~~; patients enrolled on this basis must have available tumor tissues from either archival samples or fresh tumor biopsy submitted to Foundation Medicine for confirmation of FGFR2 gene fusion or other FGFR2 rearrangements~~. It is requested that patients enrolled on this basis provide tumor tissues to Foundation Medicine, if available from either archival samples or fresh tumor biopsy.	In order to facilitate enrollment of patients, the requirement that *FGFR2* rearrangements be centrally confirmed prior to enrollment was removed in the entry criteria and throughout the protocol.
Section 12.3.3 *Determination of Sample Size (Phase 2)*	Text was amended as follows: Approximately 100 iCCA patients with ~~Foundation Medicine confirmed~~ *FGFR2* gene fusions or other *FGFR2* rearrangements will be treated.	In order to facilitate enrollment of patients, the requirement that *FGFR2* rearrangements be centrally confirmed prior to enrollment was removed.
Section 12.3.3 *Determination of Sample Size (Phase 2)*	The following text was added: After approximately 100 patients have been enrolled, if the proportion of patients at sites in Japan is <10% of the total population, enrollment may continue in Japan until the proportion is ≥10%.	Added condition to ensure the ability to enroll a suitable number of patients at sites in Japan.

Section	Description of Change	Brief Rationale
Section 12.4 *Interim Analyses*	Text was amended as follows: Interim reviews of safety data from the Phase 2 portion will be performed approximately every 3 months throughout the study, ~~until the last patient in the Phase 2 portion has been treated and followed for at least 4 cycles~~ until the interim analysis cut-off.	The schedule of safety reviews was adjusted consistent with the institution of a formal interim analysis of efficacy as described below.
Section 12.4 *Interim Analyses*	The following text was added: A formal interim analysis will be performed when approximately 70% all treated patients had 6 months of follow-up. Two-sided 95% CI and 99% CI will both be provided for the primary efficacy analysis. A safety analysis will also be performed at this time, and the results will be shared with the SRC.	An interim analysis of efficacy has been added.
Appendix G Supplemental Requirements for Japan Only	The anticipated date of study completion was amended from April 2020 to April 2021.	Revised estimate based on study progress and expected enrollment rate.

1. SYNOPSIS

Title of Study: **PHASE 1/2 STUDY OF TAS-120 IN PATIENTS WITH ADVANCED SOLID TUMORS HARBORING FGF/FGFR ABERRATIONS**	
Protocol Number:	TPU-TAS-120-101
Phase:	1 / 2
Indication:	Advanced solid tumors

Background:

Activating fibroblast growth factor receptor (FGFR) gene abnormalities are reported in various cancers including non-small cell lung cancer (NSCLC) (FGFR1 amplification), breast (FGFR1 and 2 amplification), gastric (FGFR2 amplification), bladder (FGFR3 activating mutation or gene translocation), endometrial (FGFR2 activating mutation), multiple myeloma (FGFR3 gene translocation), and rhabdomyosarcoma (FGFR4-activating mutation).

TAS-120 is a novel selective small molecule FGFR inhibitor.

TAS-120 equally inhibited all 4 subtypes of FGFR and showed high selectivity for FGFR when tested against a panel of 296 kinases. Half maximal inhibitory concentration (IC_{50}) values (nmol/L) were 3.9 for FGFR1, 1.3 for FGFR2, 1.6 for FGFR3, and 8.3 for FGFR4. TAS-120 was highly active against cancer cell lines with FGFR gene abnormalities including cancer cell lines that acquired resistance to other (adenosine triphosphate (ATP)-competitive FGFR tyrosine kinase inhibitors (TKIs). *In vitro* studies have shown that TAS-120 selectively inhibits cell growth of human cancer cell lines that have FGFR gene abnormalities. *In vivo* studies showed that TAS-120 had strong antitumor efficacy in nude mouse or nude rat xenograft models bearing tumors with various FGFR gene abnormalities (FGFR1 or FGFR2 amplification and FGFR3 translocation).

In addition, TAS-120 retained inhibitory potency against mutant FGFR2 including the V565I gatekeeper mutation with a similar potency compared to wild type FGFR2. N550H and E566G mutations in the FGFR2 hinge region, which were reported to cause resistance to dovitinib (another FGFR inhibitor), were also sensitive to TAS-120. Furthermore, TAS-120 showed inhibitory potency against mutant FGFR2 including a K660M activation loop mutation. IC_{50} values for pFGFR2 inhibition (nmol/L) were 0.9 for WT, 1.3 for V565I, 3.6 for N550H, 2.3 for E566G, and 5.2 for K660M. In contrast, when several ATP competitive inhibitors of FGFR were tested against these FGFR2 mutants, their inhibitory potencies were reduced compared to their potency against the wild type.

Cholangiocarcinoma (CCA), a bile duct cancer, is a rare tumor that arises from the malignant transformation of epithelial cells of the bile ducts. It is typically classified as either intrahepatic (iCCA) or extrahepatic (eCCA). Intrahepatic cholangiocarcinoma develops in the smaller bile ducts inside the liver and is the least common form of the disease (approximately 10%), whereas eCCA includes cancers in the peri-hilar (also known as Klatskin tumor) and distal bile duct area and is most common (approximately 90%).

Although CCA is known to have the histological and molecular features of an adenocarcinoma of epithelial cells lining the biliary tract, the actual cell of origin is unknown. Fibroblast growth factor/fibroblast growth factor receptor aberrations are a reported genetic modification in CCA. In iCCA, FGFR2 gene rearrangement including fusions has been identified as an early driver of oncogenic events. These gene rearrangement/fusions are present in an estimated 10% to 20% of patients.[1, 11, 12] Therefore, inhibiting the FGFR pathway in patients with iCCA is a plausible therapeutic strategy for appropriately selected patients with this disease.

For disease that is localized at diagnosis, surgical resection offers the only chance of cure for patients with CCA. Unfortunately, symptoms are not usually apparent until CCA is at an advanced stage, and thus, most patients (>65%) have disease which is unresectable at diagnosis. Unresectable locally advanced (stage III) and metastatic (stage IV) disease has a poor prognosis with 5-year overall survival (OS) of 10% and 0%, respectively. For such patients, chemotherapy and supportive care are usually offered.[13] Although there are no approved treatments for CCA, gemcitabine/cisplatin is the standard 1st line chemotherapy regimen for patients with advanced, metastatic, unresectable CCA. There is no standard regimen beyond first line treatment.[14] In the second line treatment setting, a retrospective evaluation of 761 patients with advanced biliary tract cancers,

including CCA has shown a median overall response rate of 7.7% (95% confidence interval (CI): 5% to 11%) and a median progression-free survival (PFS) of 3.2 months (95% CI: 2.7 – 3.7 months).[13] These poor results confirm a substantial unmet medical need for new therapies in patients with advanced CCA who have failed initial chemotherapy.

The FGFR signaling axis has been well characterized for its role in proliferation, differentiation, migration, and survival, and it is fundamental to embryonic development, regulation of angiogenesis, and wound healing in adults. Dysregulation of the FGFR signaling pathway has been associated with many developmental disorders and with cancer. An extensive amount of literature indicates that FGFR is one of the receptor tyrosine kinases most frequently mutated or otherwise abnormally activated in late-stage human cancer.

Therefore, FGFR has been shown to be a valid target, and TAS-120 is a selective inhibitor of FGFR. TAS-120 exhibits convincing antitumor activity in several xenograft models. Importantly, it delivers antitumor efficacy in xenograft models with a large safety window.

This Phase 1/2 clinical trial was planned to investigate the pharmacokinetics (PK), pharmacodynamics, efficacy, safety, and tolerability of TAS-120 in patients with advanced solid tumors, with or without FGFR abnormalities who have failed all standard therapies or for whom standard therapy does not exist.

During the Phase 1 Dose Escalation part of the study, dose levels of 4, 8, 16, 20 and 24 mg once daily (QD) were evaluated. At 24 mg, 3 of 9 evaluable patients experienced a dose-limiting toxicity (DLT) during Cycle 1, thus, 24 mg was determined as the DLT dose level. At 20 mg QD, no DLT was reported in the 5 evaluable patients during Cycle 1, and thus, 20 mg QD was determined as the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D).

The original design of the Phase 2 portion of the study (enrolling patients with iCCA harboring FGFR2 gene fusions) was based on preliminary anti-tumor activity observed in this population in the Phase 1 portions of the study. Specifically, at the time the Phase 2 portion was designed (data cut off 17 September 2017), a total of 3 confirmed partial responses had been observed among 14 response-evaluable patients with iCCA harboring FGFR2 gene fusions. Accordingly, as of Amendment 7 to this protocol, the study population for the Phase 2 portion of the study is to include approximately 100 patients with iCCA harboring confirmed FGFR2 gene fusions or other FGFR2 rearrangements.

A formal interim analysis will be performed when approximately 70% all treated patients had 6 months of follow-up. Two-sided 95% CI and 99% CI will both be provided for the primary efficacy analysis. A safety analysis will also be performed at this time, and the results will be shared with the SRC.

Study Objectives:

Phase 1 Dose Escalation

Phase 1 Dose Escalation has been completed as of Amendment 6.

Phase 1 Expansion

Primary

- To evaluate ORR in cholangiocarcinoma (intra-hepatic [iCCA] or extra-hepatic [eCCA]) patients with tumors harboring FGFR2 gene fusions or other FGFR abnormalities.
- To evaluate ORR and EPR (defined as progression-free rate at the end of Cycle 2) in patients with primary CNS tumors harboring FGFR gene fusions or FGFR1 activating mutations (Appendix A).
- To evaluate ORR in a basket of tumor types with tumors harboring FGFR2 amplifications.
- To evaluate ORR in a basket of tumor types with tumors harboring any FGFR gene fusions or activating mutations Appendix A).

Secondary

- To investigate the safety of TAS-120.
- To evaluate disease control rate (DCR), DOR, PFS and OS in each treatment group.

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[redacted]

Phase 2

Primary

- To confirm ORR in iCCA patients with FGFR2 gene fusions or other FGFR2 rearrangements based on independent central radiology review.

Key secondary

- To evaluate DOR

Other secondary

- To evaluate the safety and tolerability of TAS-120
- To evaluate DCR, PFS, and OS
- To evaluate Patient-Reported Outcomes (PROs)

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[redacted]

Study Design:

This is an open-label, nonrandomized, dose-escalation and dose-expansion, Phase 1/2 study of TAS-120, evaluating the safety, tolerability, PK, pharmacodynamic, and antitumor activity of TAS-120 in patients with advanced solid tumors with FGF/FGFR-related abnormalities who have failed all standard therapies or for whom standard therapy does not exist or is not tolerated.

The study will be conducted in 3 parts:

- Phase 1 Dose Escalation: to determine the MTD and/or RP2D of TAS-120
- Phase 1 Expansion: to further evaluate the efficacy and safety of the MTD and/or RP2D of TAS-120 in patients with tumors harboring specific FGF/FGFR aberrations;
- Phase 2: to confirm the ORR of TAS-120 in iCCA patients with tumors harboring FGFR2 gene fusions or other FGFR2 rearrangements.

As of Amendment 6, the Phase 1 Dose Escalation Phase is completed and the MTD/RP2D of 20 mg QD was established. Details of the Phase 1 Dose Escalation study design can be found in previous versions of the study protocol.

Study Duration:

Patients will receive study drug (TAS-120) according to the proposed treatment schedule until disease progression, occurrence of intolerable side effects, removal by the investigator, withdrawal of consent, or other criteria for discontinuation are met (Section 7.3, Discontinuation Criteria).

For the Phase 1 Expansion part of the study, patients in each treatment group should be followed for survival for up to 12 months after the last patient enrolled in that group.

For Phase 2, patients should be followed for survival for up to 18 months after the last patient enrolled in this phase of the study.

Study Population:

Phase 1 Dose Escalation

Phase 1 Dose Escalation has been completed as of Amendment 6. Patients with advanced solid tumors, with or without FGFR abnormalities who have failed all standard therapies or for whom standard therapy does not exist.

Phase 1 Expansion and Phase 2

Has histologically or cytologically confirmed, locally advanced, metastatic cancer meeting the following criteria:

a. Phase 1 Expansion

   I. Patient has failed (or in the case of Group 2, failed or refused) all standard therapies or standard therapy does not exist or is not tolerated.

   II. Patient is eligible for 1 of the following enrollment groups, based on diagnosis, prior therapy, and FGF/FGFR aberrations as shown:

      a. **Group 1** (enrollment suspended as of Amendment 7): Patient has intrahepatic or extrahepatic cholangiocarcinoma harboring FGFR2 gene fusions.

      b. **Group 2**: Patient has intrahepatic or extrahepatic cholangiocarcinoma harboring FGFR2 gene fusions, and has not received or received less than 1 cycle of prior chemotherapy (due to intolerance or patient refusal).

      c. **Group 3** (enrollment suspended as of Amendment 7): Patient has intrahepatic or extrahepatic cholangiocarcinoma harboring FGFR2 gene fusions and has received prior treatment with FGFR inhibitors.

      d. **Group 4** (enrollment suspended as of Amendment 7): Patient has intrahepatic or extrahepatic cholangiocarcinoma harboring FGFR abnormalities other than FGFR2 gene fusions (for example, mutations, rearrangements, or amplifications).

e. **Group 5**: Patient has a primary CNS tumor harboring FGFR gene fusion or FGFR1 activating mutation and fulfills the following criteria (i and ii).

i. Patients who are presenting in recurrence or relapse must have at least one measurable enhancing mass lesion with 2 perpendicular diameters of at least 10 mm documented on baseline contrast magnetic resonance imaging (MRI) (gadolinium-based MRI).

ii. Patients should be on a stable dose of steroids for at least 7 days prior to obtaining the baseline contrast MRI of the brain and at least 7 days prior to starting study drug.

f. **Group 6** (enrollment suspended as of Amendment 7): Patient has advanced urothelial carcinoma harboring FGFR3 fusions or FGFR3 activating mutations.

g. **Group 7**: Patient has any tumor type not included in one of the prior groups, harboring FGFR2 amplification (no minimum number of copies).

h. **Group 8** (enrollment suspended as of Amendment 7): Patient has any tumor type not included in one of the prior groups, harboring FGFR gene fusions or activating mutations.

b. Phase 2

I. Patient has histologically or cytologically confirmed, locally advanced, metastatic, unresectable iCCA harboring FGFR2 gene fusions or other FGFR2 rearrangements based on results from either of the following (see Section 9.1 for details):

a. Testing by Foundation Medicine:

i. As part of study pre-screening; or

ii. Previously tested by Foundation Medicine; in this case, it is requested that tumor tissue be provided to Foundation Medicine if available.

b. Local laboratory testing using next generation sequencing [NGS], fluorescence in situ hybridization [FISH], or other assays that can determine FGFR2 gene fusions or other FGFR2 rearrangements on tumor tissues or from ctDNA. It is requested that patients enrolled on this basis provide tumor tissues to Foundation Medicine, if available from either archival samples or fresh tumor biopsy.

II. Patient has been treated with at least one prior systemic gemcitabine and platinum-based chemotherapy. Patients with prior adjuvant gemcitabine-platinum chemotherapy are eligible if the patient had recurrence within 6 months of the last dose of the regimen.

III. Patient has documentation of radiologic disease progression following the most recent prior therapy.

Planned Sample Size:

For the Phase 1 Expansion, approximately 185 patients will be enrolled. For Phase 2, approximately 100 patients with iCCA harboring confirmed FGFR2 gene fusions or other FGFR2 rearrangements will be treated.

Dosing and Treatment Schedule Rationale:

The 20 mg QD of TAS-120 has been selected as the dose for the Phase 2 part of the study in iCCA patients as well as all Phase 1 Expansion cohorts.

Treatment Regimen:

TAS-120 will be administered as a daily, continuous, 21-day treatment cycle until at least 1 of the criteria for study discontinuation is met (Section 7.3, Discontinuation Criteria). There are no breaks in dosing between cycles. Patients should follow the instructions of the treating physician on study drug administration during treatment. Patients are required to fast for at least 2 hours before and 1 hour after administration of TAS-120. Patients will be permitted to drink water during this period. Dietary restrictions that limit phosphate intake may reduce the risk of hyperphosphatemia (see Section 7.8). On non-PK sampling days, TAS-120 can be administered in the morning or evening at the same time (if possible) each day. If a patient misses a dose (i.e., did not take TAS-120 for > 12 hours of the scheduled time of that day), the patient should take the dose on the next day.

Safety Criteria for Evaluation:

Standard safety monitoring and grading using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (version 4.03) will be used.

Efficacy Criteria for Evaluation:

Please note: for patients who discontinued treatment for reasons other than disease progression, tumor assessments should be continued until radiologic disease progression or initiation of new anticancer therapy (whichever occurs first).

Solid Tumors

Measurements of solid tumors will be performed throughout study treatment using Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1, 2009). Radiographic tumor assessments (computed tomography [CT] scan with contrast will be performed at baseline and at the end of every 2 cycles (up to + 2 weeks) up to Cycle 4 (or as clinically indicated). Following Cycle 4, CT scans will be performed after every 3 cycles (± 7 days) or as clinically indicated, and at study completion.

Brain Tumors

Patients with brain tumors will be assessed using Response Assessment in Neuro-Oncology (RANO) criteria (2010). Patients with brain tumors will be evaluated for response by contrast magnetic resonance imaging (MRI) (gadolinium-based magnetic resonance imaging [Gd-MRI]). All MRIs should be performed when the patient is on a stable dose of steroids. Gd-MRI will be performed at baseline and at the end of every 2 cycles (up to + 2 weeks) up to Cycle 4 (or as clinically indicated). Following Cycle 4, Gd-MRI scans will be performed after every 3 cycles (± 7 days) or as clinically indicated, and at study completion.

Neurological examination for patients with brain tumors must always be performed within one week of the date of the Gd-MRI as part of the response assessment.

Endpoints

Phase 1 Expansion: the primary endpoint is ORR in each treatment group (and EPR for primary CNS tumors) and the secondary endpoints of DOR, DCR, PFS, and OS in each treatment group.

Phase 2: the primary endpoint is ORR and the secondary endpoints of DOR, DCR, PFS, PROs and OS.

Primary endpoints will be based on the independent review of images by the Core Imaging Laboratory. In addition, for the Phase 2 part of the study, sensitivity analyses for some key efficacy endpoints (e.g., ORR, and PFS) will be performed based on investigators or local radiologist assessments.

Statistical Methods:

Analysis Populations

The *Safety Population* will include all patients who received at least 1 dose of TAS-120. This population will be the primary population for safety evaluation.

The *DLT Evaluable Population* was defined for Phase 1 Dose Escalation only; Phase 1 Dose Escalation has been completed as of Amendment 6.

The *PK and Pharmacodynamic Population* will consist of all patients who received TAS-120 and have TAS-120 evaluable plasma and/or urine data. All such patients will be evaluated for PK and pharmacodynamics unless significant protocol deviations have impacted the data or key dosing information is missing. Changes to the procedures, which may impact the quality of PK and pharmacodynamic data, will be considered "PK and pharmacodynamics relevant protocol deviations." Examples include sample processing errors that lead to inaccurate bioanalytical results and/or inaccurate dosing on the day of PK and pharmacodynamic sampling.

The *Efficacy Population* is defined for each portion of the study as follows:

- Phase 1 Dose Escalation: All treated patients (safety population)
- Phase 1 Expansion: All treated patients (safety population)
- Phase 2: All treated iCCA patients with confirmed FGFR2 gene fusions or other FGFR2 rearrangements

Efficacy Analyses

For Phase 1 Expansion, efficacy data for the primary endpoint of ORR (and EPR for primary CNS tumors), and secondary endpoints of PFS, DCR, DOR, and OS will be summarized for each treatment group.

For Phase 2, efficacy data for the primary endpoint of ORR and secondary endpoints of DOR, PFS, DCR, Patient-Reported Outcomes (PROs) and OS will be summarized. For PROs, the analysis of a EuroQol-5D measure of health-related quality of life (EQ-5D) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) will be performed in all treated patients who have an assessment at baseline and at least one subsequent assessment.

Determination of Sample Size:

Phase 1 Dose Escalation:

There were 86 patients enrolled in the Phase 1 Dose Escalation part of the study which has been completed as of Amendment 6.

Phase 1 Expansion:

Up to approximately 185 patients will be enrolled as outlined below:

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Phase 2:

Approximately 100 iCCA patients with FGFR2 gene fusions or other FGFR2 rearrangements will be treated.

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Interim Analyses:

Interim reviews of safety will be performed approximately every 3 months throughout the study, until the interim analysis cut-off. These interim reviews will be performed by a Safety Review Committee (SRC), comprising, at minimum:

- 1 independent investigator and 1 independent statistician, neither of whom is directly involved in the conduct or analysis of the study; and
- A total of 5-6 study investigators representing each region in which patients are enrolled.

A complete description of the composition of the SRC and details on the interim analysis process will be provided in a separate safety review charter.

In addition to these reviews, the Sponsor will share safety data from the trial with all primary investigators throughout the conduct of the study.

A formal interim analysis will be performed when approximately 70% all treated patients had 6 months of follow-up. Two-sided 95% CI and 99% CI will both be provided for the primary efficacy analysis. A safety analysis will also be performed at this time, and the results will be shared with the SRC.

2. STUDY SCHEDULES

Table 1: Study Schedule for Phase 1 Expansion

NOTE: Evaluations on D1 of a cycle should be performed within 24 hours prior to dosing, unless otherwise noted. Procedures already performed during the screening period within 72 hours prior to dosing do not need to be repeated on 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 = 21 days)					Safety Follow-up		Survival Follow-up Period	Notes
		Cycle 1				Cycles ≥2				
		Day				Day	End of Tx (+0-7 days)	30 (±3) days After Last		
		1	4 (±1d)	8 (±3d)	15 (±3d)	1 (±3d)				
Written informed consent	X									
Review eligibility criteria	X	X								
Demographics/medical history	X									
Physical examination	X	X				X	X	X		
Review of pre-existing signs and symptoms	X	X								
Tumor tissue sample collection	(X)									At any time during the study; tumor tissue collection is mandatory if tissue is available.
Vital signs	X	X				X	X	X		Heart rate, blood pressure, body temperature, and respiration rate.
Height and Weight	X	X				X	X	X		Height at screening only.
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.
Neurological examination	X	(X)				(X)	X	X		As clinically indicated after screening, using same methods used at screening.
Neurological examination as part of RANO (Group 5)	X	(X)				(X)	X	X		For patients with primary CNS tumors, a neurological examination must be performed within 1 week of the date of the Gd-MRI performed at screening and as part of RANO response assessment.

	Screening Period (Within 28 Days Prior to First Dose)	Treatment Period (1 cycle = 21 days)					Safety Follow-up		Survival Follow-up Period	Notes
		Cycle 1				Cycles ≥2				
		Day				Day				
		1	4 (±1d)	8 (±3d)	15 (±3d)	1 (±3d)	End of Tx (+0-7 days)	30 (±3) days After Last D		
ECOG performance status	X	X				X	X	X		
12-Lead Electrocardiogram	X	X				X	X	X		At screening and 2 hours (±15 minutes) after dosing on D1 of each cycle.
Hematology and coagulation	X	X		X	X	X	X	X		Within 24 hours prior to treatment on D1 of each cycle, any time on C1D8 and C1D15, and as clinically indicated.
Chemistry (Serum or plasma)	X	X	(X)	X	X	X	X	X		Within 24 hours prior to treatment on D1 of each cycle, any time on C1D8 and C1D15, and as clinically indicated. Additional collection for phosphorus only at C1D4.
Urinalysis (Urine dipstick)	X	X				X	X	X		
Pregnancy test	X	X				X	X	X		Serum pregnancy test required for WOCBP at screening and end of treatment; serum or urine pregnancy test required at all other timepoints.
Blood PK Sampling (Required)						X				Blood samples (1 mL) collected C2D1 pre-dose and at 1h and 3h (±30 min) post-dose. Additional samples collected pre-dose on C3D1 and C4D1.
Blood PK Sampling (Optional)		Blood samples (minimum 1 mL) collected any day if needed, prior to dose and 1, 2, 3, 4, 6, and 24 hours post-dose.								See also Section 9.13.1
Blood and CSF PK Sampling (Blood, CSF; Optional) (Group 5 only)						(X)				Blood and CSF samples (minimum 1 mL of whole blood and CSF each) collected 2-4 hours after dose on C2D1. See also Section 9.13.1
ctDNA blood samples	X						(X)			Minimum of 20 mL whole blood at screening (mandatory) and EOT (optional).

	Screening Period (Within 28 Days Prior to First Dose)	Treatment Period (1 cycle = 21 days)					Safety Follow-up		Survival Follow-up Period	Notes
		Cycle 1				Cycles ≥2				
		Day				Day				
		1	4 (±1d)	8 (±3d)	15 (±3d)	1 (±3d)	End of Tx (+0-7 days)	30 (±3) days After Last D		
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Prior & concomitant medications, AE assessments	X	→					X	X		Collect from the time informed consent (ICF) is signed through 30 days after administration of the last dose of TAS-120.
Tumor assessments / scans	X					X	X		(X)	Perform the same tumor assessments/scans obtained at screening at the end of every 2 cycles (up to +2 weeks) up to Cycle 4. Thereafter tumor assessments may be performed every 3 cycles (± 7 days), or as clinically indicated, until radiologic disease progression or initiation of new anticancer therapy (whichever occurs first). At EOT, tumor assessment must be performed if the prior scan was performed ≥9 weeks prior to discontinuation of treatment if the patient discontinued for reasons other than radiologic disease progression. See also Section 9.17. After EOT, patients who discontinued for reasons other than radiologic disease progression should continue to receive tumor assessments every 3 cycles (± 7 days), or as clinically indicated, until radiologic disease progression or initiation of new anticancer therapy (whichever occurs first).

	Screening Period (Within 28 Days Prior to First Dose)	Treatment Period (1 cycle = 21 days)					Safety Follow-up		Survival Follow-up Period	Notes
		Cycle 1				Cycles ≥2				
		Day				Day				
		1	4 (±1d)	8 (±3d)	15 (±3d)	1 (±3d)	End of Tx (+0-7 days)	30 (±3) days After Last D		
Survival status									X	After discontinuation of treatment, survival follow-up in a given group should occur every 3 months (±2 weeks) for up to 12 months after last patient enrolled in that group.
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. See Section 8.1.1.

Table 2: Study Schedule for Phase 2

NOTE: Evaluations on D1 of a cycle should be performed within 24 hours prior to dosing, unless otherwise noted. Procedures already performed during the screening period within 72 hours prior to dosing do not need to be repeated on 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).

	Pre-Screening	Screening Period (Within 28 Days Prior to First Dose)	Treatment Period (1 cycle = 21 days)					Safety Follow-up		Survival Follow-up Period	Notes
			Cycle 1				Cycles ≥2				
			Day				Day				
			1	4 (±1d)	8 (±3d)	15 (±3d)	1 (±3d)	End of Tx (+0-7 days)	30 (±3) days After Last		
Written informed consent	(X)	X									Pre-screening ICF if required for determination of eligibility.
Tumor tissue testing of FGFR2 gene fusions / rearrangements	Tumor tissue may be tested by central laboratory during pre-screening. If previously tested by central laboratory, it is requested that tumor tissue be provided if available. In cases where local laboratory testing is used to determine eligibility, it is requested that tumor tissue be provided, if available from either archival samples or fresh tumor biopsy.										
Review eligibility criteria		X	X								
Demographics/medical history		X									
Review of pre-existing signs and symptoms		X	X								
Physical examination		X	X				X	X	X		Within 24 hours prior to dosing on D1 of each cycle.
Vital signs		X	X				X	X	X		Heart rate, blood pressure, body temperature, and respiration rate.
Height and Weight		X	X				X	X	X		Height at screening only.
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.
Neurological examination		X	(X)				(X)	X	X		As clinically indicated after screening, using same methods used at screening.
ECOG performance status		X	X				X	X	X		Within 24 hours prior to dosing on D1 of each cycle.
12-Lead Electrocardiogram		X	X				X	X	X		At screening and 2 hours (±15 minutes) after dosing on D1 of each cycle.

	Pre-Screening	Screening Period (Within 28 Days Prior to First Dose)	Treatment Period (1 cycle = 21 days)					Safety Follow-up		Survival Follow-up Period	Notes
			Cycle 1				Cycles ≥2				
			Day				Day	End of Tx (+0-7 days)	30 (±3) days After Last		
			1	4 (±1d)	8 (±3d)	15 (±3d)	1 (±3d)				
Hematology and coagulation		X	X		X	X	X	X	X		Within 24 hours prior to treatment on D1 of each cycle, any time on C1D8 and C1D15, and as clinically indicated.
Chemistry (Serum or plasma)		X	X	(X)	X	X	X	X	X		Within 24 hours prior to treatment on D1 of each cycle, any time on C1D8 and C1D15, and as clinically indicated. Additional collection for phosphorus only at C1D4.
Urinalysis (Urine dipstick)		X	X				X	X	X		
Pregnancy test		X	X				X	X	X		Serum pregnancy test required for WOCBP at screening and end of treatment; serum or urine pregnancy test required at all other timepoints.
Blood PK Sampling (Required)							X				Blood samples (1 mL) collected C2D1 pre-dose and at 1h and 3h (±30 min) post-dose. Additional samples collected pre-dose on C3D1 and C4D1.
ctDNA blood samples		X						(X)			Minimum of 20 mL whole blood at screening (mandatory) and EOT (optional).
CCI [redacted]											
Prior & concomitant medications, AE assessments	X	X	→					X	X		Collect from the time main informed consent is signed through 30 days after administration of the last dose of TAS-120 or until the start of new anticancer therapy, whichever is earlier. AEs directly associated with a pre-screening procedure should be reported as described in Section 11.1.

	Pre-Screening	Screening Period (Within 28 Days Prior to First Dose)	Treatment Period (1 cycle = 21 days)					Safety Follow-up		Survival Follow-up Period	Notes
			Cycle 1				Cycles ≥2	End of Tx (+0-7 days)	30 (±3) days After Last		
			Day				Day				
			1	4 (±1d)	8 (±3d)	15 (±3d)	1 (±3d)				
PRO (EQ-5D and EORTC QLQ-C30)		X					X	X			Evaluated at screening and as close as possible to the tumor assessment schedule: at the end of every 2 cycles (up to +2 weeks) through Cycle 4 and every 3 cycles (±7 days) thereafter until disease progression or initiation of new anticancer therapy (whichever is first).
Tumor assessments / scans		X					X	X		(X)	Same tumor assessments/scans obtained at screening at the end of every 2 cycles (up to +2 weeks) up to Cycle 4. Thereafter tumor assessments may be performed every 3 cycles (± 7 days), or as clinically indicated, until radiologic PD or initiation of new anticancer therapy (whichever occurs first). At EOT, tumor assessment must be performed if the prior scan was performed ≥9 weeks prior to discontinuation of treatment if the patient discontinued for reasons other than radiologic disease progression. See also Section 9.17. After EOT, patients who discontinued for reasons other than radiologic disease progression should continue to receive tumor assessments every 3 cycles (± 7 days), or as clinically indicated, until radiologic disease progression or initiation of new anticancer therapy (whichever occurs first).

	Pre-Screening	Screening Period (Within 28 Days Prior to First Dose)	Treatment Period (1 cycle = 21 days)					Safety Follow-up		Survival Follow-up Period	Notes
			Cycle 1				Cycles ≥2	End of Tx (+0-7 days)	30 (±3) days After Last		
			Day				Day				
			1	4 (±1d)	8 (±3d)	15 (±3d)	1 (±3d)				
Survival status										X	After discontinuation of treatment, survival follow-up should occur every 3 months (±2 weeks) for up to 18 months after last patient enrolled in the Phase 2 portion of the study.
TAS-120 Dosing			→								Patients are required to fast for ≥2 hours before and 1 hour after each administration of TAS-120; patients are permitted to drink water. TAS-120 should be administered in the morning or evening, at the same time (if possible) each day. See Section 8.1.1.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

SUMMARY OF CHANGES 2
1. SYNOPSIS 4
2. STUDY SCHEDULES 12
3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES 20
4. LIST OF ABBREVIATIONS AND TERMS 28
5. INTRODUCTION AND STUDY RATIONALE 31
5.1. Unmet Medical Need in Treatment of Cholangiocarcinoma 31
5.2. TAS-120 32
5.2.1. Preclinical Experience with TAS-120 32
5.2.2. Clinical Experience with TAS-120 32
5.3. Study Rationale 33
5.4. Rationale for Selection of RP2D of TAS-120 33
5.5. Rationale for the Phase 1 Expansion Part of the Study 33
5.6. Rationale for Phase 2 Part of the Study 34
6. STUDY OBJECTIVES 35
6.1. Phase 1 Dose Escalation 35
6.2. Phase 1 Expansion 35
6.3. Phase 2 36
7. INVESTIGATIONAL PLAN 37
7.1. Study Design 37
7.1.1. Phase 1 Expansion 38
7.1.2. Phase 2 39
7.1.3. Study Duration 40
7.2. Study Population 40
7.2.1. Inclusion Criteria 40
7.2.2. Exclusion Criteria 42
7.3. Discontinuation Criteria 44
7.3.1. End of Treatment Discontinuation Criteria 44
7.4. Patient Numbering and Treatment Allocation 44

7.5. Replacement Criteria 45
7.6. Prohibited Medications and Therapies 45
7.7. Concomitant Medications and Therapies 45
7.7.1. Effective Contraception During Study 47
7.8. Dietary Restrictions 48
8. STUDY DRUG 49
8.1. Study Drug Administration and Dose Modification Procedures 49
8.1.1. Study Drug Administration 49
8.1.2. Treatment Regimen 49
8.1.3. Dose Reduction/Modification Procedures 49
8.1.3.1. TAS-120 Dose Reductions for Treatment-emergent Toxicities 49
8.2. Description and Labeling 53
8.2.1. TAS-120 53
8.2.2. Packaging and Labeling 54
8.2.3. Storage 54
8.2.4. Patient Instructions for Handling Study Drug 54
8.3. Drug Accountability 54
8.4. Blinding 55
9. STUDY PROCEDURES 56
9.1. Pre-screening of Tumor Tissue Sample for FGFR2 Gene Fusions or other FGFR2 Rearrangements in Patients with iCCA (Phase 2 Only) 56
9.2. Informed Consent 57
9.3. Medical History 57
9.4. Physical Examination 57
9.5. Height, Vital Signs, and Weight 57
9.6. Performance Status 57
9.7. Electrocardiogram 58
9.8. Ophthalmological Examination 58
9.9. Neurological Examination 59
9.9.1. Neurological Examination as part of RANO Evaluation for Patients with Primary CNS Tumors 59
9.10. Clinical Laboratory Evaluations 60
9.10.1. Hematology and Coagulation 60

9.10.2. Chemistry....61
9.10.3. Urinalysis....62
CCI
9.12. Pregnancy Test....62
9.13. Pharmacokinetic Sample Collection....63
9.13.1. Optional Pharmacokinetic Sample Collection for Phase 1 Expansion....63
9.13.2. Pharmacokinetic Blood Sample Collection for Phase 1 Expansion/Phase 2....63
9.14. ctDNA Analysis of FGF/FGFR Aberrations....64
9.14.1. ctDNA from Blood Sample for the Analysis of FGF/FGFR Aberrations....64
9.15. Prior and Concomitant Medications and Therapies....64
9.16. Adverse Event Assessment....64
9.17. Tumor Assessments/Scans....65
9.17.1. Tumor Assessment for Advanced Solid Tumors....65
9.17.2. Tumor Assessment for Brain Tumors....66
9.18. Patient-Reported Outcomes....66
9.19. End-of-treatment Visit....67
9.20. 30-Day Safety Follow-up....67
9.21. Survival Status Follow-up....67
9.22. Tumor Tissue Sample Collection (Phase 1 Expansion)....67
10. EFFICACY ASSESSMENT CRITERIA....68
10.1. Efficacy Assessment for Solid Tumors....68
10.1.1. Method of Imaging....68
10.1.2. Tumor Definitions....69
10.1.3. Response Criteria....70
10.1.3.1. Target and Non-Target Response Assessments....71
10.1.3.2. Objective Response Assessment....72
10.1.4. Best Objective Response Assessment for Solid Tumors....73
10.2. Efficacy Assessment for Brain Tumors....73
10.2.1. Method of Imaging....73
10.2.2. Tumor Definitions....73
10.2.2.1. Measurable and Non-measurable Contrast Enhancing Lesions....73
10.2.2.2. Non-enhancing Lesions....74
10.2.3. Response Definitions....74

11. REPORTING SAFETY INFORMATION 77
11.1. Adverse Events/Serious Adverse Events 77
11.1.1. Adverse Events 77
11.1.2. Serious Adverse Events 78
11.1.3. Reporting of Deaths 79
11.1.4. Disease Progression 79
11.1.5. Pregnancy 80
11.1.6. Overdose 80
11.1.7. Medication Errors 80
11.1.8. Breaking the Study Blind 81
11.2. Laboratory Evaluations 81
11.2.1. Reporting and Evaluation of Laboratory Test Results 81
11.2.2. Repeat Testing 81
11.3. Physical Examination and Performance Status 81
11.4. Vital Signs and Body Weight 81
12. STATISTICS 82
12.1. Study Populations 82
12.2. Statistical Analysis 82
12.2.1. Patient Disposition, Baseline and Treatment Characteristics 82
12.2.1.1. Patient Disposition 82
12.2.1.2. Patient Baseline Characteristics 83
12.2.1.3. Study Treatment 83
12.2.2. Efficacy Analysis 83
12.2.2.1. Objective Response Rate 83
12.2.2.2. Disease Control Rate 83
12.2.2.3. Duration of Response 84
12.2.2.4. Progression-free Survival 84
12.2.2.5. Overall Survival 84
12.2.2.6. Patient-Reported Outcomes 84
12.2.3. Safety 85
12.2.4. Pharmacokinetic Analysis 85
12.2.5. Pharmacodynamic Analysis (Phase 1 Dose Escalation only) 86
12.3. Determination of Sample Size 86

CCI [redacted]
CCI [redacted]
12.3.3. Phase 2 89
12.4. Interim Analyses 89
13. ETHICS 90
13.1. Ethical Considerations 90
13.2. Informed Consent and Patient Information 90
13.3. Institutional Review Board/Independent Ethics Committee Approval 90
13.4. Post-study Provisions 91
14. ADMINISTRATIVE CONSIDERATIONS 92
14.1. Protocol Amendments 92
14.2. Curriculum Vitae 92
14.3. Administrative Structure 92
14.4. Monitoring Procedures 92
14.4.1. Investigator's Responsibilities 92
14.4.2. Sponsor's Responsibilities 92
14.4.3. Source Documents 93
14.4.4. Case Report Form 93
14.4.5. Sponsor's Audits and Regulatory Inspections 93
14.5. Archiving of Records 94
14.6. Final Report 94
14.7. Use and Publication of Study Results 94
14.8. Financial Disclosure 95
14.9. Termination of the Study 95
15. CONFIDENTIALITY AND DATA PROTECTION 96
16. SIGNATURES OF SPONSOR AND INVESTIGATOR 97
17. REFERENCES 98
APPENDIX A. LIST OF FGFR MUTATIONS 100
APPENDIX B. FGFR3 MUTATIONS 102
APPENDIX C. ECOG PERFORMANCE STATUS 103
APPENDIX D. NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION 104
APPENDIX E. DIETARY GUIDELINES FOR TREATMENT OF HYPERPHOSPHATEMIA 105

APPENDIX F. CLASSIFICATION OF SUBSTRATES, INHIBITORS, AND INDUCERS OF CYP ENZYMES AND TRANSPORTERS 106
APPENDIX G. SUPPLEMENTAL REQUIREMENTS FOR JAPAN ONLY 109
APPENDIX H. SUMMARY OF PROTOCOL AMENDMENTS 111

LIST OF TABLES

Table 1: Study Schedule for Phase 1 Expansion 12
Table 2: Study Schedule for Phase 2 16
Table 3: Abbreviations and Terms....28
Table 4: List of TAS-120 Clinical Trials....33
Table 5: TAS-120 Dose Reduction Levels 49
Table 6: TAS-120 Dosing Modification for Nonhematologic Toxicities....50
Table 7: Recommendations for Hyperphosphatemia Management....51
Table 8: TAS-120 Dose Interruption and Modification Criteria for Hematologic Toxicities 52
Table 9: Required Follow-up for Toxicities 53
Table 10: TAS-120 Product description and packaging information 54
Table 11: Laboratory Assessments for TAS-120-101 61
Table 12: Pharmacokinetic Blood Sample Collection for Phase 1 Expansion/Phase 2....64
Table 13: Time Point Response for Patients with Target (+/- Non-Target) Disease....72
Table 14: Time Point Response for Patients with Only Non-Target Disease....73
Table 15: Summary of RANO Response Criteria....76
Table 16: Multinomial Two-stage Design Boundaries for Group 5 (Based on Objective Response and Early Progression) 87
Table 17: Summary of Group 7 Design....88
Table 18: Observed ORR with Exact 95% Confidence Interval 89

LIST OF FIGURES

Figure 1: Overall Study Schema 37
Figure 2: Group 7 Tumor Types 38
Figure 3: Study Schema for Phase 2 39
Figure 4: Algorithm for Selection of Target Lesions: RANO Criteria 74

4. LIST OF ABBREVIATIONS AND TERMS

Table 3: Abbreviations and Terms

Abbreviation or Term	Explanation
AE	Adverse event
Ae%	Urinary excretion rate as % of dose (QOD arm)
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the concentration time curve
β-HCG	Beta-human chorionic gonadotropin
BID	Twice a day
BUN	Blood urea nitrogen
CCA	Cholangiocarcinoma
Ccr	Calculated creatinine clearance
CFR	Code of Federal Regulations
CI	Confidence interval
CK	Creatinine kinase
CL/F	Oral clearance
CLr	Renal clearance
C_{max}	Maximum observed plasma concentration
CR	Complete response
CRA	Clinical Research Associate
CRO	Contract Research Organization
CSF	Cerebrospinal fluid
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CYP	Cytochrome P450
DCR	Disease control rate
DLT	Dose-limiting toxicity
DOR	Duration of response
eCCA	Extra-hepatic cholangiocarcinoma
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture

Abbreviation or Term	Explanation
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EOT	End-of-treatment
EP	Early progression
EPR	Early progression rate
EQ-5D	EuroQol-5D measure of health-related quality of life
EU	European Union
FFPE	Formalin fixed paraffin embedded
FGF	Fibroblast growth factor
FGFR	Fibroblast growth factor receptor
FISH	Fluorescence in situ hybridization
GBM	Glioblastoma multiforme
G-CSF	Granulocyte colony-stimulating factor
GCP	Good Clinical Practice
Gd-MRI	Gadolinium-based magnetic resonance imaging
GnRH	Gonadotropin-releasing hormone
Hgb	Hemoglobin
IB	Investigator's Brochure
iCCA	Intra-hepatic cholangiocarcinoma
IC_{50}	50% inhibitory concentration
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IU	International Units
IXRS	Interactive voice/web response system
LH-RH	Luteinizing hormone-releasing hormone
LLN	Lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MRT	Mean residence time
ms	Milliseconds
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NGS	Next generation sequencing
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association

Abbreviation or Term	Explanation
ORR	Objective response rate
OS	Overall survival
P	Phosphorus
PD	Progressive disease
PFS	Progression-free survival
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PLT	Platelets
PMDA	Pharmaceuticals and Medical Devices Agency
PR	Partial response
PROs	Patient-Reported Outcomes
PT	Preferred term
QD	Once daily (continuous) dosing
QOD	3-times-a-week (Monday, Wednesday, and Friday) dosing
QoL	Quality of life
QTcF	Fridericia's corrected QT interval
R	Response
RANO	Response Assessment in Neuro-Oncology
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SIRT	Selective internal radiotherapy
SOC	System Organ Class
SOP	Standard operating procedure
TACE	Transarterial chemoembolization
$t_{1/2}$	Elimination half-life
TID	Three times a day
T_{max}	Time to maximum plasma concentration
TOI	Taiho Oncology, Incorporated
ULN	Upper limit of normal
USA	United States of America
Vd/F	Volume of distribution
WBC	White blood cell
WHO	World Health Organization
WOCBP	Women of child-bearing potential

5. INTRODUCTION AND STUDY RATIONALE

The progression of cancers is caused by a complex series of multiple genetic and molecular events including gene mutations and chromosomal translocations.[1]

The fibroblast growth factor/fibroblast growth factor receptor (FGF/FGFR) signaling axis plays an important role in normal organ, vascular, and skeletal development. On the other hand, activating FGFR gene abnormalities are reported in various tumor types, and FGFR abnormalities are considered a driving event for tumor formation.[2, 3, 4] Genetic modifications or overexpression of FGFRs have been associated with tumorigenesis and progression in breast, lung, gastric, hematologic malignancies, and others.[4, 5, 6, 7, 8, 9] Activating FGFR gene abnormalities are reported in various cancers including non-small cell lung cancer (NSCLC) (FGFR1 amplification), breast (FGFR1 and 2 amplification), gastric (FGFR2 amplification), bladder (FGFR3 activating mutation or gene translocation), endometrial (FGFR2 activating mutation), multiple myeloma (FGFR3 gene translocation), and rhabdomyosarcoma (FGFR4 activating mutation).

Of note, according to published results, 22% of patients with squamous cell lung cancer have an FGFR1 amplification, 10% of patients with breast cancer have FGFR1 and 2 amplifications, 10% of patients with gastric cancer have an FGFR2 amplification, more than 50% of patients with nonmuscle invasive bladder cancer have an FGFR3-activating mutation or gene translocation, 12% of patients with endometrial cancer have an FGFR2-activating mutation, 5% of patients with multiple myeloma have an FGFR3 gene-involving translocation, 7.5% of patients with rhabdomyosarcoma have an FGFR4-activating mutation, and 3% of patients with small-cell lung cancer have an FGFR1 amplification.[3, 10, 11, 12] . In all the tumor types described above for which FGFR abnormalities have been described, nonresectable advanced or metastatic disease remains incurable and ultimately resistant to currently available chemotherapies.

5.1. Unmet Medical Need in Treatment of Cholangiocarcinoma

Cholangiocarcinoma (CCA), a bile duct cancer, is a rare tumor that arises from the malignant transformation of epithelial cells of the bile ducts. It is typically classified as either intrahepatic (iCCA) or extrahepatic (eCCA). Intrahepatic cholangiocarcinoma develops in the smaller bile ducts inside the liver and is the least common form of the disease (approximately 10%), whereas eCCA includes cancers in the peri-hilar (also known as Klatskin tumor) and distal bile duct area and is most common (approximately 90%).

Although CCA is known to have the histological and molecular features of an adenocarcinoma of epithelial cells lining the biliary tract, the actual cell of origin is unknown. Fibroblast growth factor/fibroblast growth factor receptor aberrations are a reported genetic modification in CCA. In iCCA, FGFR2 gene rearrangement, including fusions, has been identified as an early driver of oncogenic events. These gene rearrangements/fusions are present in an estimated 10% to 20% of patients.[1, 11, 12] Therefore, inhibiting the FGFR pathway in patients with iCCA is a plausible therapeutic strategy for appropriately selected patients with this disease.

For disease which is localized at diagnosis, surgical resection offers the only chance of cure. Unfortunately, symptoms are not usually apparent until CCA is at an advanced stage, and thus, most patients (>65%) have disease which is unresectable at diagnosis. Unresectable, locally advanced (stage III) and metastatic (stage IV) disease has a poor prognosis with 5-year overall

survival (OS) of 10% and 0%, respectively. For such patients, chemotherapy and supportive care are usually offered.[13] Although there are no approved treatments for CCA, gemcitabine/cisplatin is the standard 1st line chemotherapy regimen for patients with advanced, metastatic, unresectable CCA. There is no standard regimen beyond first line.[14] In the second line treatment setting of chemotherapy, a retrospective evaluation of 761 patients with advanced biliary tract cancers, including CCA has shown a median overall response rate of 7.7% (95% confidence interval (CI): 5% to 11%) and a median progression-free survival (PFS) of 3.2 months (95% CI: 2.7 – 3.7 months).[13] These poor results confirm a substantial unmet medical need for new therapies in patients with advanced CCA who have failed initial chemotherapy.

5.2. TAS-120

TAS-120 is a novel selective and irreversible small molecule FGFR inhibitor.

5.2.1. Preclinical Experience with TAS-120

TAS-120 equally inhibited all 4 subtypes of FGFR and showed high selectivity for FGFR when tested against a panel of 296 kinases. Half maximal inhibitory concentration (IC_{50}) values (nmol/L) were 3.9 for FGFR1, 1.3 for FGFR2, 1.6 for FGFR3, and 8.3 for FGFR4. TAS-120 was highly active against cancer cell lines with FGFR gene abnormalities including cancer cell lines that acquired resistance to other ATP-competitive FGFR tyrosine kinase inhibitors (TKIs). *In vitro* studies have shown that TAS-120 selectively inhibits cell growth of human cancer cell lines that have FGFR gene abnormalities. *In vivo* studies showed that TAS-120 had 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 addition, TAS-120 retained inhibitory potency against mutant FGFR2 including the V565I gatekeeper mutation with a similar potency compared to wild type FGFR2. N550H and E566G mutations in the FGFR2 hinge region, which were reported to cause resistance to dovitinib (another FGFR inhibitor), were also sensitive to TAS-120. Furthermore, TAS-120 showed inhibitory potency against mutant FGFR2 including a K660M activation loop mutation. IC_{50} values for pFGFR2 inhibition (nmol/L) were 0.9 for WT, 1.3 for V565I, 3.6 for N550H, 2.3 for E566G, and 5.2 for K660M. In contrast, when several competitive inhibitors of FGFR were tested against these FGFR2 mutants, their inhibitory potencies were reduced compared to their potency against the wild type. See the current TAS-120 Investigator's Brochure (IB) for additional information.

5.2.2. Clinical Experience with TAS-120

CCI

Table 4: List of TAS-120 Clinical Trials

Study Number	Number of Patients Enrolled[a]	Number of Patients Ongoing[a]	Dose and schedule: number of patients enrolled[a]
CCI			

QD = once daily; QOD = every other day

[a] As of 20 September 2017

5.3. Study Rationale

The FGF/FGFR signaling axis has been well characterized for its role in proliferation, differentiation, migration, and survival, and it is fundamental to embryonic development, regulation of angiogenesis, and wound healing in adults. Dysregulation of the FGFR signaling pathway has been associated with many developmental disorders and with cancer. An extensive amount of literature indicates that FGF/FGFR is one of the receptor tyrosine kinases most frequently mutated or otherwise abnormally activated in late-stage human cancer.

Therefore, FGFR has been shown to be a valid target, and TAS-120 is a selective inhibitor of FGFR. TAS-120 exhibits convincing antitumor activity in several xenograft models. Importantly, it delivers antitumor efficacy in xenograft models with a large safety window.

This Phase 1/2 clinical trial was planned to investigate the PK, pharmacodynamics, efficacy, safety, and tolerability of TAS-120 in patients with advanced solid tumors, with FGF/FGFR abnormalities who have failed all standard therapies or for whom standard therapy does not exist.

5.4. Rationale for Selection of RP2D of TAS-120

During the Phase 1 Dose Escalation part of the study, dose levels of 4, 8, 16, 20 and 24 mg QD were evaluated. At 24 mg, 3 of 9 evaluable patients experienced a dose-limiting toxicity (DLT) during Cycle 1, thus, 24 mg was determined as the DLT dose level. At 20 mg QD, no DLT was reported in the 5 evaluable patients during Cycle 1, and thus, 20 mg QD was determined as the maximum tolerated dose (MTD) and RP2D.

5.5. Rationale for the Phase 1 Expansion Part of the Study

The Phase 1 Expansion part of the study included a total of 8 treatment groups enrolling different patient populations; 3 of these groups remain open as of Amendment 7 to this protocol. This includes a group of patients with cholangiocarcinoma (CCA), a group of patients with primary CNS tumors harboring FGFR gene fusion or FGFR1 activating mutation, and 1 basket cohort including patients with solid tumors that harboring FGFR2 amplifications.

Expansion in patients with CCA is based upon clinical evidence of preliminary anti-tumor activity in this condition observed during the Phase I Dose Escalation portion of the study (please see Section 5.6 for additional detail).

The group of patients with primary CNS tumors is included on the basis of nonclinical studies demonstrating the viability of FGFR1 activating mutations and FGFR gene fusions as therapeutic targets in human gliomas.[20,21]

Group 7 (basket of tumor types harboring FGFR2 amplifications) was designed based on research suggesting that response to treatment targeting the FGFR may be increased across a wide range of different solid tumors harboring this form of mutation.[22] As FGFR2 amplifications are most common in ovarian and upper gastrointestinal tumors, these 2 cancer types will be included in distinct subgroups of Group 7, with a third subgroup encompassing all other tumors with FGFR2 amplifications.

5.6. Rationale for Phase 2 Part of the Study

The original design of the Phase 2 portion of the study (enrolling patients with iCCA harboring FGFR2 gene fusions) was based on preliminary anti-tumor activity observed in this population in the Phase 1 portions of the study. Specifically, at the time the Phase 2 portion was designed (data cut off 17 September 2017), a total of 3 confirmed partial responses had been observed among 14 response-evaluable patients with iCCA harboring FGFR2 gene fusions. Accordingly, as of Amendment 7 to this protocol, the study population for the Phase 2 portion of the study is to include approximately 100 patients with iCCA harboring confirmed FGFR2 gene fusions or other FGFR2 rearrangements.

6. STUDY OBJECTIVES

6.1. Phase 1 Dose Escalation

Phase 1 Dose Escalation has been completed as of Amendment 6.

6.2. Phase 1 Expansion

Primary

- To evaluate ORR in cholangiocarcinoma (intra-hepatic [iCCA] or extra-hepatic [eCCA]) patients with tumors harboring FGFR2 gene fusions or other FGFR abnormalities.
- To evaluate ORR and EPR (defined as progression-free rate at the end of Cycle 2) in patients with primary CNS tumors harboring FGFR gene fusions or FGFR1 activating mutations (Appendix A).
- To evaluate ORR in a basket of tumor types with tumors harboring FGFR2 amplifications.
- To evaluate ORR in a basket of tumor types with tumors harboring any FGFR gene fusions or activating mutations Appendix A).

Secondary

- To investigate the safety of TAS-120.
- To evaluate DCR, DOR, PFS, and OS in each treatment group.

CCI

6.3. Phase 2

Primary

- To confirm ORR in iCCA patients with FGFR2 gene fusions or other FGFR2 rearrangements based on independent central radiology review.

Key secondary

- To evaluate DOR

Other secondary

- To evaluate the safety and tolerability of TAS-120.
- To evaluate DCR, PFS, and OS
- To evaluate Patient-Reported Outcomes (PROs)

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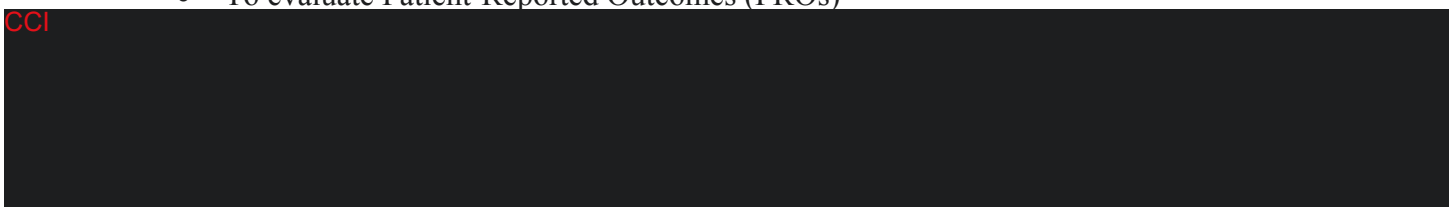


7. INVESTIGATIONAL PLAN

7.1. Study Design

This is an open-label, nonrandomized, dose-escalation and dose-expansion, Phase 1/2 study of TAS-120, evaluating the safety, tolerability, PK, pharmacodynamic, and antitumor activity of TAS-120 in patients with advanced solid tumors with FGF/FGFR abnormalities who have failed all standard therapies or for whom standard therapy does not exist.

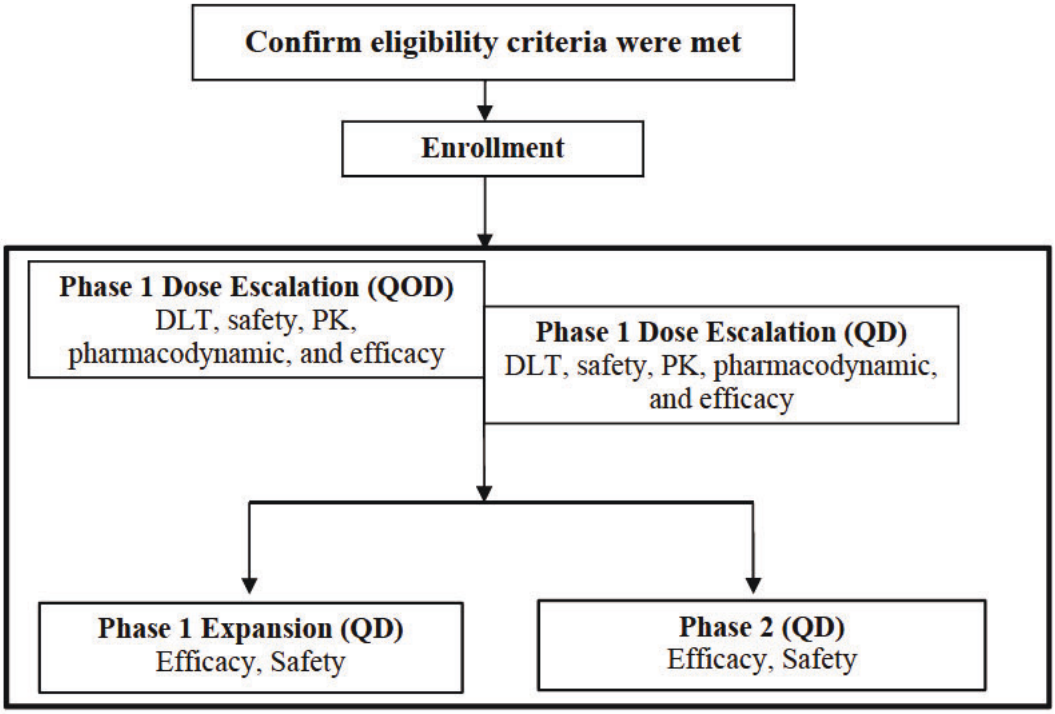
The study will be conducted in 3 parts:

- Phase 1 Dose Escalation: to determine the MTD and/or RP2D of TAS-120
- Phase 1 Expansion: to further evaluate the efficacy and safety of the MTD and/or RP2D of TAS-120 in patients with tumors harboring specific FGF/FGFR aberrations
- Phase 2: to confirm the ORR of TAS-120 in iCCA patients with tumors harboring FGFR2 gene fusions or other FGFR2 rearrangements.

As of Amendment 6, the Phase 1 Dose Escalation Phase is completed and the MTD/RP2D of 20 mg QD was established. Details of the Phase 1 Dose Escalation study design can be found in previous versions of the study protocol.

The overall study design is described in Figure 1.

Figure 1: Overall Study Schema



Abbreviations: DLT = dose-limiting toxicity; PK = pharmacokinetics; QD = once daily (continuous) dosing; QOD = 3-times-a-week (Monday, Wednesday, Friday) dosing.

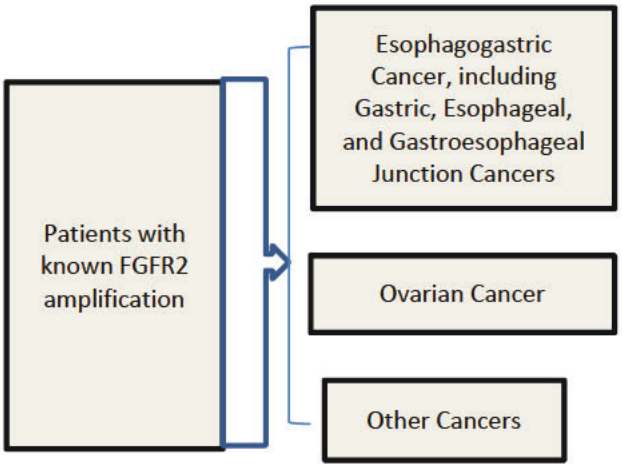
7.1.1. Phase 1 Expansion

TAS-120 will be administered orally at 20 mg, QD in 21-day cycles. Approximately 185 patients will be enrolled. Patients are assigned to one of 8 groups based on tumor type and FGFR aberration, as described below.

Additional patients may be enrolled to any of the groups as promising clinical activity emerges.

- Group 1 (Enrollment suspended as of Amendment 7): Patients with intrahepatic or extrahepatic CCA harboring FGFR2 gene fusions
- Group 2: Patients with intrahepatic or extrahepatic CCA harboring FGFR2 gene fusions that have not received or received less than 1 cycle of prior chemotherapy (due to intolerance or patient refusal)
- Group 3 (Enrollment suspended as of Amendment 7): Patients with intrahepatic or extrahepatic CCA harboring FGFR2 gene fusions that have been treated with prior FGFR inhibitors
- Group 4 (Enrollment suspended as of Amendment 7): Patients with intrahepatic or extrahepatic CCA harboring FGFR abnormalities other than FGFR2 gene fusions (for example, mutations, rearrangements, or amplifications)
- Group 5: Patients with primary CNS tumors harboring FGFR gene fusions or FGFR1 activating mutations
- Group 6 (Enrollment suspended as of Amendment 7): Patients with advanced urothelial carcinoma harboring FGFR3 gene fusions or FGFR3 activating mutations
- Group 7: Patients with any tumor type not included in one of the prior groups, harboring FGFR2 amplification (no minimum number of copies) (Figure 2).
- Group 8 (Enrollment suspended as of Amendment 7): Patients with any tumor type not included in one of the prior groups, harboring FGFR gene fusions or activating mutations

Figure 2: Group 7 Tumor Types

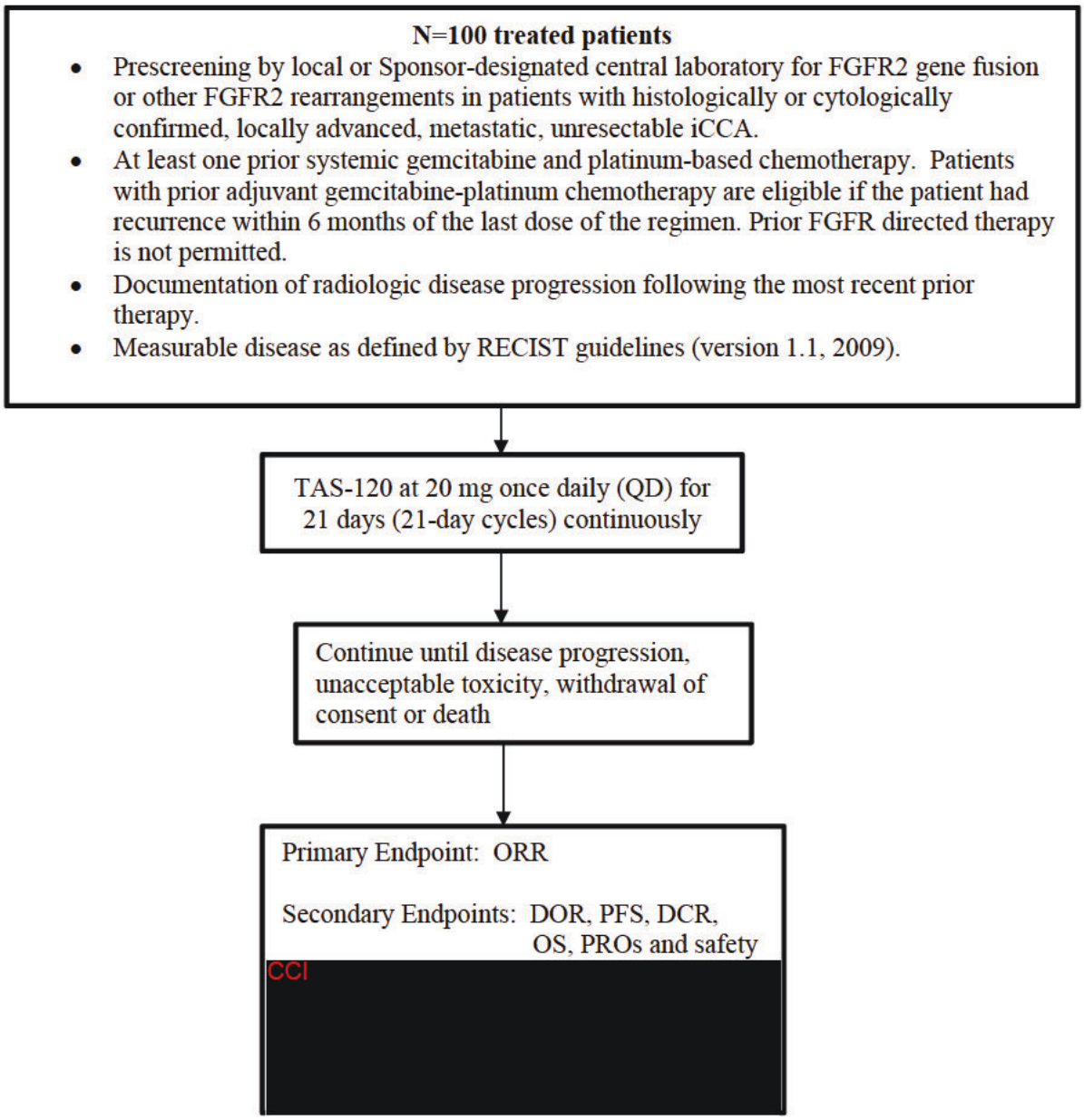


7.1.2. Phase 2

During Phase 2, TAS-120 will be administered orally at 20 mg, once daily (QD) in 21-day cycles.

The overall study design for Phase 2 of the study is described in Figure 3.

Figure 3: Study Schema for Phase 2



ORR = Objective response rate; PFS = Progression-free survival; DCR = Disease control rate; DOR = Duration of response; OS = Overall survival; PROs = Patient-Reported Outcomes; PK = Pharmacokinetics.

7.1.3. Study Duration

Safety monitoring will begin from the time the main study informed consent form (ICF) is signed and will continue for 30 days after the last dose of TAS-120 or until the initiation of another anticancer therapy, whichever occurs first.

Patients will receive study treatment until disease progression, occurrence of intolerable side effects, discontinued from treatment by the investigator, withdrawal of consent, or other criteria for discontinuation is met (see Section 7.3, Discontinuation Criteria). A patient is considered discontinued from study treatment when TAS-120 is discontinued.

For the Phase 1 Expansion part of the study, patients in each treatment group should be followed for survival for up to 12 months after the last patient enrolled in that group.

For Phase 2, patients should be followed for survival for up to 18 months after the last patient enrolled in this phase of the study.

7.2. Study Population

The study population will include male and female patients with advanced solid tumors or primary CNS tumors, according to the following inclusion and exclusion criteria.

7.2.1. Inclusion Criteria

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

1. Provide written informed consent.
2. Is ≥ 18 years (or according the country's regulatory definition for legal adult age).
3. Has histologically or cytologically confirmed, locally advanced, metastatic cancer meeting the following criteria:
    a. Phase 1 Expansion
        i. Patient has failed (or in the case of Group 2, failed or refused) all standard therapies or standard therapy does not exist or is not tolerated.
        ii. Patient is eligible for 1 of the following enrollment groups, based on diagnosis, prior therapy, and FGF/FGFR aberrations as shown:
            a. **Group 1 (Enrollment Suspended as of Amendment 7):** Patient has intrahepatic or extrahepatic cholangiocarcinoma harboring FGFR2 gene fusions.
            b. **Group 2:** Patient has intrahepatic or extrahepatic cholangiocarcinoma harboring FGFR2 gene fusions, and has not received or received less than 1 cycle of prior chemotherapy (due to intolerance or patient refusal).
            c. **Group 3 (Enrollment Suspended as of Amendment 7):** Patient has intrahepatic or extrahepatic cholangiocarcinoma harboring FGFR2 gene fusions and has received prior treatment with FGFR inhibitors.

d. **Group 4 (Enrollment suspended as of Amendment 7):** Patient has intrahepatic or extrahepatic cholangiocarcinoma harboring FGFR abnormalities **other than** FGFR2 gene fusions (for example, mutations, rearrangements, or amplifications).

e. **Group 5:** Patient has a primary CNS tumor harboring FGFR gene fusion or FGFR1 activating mutation and fulfills the following criteria (i and ii):

   i. Patients who are presenting in recurrence or relapse must have at least one measurable enhancing mass lesion with 2 perpendicular diameters of at least 10 mm documented on baseline contrast magnetic resonance imaging (MRI) (gadolinium-based MRI).

   ii. Patients should be on a stable dose of steroids for at least 7 days prior to obtaining the baseline contrast MRI of the brain and at least 7 days prior to starting study drug.

f. **Group 6 (Enrollment Suspended as of Amendment 7):** Patient has advanced urothelial carcinoma harboring FGFR3 fusions or FGFR3 activating mutations.

g. **Group 7:** Patient has any tumor type not included in one of the prior groups, harboring FGFR2 amplification (no minimum number of copies).

h. **Group 8 (Enrollment Suspended as of Amendment 7):** Patient has any tumor type not included in one of the prior groups, harboring FGFR gene fusions or activating mutations.

b. Phase 2

i. Patient has histologically or cytologically confirmed, locally advanced, metastatic, unresectable iCCA harboring FGFR2 gene fusions or other FGFR2 rearrangements based on results from *either* of the following (see Section 9.1 for details):

   a. Testing by Foundation Medicine:
      i. As part of study pre-screening; or
      ii. Previously tested by Foundation Medicine; in this case, it is requested that tumor tissue be provided to Foundation Medicine if available.
   b. Local laboratory testing using next generation sequencing [NGS], fluorescence in situ hybridization [FISH], or other assays that can determine FGFR2 gene fusions or other FGFR2 rearrangements on tumor tissues or from ctDNA. It is requested that patients enrolled on this basis provide tumor tissues to Foundation Medicine, if available from either archival samples or fresh tumor biopsy.

ii. Patient has been treated with at least one prior systemic gemcitabine and platinum-based chemotherapy. Patients with prior adjuvant gemcitabine-platinum chemotherapy are eligible if the patient had recurrence within 6 months of the last dose of the regimen.

iii. Patient has documentation of radiographic disease progression on the most recent prior therapy

4. Patient has measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1, 2009) for advanced solid tumors or RANO criteria (2010) for brain tumors.
5. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 on Day 1 of Cycle 1 (see Appendix C, ECOG Performance Status).
6. Able to take medications orally (e.g., no feeding tube).
7. Adequate organ function as defined by the following criteria:
    a. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 ×upper limit of normal (ULN); if liver function abnormalities are due to underlying liver metastasis, AST and ALT ≤ 5 × ULN.
    b. Total bilirubin ≤ 1.5 × ULN, or ≤ 3.0 mg/dL for patients with Gilbert's syndrome.
    c. International normalized ratio (INR) <1.3 (or < 3.0 on anticoagulants)
    d. Absolute neutrophil count ≥ 1000/mm^3 (i.e., ≥ 1.0 × 10^9/L by International Units [IU])
    e. Platelet count ≥ 75,000/mm^3 (IU: ≥ 75 × 10^9/L)
    f. Hemoglobin ≥ 9.0 g/dL
    g. Phosphorus ≤ ULN.
8. Creatinine clearance (calculated* or measured value**): ≥ 40 mL/min
   * For a calculated creatinine clearance (Ccr) value, the eligibility should be determined using the Cockcroft-Gault formula:
    a. Male Ccr (mL/min) = Body weight (kg) × (140 – age)/[72 × creatinine (mg/dL)]
    b. Female Ccr (mL/min) = male Ccr × 0.85

   **A measured Ccr value (i.e., not calculated) should meet this criterion.
9. Women of child-bearing potential (WOCBP) must have a negative pregnancy test (urine or serum) within 7 days 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 6 months after the last dose. Section 7.7.1 provides a list of effective contraceptive methods for this protocol.
10. Willing and able to comply with scheduled visits and study procedures.

7.2.2. Exclusion Criteria

A patient will be excluded from this study if any of the following criteria are met:

1. History and/or current evidence of clinically significant non-tumor related alteration of calcium-phosphorus homeostasis.

2. History and/or current evidence of clinically significant ectopic mineralization/calcification.
3. History and/or current evidence of clinically significant retinal disorder confirmed by retinal examination.
4. History or current evidence of serious uncontrolled ventricular arrhythmias
5. Fridericia's corrected QT interval (QTcF) > 470 ms on ECG conducted during Screening.
6. Treatment with any of the following within the specified time frame prior to the first dose of TAS-120:
    a. Major surgery within the previous 4 weeks (the surgical incision should be fully healed prior to the first dose of TAS-120).
    b. Radiotherapy for extended field within 4 weeks or limited field radiotherapy within 2 weeks.
    c. Patients with locoregional therapy, e.g., transarterial chemoembolization (TACE), selective internal radiotherapy (SIRT) or ablation within 4 weeks.
    d. Any noninvestigational anticancer therapy within 3 weeks or have not recovered from side effects of such therapy prior to TAS-120 administration (mitomycin within prior 5 weeks).
        - Targeted therapy or immunotherapy within 3 weeks or within 5 half-lives (whichever is shorter)
    e. Any investigational agent received within 5 half-lives of the drug or 4 weeks, whichever is shorter. Concurrent participation in an observational study may be allowed after review by the Sponsor's Medical Monitor.
    f. Patients with prior FGFR-directed therapy.
7. A serious illness or medical condition(s) including, but not limited to, the following:
    a. Known brain metastasis (not including primary brain tumors) unless patient is clinically stable for ≥ 1 month.
    b. Known acute systemic infection.
    c. Myocardial infarction, severe/unstable angina, symptomatic congestive heart failure (New York Heart Association [NYHA] Class III or IV (see Appendix D, New York Heart Association [NYHA] Classification) within the previous 2 months; if > 2 months, cardiac function must be within normal limits and the patient must be free of cardiac-related symptoms.
    d. Chronic nausea, vomiting, or diarrhea 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 in the judgment of the investigator would make the patient inappropriate for entry into this study.
8. Patients with a history of another primary malignancy that is currently clinically significant, and has potential for metastases or currently requires active intervention (except for gonadotropin-releasing hormone (GnRH) or luteinizing hormone-releasing

hormone (LH-RH) agonists in prostate cancer or adjuvant hormonal therapy in breast cancer).

9. Pregnant or lactating female.

7.3. Discontinuation Criteria

A patient is considered discontinued from study treatment when the decision to permanently stop TAS-120 is made. Any TAS-120 discontinuation should be fully documented.

7.3.1. End of Treatment Discontinuation Criteria

The reason for discontinuation should be documented in the source documents.

Patients can be withdrawn from treatment for the following reasons:

- At the patient's request at any time irrespective of the reason.
- RECIST-defined disease progression of solid tumors or RANO-defined disease progression of brain tumors.
- Clinical progression.
- Unacceptable adverse events (AEs), or change in underlying condition such that the patient can no longer tolerate therapy, as evidenced by:
  - A dose delay > 21 days from the scheduled start date of the next cycle.
  - Need for more than the allowed dose reductions of TAS-120 as described in Section 8.1.3.1, TAS-120 Dose Reductions for Treatment-emergent Toxicities.
- 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 evaluated in this protocol.
- Pregnancy.

Upon discontinuation of treatment the investigator is to ensure the following:

- The Clinical Research Associate (CRA) must be notified immediately; and
- The Study Treatment Discontinuation Form in the electronic case report form (eCRF) must be completed, specifying the primary reason for the patient's withdrawal from the study.

If there is strong evidence of clinical benefit and reasons to justify continuation of TAS-120 dosing 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. Post-study provisions are provided in Section 13.4.

7.4. Patient Numbering and Treatment Allocation

Study sites will enter patient demographic and screening data into the eCRF in order to receive a patient number.

The eCRF will assign each patient a unique patient number. This patient number will be maintained throughout the study and will not be reassigned. Patients who withdraw consent or discontinue from the study after being assigned a patient number will retain their initial number.

Phase 1 Expansion and Phase 2:

Patients will be registered by interactive voice/web response system (IXRS) into Phase 1 Expansion and Phase 2 parts of the study. The institutional designee will call/login to the IXRS and will enter patient data as outlined in the IXRS Manual. After registration of the enrollment visit, the IXRS will assign TAS-120 by kit number, inform the study site user of the kit numbers that have been assigned to the patient, and provide instructions for the dispensing of TAS-120. Please refer to the IXRS Manual for detailed information.

If a patient is mistakenly given a kit of TAS-120 that is not the correct kit number as assigned by the IXRS, the IXRS help desk must be notified immediately. The reason for the misallocation of the study medication must be documented by the study site.

7.5. Replacement Criteria

No patients will be replaced during the Phase 1 Expansion or Phase 2 parts of the study.

7.6. 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.

7.7. Concomitant Medications and Therapies

The following therapies are permitted:

- Bisphosphonate
- Denosumab
- Concomitant treatment with GnRH agonists or LH-RH agonists is permitted in prostate cancer patients.
- Non enzyme-inducing anticonvulsants such as: Gabapentin (Neurontin), Lamotrigine (Lamictal) and Levetiracetam (Keppra).
- Steroids are allowed for patients with primary brain tumors and brain metastases. Steroid use in other patients with other tumor types should be discussed between the investigator and the Sponsor's Medical Monitor.
- Local or regional palliative cryotherapy or radiation, e.g., for bone pain or palliative surgery (non-anti-neoplastic intent).

If, after assessment by the Investigator, radiation for brain metastasis, therapy for bone metastasis, or locoregional therapy e.g. local ablation, TACE, SIRT or arterial infusion chemotherapy should be initiated for the best benefit of the patient, the patient can start 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

For Phase 1 Expansion and Phase 2, hematologic support may be administered as medically indicated (e.g., blood transfusions, CCI , erythropoietin stimulating agents) according to the institutional site standards. If there are no standard procedures for the use of growth factors, the American Society of Clinical Oncology [ASCO] Guidelines for Use of Hematopoietic Colony-Stimulating Factors, available at www.asco.org, will be followed.

Management of Diarrhea

For Phase 1 Expansion and Phase 2, prophylactic treatment for diarrhea is permitted during the study if clinically indicated according to the institutional guidelines. If there are no institutional standards, refer to the guidelines published by Benson AB, et al in *Journal of Clinical Oncology*.[15]

Management of Nausea/Vomiting

Antiemetics may be administered as clinically indicated. If there are no institutional standards, refer to the ASCO Guidelines for Antiemetics in Oncology.[16]

Management of Hyperphosphatemia

Phosphate-lowering therapy must be started within 24 hours after observing elevated phosphorus (≥ 5.5 mg/dL [≥ 1.78 mmol/L]). Serum phosphorus is to be tested 4 days (± 24 hours) after Day 1 of Cycle 1 to initiate early intervention for hyperphosphatemia.

Hyperphosphatemia management should follow institutional practice with phosphate binding agents, such as Sevelamer, acetazolamide or Fosrenol, or other phosphate binders or a combination of these agents. Sevelamer (both tablets and powder) should preferably be taken during meals in order to improve gastrointestinal tolerance and compliance. Lanthanum carbonate (Fosrenol) should be taken immediately after meals; tablets may be cut if required for administration. Other phosphate binders and hyperphosphatemia treatment drugs may also be used. In addition, actively managing constipation by drinking water and following dietary guidelines (see Appendix E) may also decrease the risk of hyperphosphatemia.

Refer to Section 8.1.3.1.1 for details on dose interruption or reduction in the management of hyperphosphatemia.

Drug interactions with TAS-120

Drug interaction studies 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 F, 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.

7.7.1. Effective Contraception During Study

Female patients who are 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 trial and for 6 months after the last dose of study medication. 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 (IUD)
- intrauterine hormone-releasing system (IUS)
- 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 combination of male condom with cap, diaphragm, or sponge with spermicide during the trial and for 6 months after the last dose of study medication.

7.8. Dietary Restrictions

Limitation of phosphate intake including avoidance of foods that are especially high in phosphate, e.g., dairy products, meats, nuts, and other high-protein foods, processed foods, and colas (e.g., Pepsi) is recommended as part of hyperphosphatemia management. Dietary Guidelines for Treatment of Hyperphosphatemia are provided in Appendix E.

8. STUDY DRUG

8.1. Study Drug Administration and Dose Modification Procedures

8.1.1. Study Drug Administration

TAS-120 is supplied as 4 mg tablets. The dose for TAS-120 is 20 mg QD. Patients should follow the instructions of the treating physician on study drug administration during treatment. Patients are required to fast for at least 2 hours before and 1 hour after administration of TAS-120. Patients will be permitted to drink water during this period. Dietary restrictions that limit phosphate intake may reduce the risk of hyperphosphatemia (see Section 7.8). On non-PK sampling days, TAS-120 can be administered in the morning or evening at the same time (if possible) each day. If a patient misses a dose (i.e., did not take TAS-120 for > 12 hours of the scheduled time of that day), the patient should take the dose on the next day.

8.1.2. Treatment Regimen

TAS-120 will be administered as a daily, continuous, 21-day treatment cycle until at least 1 of the criteria for study discontinuation is met. TAS-120 must be administered as outlined in Study Drug Administration (Section 8.1.1) and Dose Reduction/Modification Procedures (Section 8.1.3). There are no breaks in dosing between cycles.

8.1.3. Dose Reduction/Modification Procedures

Dosages will be reduced or modified if AEs are observed according to the criteria described below. In the following sections, AE severity grades are based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade criteria (version 4.03).

8.1.3.1. TAS-120 Dose Reductions for Treatment-emergent Toxicities

Dose reductions must be made according to Table 5. Please note the following:

- A maximum of 2 dose reductions is permitted
- If toxicities requiring further dose reduction recur after the maximum dose reductions have been made, or when dose reduction is not permitted as defined in Table 5 the patient will be discontinued from study treatment.

Table 5: TAS-120 Dose Reduction Levels

1st Dose Reduction	2nd Dose Reduction
Dose Reduce to 16 mg	Dose Reduce to 12 mg

If dose modification fails to result in achieving minimal criteria to resume treatment, the investigator should discontinue the patient from study treatment.

8.1.3.1.1. Dose Interruption and Modification for Nonhematologic Toxicities

Dosing modifications for nonhematologic toxicities are provided in Table 6. TAS-120 will be held when the dose interruption criteria are met.

Table 6: TAS-120 Dosing Modification for Nonhematologic Toxicities

Grade[a]	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 9.	None
Grade 3[b,c]	Suspend treatment until return to Baseline or Grade ≤ 1	Reduce by 1 dose level[c] from the previous level
Grade 4[d]	Suspend treatment until return to Baseline or Grade ≤ 1	Permanent Discontinuation of TAS-120

a. At the discretion of the investigator, patients may continue/discontinue on TAS-120 at the same dose with/without reduction or interruption for AEs (irrespective of grade) considered unlikely to become serious or life-threatening (including, but not limited to, fatigue and dry skin).
b. 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 dose hold or dose reduction.
c. See Table 5 for recommended dose level reductions.
d. Grade 4 non-hematologic laboratory abnormality: TAS-120 will be permanently discontinued if it is assessed by the Investigator as life threatening.

Recommendations for hyperphosphatemia management are provided in Table 7. These are suggested guidelines based on emerging data from studies evaluating FGFR inhibitors, and from experience of participating investigators. However, clinical judgment from treating physicians and local standard practices should be followed to decide the best management for the patient.

Table 7: 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 the 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 oral tablets 800 mg TID	• 800 mg tablets Sevelamer TID • 1600 mg tablets Sevelamer TID • 2400 mg tablets Sevelamer TID • Acetazolamide 250 mg QD (and titrate up to BID or TID if required) • Lanthanum carbonate (Fosrenol) 1.0 g QD (and titrate up to BID or TID if required)[e]
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 1.0 g QD or TID, and further titration, 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 serum phosphorus level has resolved to ≤ Grade 2 within 14 days after dose reduction, continue TAS-120 at the same dose level. • If serum phosphorus level not resolved to ≤ Grade 2 after 14 days, further reduce TAS-120 from the last reduced dose level (or no lower than 12 mg) • If serum phosphorus level not resolved to ≤ Grade 2 after 14 days of the second dose reduction of TAS-120 (or no lower than 12 mg), dose interrupt 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 serum phosphorus level is 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, serum phosphorus level is not resolved to ≤Grade 2 after 14 days, permanently discontinue TAS-120.	

Abbreviations: BID = twice a day; 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.
b. mmol/L = mg/dL x 0.3229 (conversion factor)
c. This grading for the range of serum phosphorus levels will be used for the protocol.
d. Phosphate binder 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.

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.

8.1.3.1.2. Dose Interruption and Resumption Criteria for Hematologic Toxicities

Criteria for dose interruption and resumption for hematologic toxicities are described in Table 8.

Table 8: TAS-120 Dose Interruption and Modification Criteria for Hematologic Toxicities

Recommended Dose Modifications for TAS-120	
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 < 1.0 x 10^9/L, 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; Hgb = hemoglobin; LLN = lower limit of normal; PLT = platelets	

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 needs to be made prior to the dose increase.

If the toxicities requiring dose reduction as defined above do not recover based on the criteria defined in Table 6 through Table 8 within the 21 days of the last dose of TAS-120, the patient

will be discontinued permanently from the study. If resumption criteria are met within 21 days of the last dose of TAS-120, the patient can resume TAS-120 treatment at the appropriate dose level according to instructions provided in Section 9.1.3.1, TAS-120 Dose Reductions for Treatment-emergent Toxicities.

Treatment-emergent toxicities should be followed until stabilization according to Table 9.

Table 9: Required Follow-up for Toxicities

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 retreatment 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 x 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, 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 mg/dL 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 the abnormal ECG finding. 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.
Non-laboratory	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; ms = milliseconds;
QTcF = Fridericia's corrected QT interval; ULN = upper limit of normal

8.2. Description and Labeling

8.2.1. TAS-120

A description and packaging information for the study drug is described in Table 10.

Table 10: TAS-120 Product description and packaging information

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

8.2.2. 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. Tablet strength
e. Number of tablets in each container
f. Investigational caution statement

Additional statements will be printed on the label(s) as required by local regulations.

8.2.3. Storage

TAS-120 tablets should be stored in accordance with the label. All study medication must be kept in a locked area with access restricted to specific study personnel.

8.2.4. Patient Instructions for Handling Study Drug

The patient must be instructed in the handling of TAS-120 as follows:

- To only remove the amount of TAS-120 needed at the time of dosing.
- Not to remove doses in advance of the next scheduled dosing.
- To bring all used and unused blister packs to the site at each visit.
- TAS-120 should be kept in a safe place and out of sight and reach of children.
- TAS-120 should be taken with a glass of water on an empty stomach (2 hours after and 1 hour before a meal).
- Doses are not to be replaced if the patient misses a dose or vomits a dose and administration of study drug should follow the direction of the treating physician.
- Patients should make every effort to take doses on schedule.
- To report any missed doses.

8.3. Drug Accountability

In accordance with International Council for Harmonisation (ICH) and local regulatory requirements, the investigator and/or the person responsible for dispensing investigational drug

must be able at all times to account for all investigational product provided to the site. The appropriate site personnel must acknowledge receipt of all TAS-120 either by forms included in each shipment or via other means (i.e., IXRS).

Dose reductions, interruptions, and reason for these actions must be recorded in the patient's source documents.

At the conclusion of the study, all used and unused TAS-120 shipped to the investigator must be returned to the Sponsor or designated Contract Research Organization (CRO). If on-site destruction is required by site policy, such requirements must be documented in the institution's Standard Operating Procedures (SOPs) and provided to the sponsor or its representative for review.

No TAS-120 is to be used outside of this study.

8.4. Blinding

This is an open-label study.

9. STUDY PROCEDURES

The study assessments are described by procedure in the following sections. All information required by the protocol must be recorded.

The study schedule must be followed; however, in unavoidable circumstances (e.g., holidays, weekends, etc.) a window of ± 3 days is allowable for study procedures as long as the proper order of procedures and assessments is maintained. The ± 3-day window does not apply to assessments on Day 1 of Cycle 1.

For computed tomography (CT) scans, a window of ± 2 weeks (up to Cycle 4) or ± 7 days (all subsequent cycles) is allowable. These windows are not applicable during Screening. If any Screening assessments are repeated on Day 1 of Cycle 1 pre-dose, the site must ensure the patient meets the eligibility criteria listed in Section 7.2, Study Population prior to the patient taking the first dose of TAS-120.

Note: Procedures performed during screening period within 72 hours prior to dosing on C1D1 do not need to be repeated on C1D1.

9.1. Pre-screening of Tumor Tissue Sample for FGFR2 Gene Fusions or other FGFR2 Rearrangements in Patients with iCCA (Phase 2 Only)

Archived or fresh tumor tissue biopsy samples will be tested for FGFR2 gene fusions or other FGFR2 rearrangements prior to enrolling patients to the Phase 2 part of the study.

Patients can be enrolled and treated based on the following:

a. Testing by Foundation Medicine:
    i. Sent to Foundation Medicine as part of study pre-screening; or
    ii. Already tested by Foundation Medicine; in this case, it is requested that tumor tissue be sent to Foundation Medicine if available.
b. Local laboratory testing using next generation sequencing [NGS], fluorescence in situ hybridization [FISH], or other assays that can determine FGFR2 gene fusions or other FGFR2 rearrangements on tumor tissues or from ctDNA. It is requested that patients enrolled on this basis provide tumor tissues to Foundation Medicine, if available from either archival samples or fresh tumor biopsy.

Testing may be performed at any time prior to enrollment into the study. -Results from the testing if not done as part of the TAS-120-101 protocol, must be maintained in the source files at the site.

Any AEs or serious adverse events (SAEs) directly associated with a pre-screening procedure (i.e., fresh tumor biopsy) should be reported as described in Section 11.1. There is no need to record AEs and SAEs that occur between signing the pre-screening consent and full protocol consent if they are unrelated to the pre-screening tumor biopsy procedure unless it is mandatory by local regulations.

Tumor samples may be stored at the Sponsor's designated central laboratory for up to 10 years following completion of the study, to enable companion diagnostic research.

9.2. Informed Consent

A signed and dated ICF will be obtained from the patient as required by the protocol before any main screening procedures are conducted. A signed copy of the ICF will be given to the patient. Multiple ICFs covering different procedures will be required based upon local requirements.

9.3. Medical History

A complete medical history will be obtained during Screening within 28 days prior to first TAS-120 administration on Day 1 of Cycle 1.

Existing signs and symptoms will be obtained during screening (within 28 days prior to TAS-120 administration on Day 1 of Cycle 1), and reviewed on Day 1 of Cycle 1 (within 24 hours of dosing). If evaluation of signs and symptoms is performed during the screening period within 72 hours prior to dosing, the assessment does not need to be repeated on C1D1.

9.4. Physical Examination

A complete physical examination will be performed at the time points listed below.

- Screening (within 28 days prior to TAS-120 administration on Day 1 of Cycle 1).
- Within 24 hours prior to TAS-120 administration on Day 1 of each cycle. Note that procedures performed during the screening period within 72 hours prior to dosing do not need to be repeated on C1D1.
- At end of treatment (+0-7 days).
- 30-day safety follow-up visit.

9.5. Height, Vital Signs, and Weight

The patient's height will be obtained only during Screening within 28 days prior to TAS-120 administration on Day 1 of Cycle 1.

The patient's vital signs (blood pressure, heart rate, body temperature, and respiration rate) and body weight will be collected at the time points listed below. All vital signs are to be obtained with the patient in a position that is consistent for all time points for each patient.

- Screening (within 28 days prior to TAS-120 administration on Day 1 of Cycle 1).
- Within 24 hours prior to TAS-120 administration on Day 1 of each cycle. Note that procedures performed during the screening period within 72 hours prior to dosing do not need to be repeated on C1D1.
- At end of treatment (+0-7 days).
- 30-day safety follow-up visit.

9.6. Performance Status

An ECOG Performance Status score (see Appendix C ECOG Performance Status) will be obtained at the following time points:

- Screening (within 28 days prior to first TAS-120 administration on Day 1 of Cycle 1).
- Within 24 hours prior to TAS-120 administration on Day 1 of each cycle. Note that procedures performed during the screening period within 72 hours prior to dosing do not need to be repeated on C1D1.
- At end of treatment (+0-7 days).
- 30-day safety follow-up visit.

9.7. Electrocardiogram

A 12-lead resting ECG will be performed at the following time points:

- Screening (within 28 days prior to TAS-120 administration on Day 1 of Cycle 1).
- Two hours (± 15 min) after TAS-120 dose on Day 1 of Cycle 1.
- For all subsequent cycles starting with Cycle 2, ECG should be performed on Day 1 (± 3 days) of each cycle obtained 2 hours (± 15 min) after the TAS-120 dose.
- At end of treatment (+0-7 days).
- 30-day safety follow-up visit.

9.8. Ophthalmological Examination

Ophthalmological examination will be performed at the following time points:

- Screening within 28 days prior to TAS-120 administration on Day 1 of Cycle 1.
- 4-6 weeks after starting treatment with TAS-120
- Any other time due to local requirements, physician judgement and/or symptoms or signs of mineral deposits.
- At end of treatment (+0-7 days)
- 30-day safety follow-up visit.

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 ophthalmologic examination will encompass the following:

1. External ocular examination.
2. Routine slit lamp biomicroscopy of anterior ocular structures (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. Retinal exam to evaluate the anterior and posterior chamber

The examination will be repeated, if clinically indicated, and the repeat examination will include the same testing employed at Screening in addition to any other clinically indicated examination.

9.9. Neurological Examination

Neurological examination will be performed at the following time points for all patients:

- Screening (within 28 days prior to TAS-120 administration on Day 1 of Cycle 1).
- Any other time due to local requirements, physician judgement and/or symptoms or signs of mineral deposits.
- At end of treatment (+0-7 days)
- 30-day safety follow-up visit.

The basic neurologic examination should follow institutional guidelines and local clinical practice, and will encompass testing of:

- Cranial nerves II-XII.
- Muscular strength of upper and lower extremities.
- Deep tendon reflexes of upper and lower extremities.

This examination will be repeated, if clinically indicated, and the repeat examination will include the same testing employed at Screening in addition to any other clinically indicated examination.

9.9.1. Neurological Examination as part of RANO Evaluation for Patients with Primary CNS Tumors

For patients with primary CNS tumors, a complete neurological examination will include assessment of level of consciousness, mental status, speech, vision fundus (papilledema), cranial nerves III, IV, VI, cranial nerves other, motor, sensory, and gait or limb ataxia. An overall score according to a 6-point scoring code will be determined for each finding and recorded in the eCRF. Follow-up evaluation of the neurological examination will be based on any changes in the neurological clinical examination from the previous exam. Changes should be unrelated to postictal state or other unrelated events such as infection.

Neurological examination must always be performed at screening and within one week of the date of the Gd-MRI as part of the response assessment for patients with brain tumor.

Scoring code for each neurological finding:

0 = Normal

1 = Slightly or minimally abnormal

2 = Moderately abnormal

3 = Severely abnormal

4 = Grave

5 = Not able to record

Grading scale to designate relative changes:

+2 = definitely better

+1 = possible better

0 = unchanged

-1 = possible worse

-2 = definitely worse

9.10. Clinical Laboratory Evaluations

Blood samples for hematology, coagulation, and chemistry assessments will be collected and measured as described in Section 9.10.1 and Section 9.10.2, respectively. Laboratory assessments obtained prior to signing of the ICF may be used as screening laboratory values if they were obtained within 28 days prior to TAS-120 administration on Day 1 of Cycle 1.

All laboratory results must be reviewed for clinically significant events. Any clinically significant events must be followed and reported as required by the protocol (see Section 11.1, Adverse Events/Serious Adverse Events and Section 11.2, Laboratory Evaluations).

9.10.1. Hematology and Coagulation

Blood for hematology and coagulation assessments will be collected at the following time points and when clinically indicated:

- Screening (within 7 days prior to first TAS-120 administration on Day 1 of Cycle 1).
- Obtain within 24 hours before TAS-120 administration on Day 1 of each cycle, and anytime on Day 8 and Day 15 of Cycle 1. Note that procedures performed during the screening period within 72 hours prior to dosing do not need to be repeated on C1D1.
- At end of treatment (+0-7 days)
- 30-day safety follow-up visit.

In addition, the criteria for repeat testing listed in Section 11.2.2, Repeat Testing, will be followed as needed.

The following hematology and coagulation parameters will be measured:

Red blood cell (RBC) count	White blood cell (WBC) count with differential
Hemoglobin	Neutrophils[1]
Hematocrit	Lymphocytes
Platelets	Monocytes
International normalized ratio (INR)	Eosinophils
Activated partial thromboplastin time (APTT)	Basophils

[1] Includes both segmented and band neutrophils.

9.10.2. Chemistry

Blood (serum or plasma) will be collected at the following time points for serum chemistry assessments:

- Screening (within 28 days prior to first TAS-120 administration on Day 1 of Cycle 1).
- Obtain within 24 hours before TAS-120 administration on Day 1 of each cycle, and anytime on Day 8 and Day 15 of Cycle 1. Note that procedures performed during the screening period within 72 hours prior to dosing do not need to be repeated on C1D1.
- Phosphorus is to be tested 4 days (±24 hours) after Day 1 of Cycle 1 to initiate early intervention for hyperphosphatemia.
- As clinically indicated by the investigator or if previous chemistries showed an elevation of phosphorus that required action as specified in Section 8.1.3.1.1.
- At the end of treatment (+0-7 days).
- 30-day safety follow-up visit.

In addition, the criteria for repeat testing listed in Section 11.2.2, Repeat Testing, will be followed as needed.

The following chemistry parameters will be measured:

Table 11: Laboratory Assessments for TAS-120-101

Alanine aminotransferase (ALT)	Blood urea nitrogen (BUN) or Urea	Creatinine kinase (CK)
Aspartate aminotransferase (AST)	Phosphorus	Troponin I or T (quantitative)[c]
Alkaline phosphatase	Calcium	
Total bilirubin[b]	Chloride	
Glucose	Sodium	
Creatinine clearance[a]	Potassium	

[a] Calculated (Ccr) or measured creatinine clearance.
[b] Fractionation of bilirubin (= direct/indirect bilirubin or conjugated/unconjugated) must be performed/calculated in case of an elevation of total bilirubin.
[C] Quantitative evaluation of either Troponin I or Troponin T (not both) required at each time point. Evaluation of the same parameter (Troponin I or Troponin T) at different timepoints for the same patient is not required.

9.10.3. Urinalysis

Urine samples for qualitative analysis ("urine dipstick") will be collected at the time points listed below:

- Screening (within 28 days prior to first TAS-120 administration on Day 1 of Cycle 1).
- Within 24 hours prior to TAS-120 administration on Day 1 of each cycle. Note that procedures performed during the screening period within 72 hours prior to dosing do not need to be repeated on C1D1.
- At end of treatment (+0-7 days).
- 30-day safety follow-up visit.

In addition, the criteria for repeat testing listed in Section 11.2.2, Repeat Testing, will be followed as needed. At all time-points, urinalysis should include:

- PH
- Specific gravity
- Protein
- Glucose
- Ketones
- Blood
- Leukocyte esterase
- Nitrite with microscopic examination if indicated

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9.12. Pregnancy Test

For patients who are WOCBP, pregnancy testing by assessment of serum beta-human chorionic gonadotropin (β-HCG) will be conducted:

- At screening (28 days prior to the first administration of TAS-120); and
- At end of treatment (+0-7 days).

Serum or urine pregnancy test is also required:

- Within 24 hours prior to TAS-120 administration on Day 1 of each cycle, or additionally according to local requirements. Note that procedures performed during the screening period within 72 hours prior to dosing do not need to be repeated on C1D1.
- 30-day safety follow-up visit.

The date, time, and test results will be recorded in the patient's source documents.

Female patients who are not considered to be of child-bearing potential must have a history of being post-menopausal (no menses for 12 months without an alternative medical cause), surgical sterilization, or hysterectomy that is clearly documented in the patient's source documents.

9.13. Pharmacokinetic Sample Collection

9.13.1. Optional Pharmacokinetic Sample Collection for Phase 1 Expansion

For all patients in the Phase 1 Expansion, optional blood PK samples (a minimum of 1 mL) may be collected per the investigator's discretion in any patient at the following time points: prior to dosing (0 hour) and post-dose at 1, 2, 3, 4, 6, and 24 hours (± 10 minutes). The 24-hour post-dose sample should be collected prior to next TAS-120 administration. These optional blood PK samples could be collected on any day in Cycle 1 and Cycle 2 when PK should be collected as part of the safety evaluation.

For patients in the Phase I Expansion with primary CNS tumors only, optional blood and CSF samples will be collected 2-4 hours post-dose on Day 1 of Cycle 2 to assess the TAS-120 concentration ratio of CSF to plasma. Blood and CSF samples must be collected at the same time point (within 15 minutes). A minimum of 1 mL each of whole blood and CSF will be collected for the PK analysis.

Blood and CSF samples for PK evaluation will be collected and processed according to instructions provided in the Laboratory Manual.

9.13.2. Pharmacokinetic Blood Sample Collection for Phase 1 Expansion/Phase 2

During Phase 1 Expansion and Phase 2, blood samples of TAS-120 will be collected on Day 1 of Cycle 2 pre-dose, 1 h ± 30 min. and 3 h ± 30 min. post-dose to assess the plasma exposure at 20 mg QD. In addition, blood samples will be collected on Day 1 of Cycle 3 and Cycle 4 pre-dose. A minimum of 1 mL of whole blood will be collected for the PK analysis per Table 12. The total blood volume collected for the PK samples will be approximately 5 mL per patient.

Blood samples for PK evaluation will be collected and processed according to instructions provided in the Laboratory Manual.

Table 12: Pharmacokinetic Blood Sample Collection for Phase 1 Expansion/CCI

Day of Study	Collection Time Point (hours [h]) in Relation to TAS-120 Administration (Time Window)	Blood Volume
Day 1 of Cycle 2	pre-dose	1 mL
	1 h ± 30 min post-dose	1 mL
	3 h ± 30 min post-dose	1 mL
Day 1 of Cycle 3	pre-dose	1 mL
Day 1 of Cycle 4	pre-dose	1 mL
Total volume per patient		Approximately 5 mL
h = hour		

9.14. ctDNA Analysis of FGF/FGFR Aberrations

9.14.1. ctDNA from Blood Sample for the Analysis of FGF/FGFR Aberrations

For the Phase 1 Expansion and Phase 2, a blood sample will be collected to assess FGF/FGFR aberrations in ctDNA at Screening within 28 days prior to the first TAS-120 administration on Day 1 of Cycle 1 (required) and at the EOT visit (optional). A minimum of 20 mL of whole 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. Sample collection and preparation will be according to instructions provided in the Laboratory Manual.

9.15. Prior and Concomitant Medications and Therapies

All therapies and medications, prescription and over-the-counter, will be collected from the time the main study ICF is signed through the 30-day safety follow-up visit, including any medication used to treat AEs or SAEs during the 30-day follow-up period. Use of concomitant medication and/or therapy should be documented in the patient's source documents. In addition, the time of initiation of new anticancer therapy received during the 30-day follow-up period will be collected.

9.16. Adverse Event Assessment

Patients will be monitored for any untoward medical events (AEs or SAEs) from the time the main study ICF is signed through 30 days after last dose of TAS-120 or until the start of new antitumor therapy, whichever is earlier. For the Phase 2 part of the study, any AEs or SAEs that occur after the signing of pre-screening consent and are directly associated with a pre-screening procedure (i.e., fresh tumor biopsy) should be reported as described in Section 12.1. For AEs and SAEs 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.
Serious AEs should be reported to Taiho Oncology, Incorporated (TOI) Pharmacovigilance or its designee. If serious medical occurrences or deaths **outside** the 30-day follow-up period are

reported to or observed by the investigator that he/she believes are related to the administration of the TAS-120, it is the investigator's responsibility to report this occurrence to TOI Pharmacovigilance or its designee. See Section 11.1.1, Adverse Events, and Section 11.1.2, Serious Adverse Events, for definitions and detailed reporting of AEs and SAEs.

9.17. Tumor Assessments/Scans

9.17.1. Tumor Assessment for Advanced Solid Tumors

Tumor assessments/imaging studies of the chest, abdomen, and pelvis (as clinically indicated) must be obtained at each time point listed below for all patients with solid tumors.

- Screening within 28 days prior to Day 1 of Cycle 1. Computed tomography scans obtained prior to the signed ICF may be used as the screening scan if they were obtained within 28 days of the first dose of TAS-120.
- At the end of every 2 cycles (up to +2 weeks), up to Cycle 4.
- Following Cycle 4, at least after every 3 cycles (± 7 days) or as clinically indicated, until documented progression (including after end of treatment if the patient discontinues for reasons other than radiologic disease progression).
- At end of treatment (+0-7 days), a CT scan must be performed if the prior scan was performed ≥ 9 weeks prior to discontinuation of TAS-120 treatment if the patient discontinued for reasons other than radiologic disease progression.

On-site tumor assessments will be performed by the investigator/local radiologist according to RECIST guidelines (version 1.1, 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 TAS-120. Response definitions are provided in Section 10, Efficacy Assessment Criteria.

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

On-site tumor assessments will be conducted. Tumor assessment scans from patients with iCCA treated at 16, 20 and 24 mg QD and patients with primary brain tumors may also be prospectively or retrospectively collected and forwarded to the core imaging laboratory.

If a patient in Phase 1 Expansion or Phase 2 has a response, response confirmation should be obtained through tumor assessments/scans 4 to 6 weeks after the first documentation of response. Patients must then return to their original schedule of assessments (i.e., every 2 cycles [or every 3 cycles after Cycle 4]).

9.17.2. Tumor Assessment for Brain Tumors

Patients will be evaluated for response by Gd-MRI. All Gd-MRIs (standard brain tumor MRI including both precontrast and postcontrast images using a Gadolinium (Gd) chelate as the contrast agent) should be performed when the patient is on a stable dose of steroids for at least 7 days. Gd-MRI will be performed at the following time points:

- Screening within 28 days prior to Day 1 of Cycle 1. Gd-MRI scans obtained prior to the signed ICF may be used as the screening scan if they were obtained within 28 days of the first dose of TAS-120.
- At the end of every 2 cycles (up to +2 weeks), up to Cycle 4, until documented progression (including after end of treatment if the patient discontinues for reasons other than radiologic disease progression).
- Following Cycle 4, at least after every 3 cycles (± 7 days) or as clinically indicated.
- At end of treatment (EOT), a Gd-MRI scan must be performed if the prior scan was performed ≥ 9 weeks prior to discontinuation of TAS-120 treatment if the patient discontinued for reasons other than radiologic disease progression.

If a patient has a response, response confirmation should be obtained through tumor assessments/scans 4 to 6 weeks after the first documentation of response. Patients must then return to their original schedule of assessments.

Neurological examination for patients with brain tumors must always be performed within one week of the date of the Gd-MRI as part of the response assessment. Response will be based on RANO criteria.

All patients' files and radiological assessments must be available for source verification and may be submitted for extramural review for final assessment of antitumor activity. Results of any unscheduled evaluations should be recorded in the patient's source documents.

9.18. Patient-Reported Outcomes

Two Patient-Reported Outcome (PRO) instruments, EuroQol-5D measure of health-related quality of life (EQ-5D) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) will be used in the Phase 2 part of the study. EQ-5D is a standardized measure of health status as patient-reported outcome assessment. EORTC QLQ-C30 is an integrated system for assessing the health-related quality of life of cancer patients participating in international clinical trials. These assessments will be collected at the following time points (as close as possible to the time points when tumor assessment is performed):

- Screening within 28 days prior to Day 1 of Cycle 1.
- At the end of every 2 cycles (up to +2 weeks), up to Cycle 4.
- Following Cycle 4, at least after every 3 cycles (± 7 days) or as clinically indicated.
- At end of treatment (EOT)

9.19. End-of-treatment Visit

An end-of-treatment (EOT) visit is required for all living patients who discontinue treatment. 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).

9.20. 30-Day Safety Follow-up

A safety follow-up visit will be conducted 30 days after the last dose of TAS-120. 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 prior to the start of new anticancer therapy within the 30-day window. If the evaluation of EOT and 30-day Safety Follow-up is within ± 14 days, only the 30-day Safety Follow-up will be performed. If the patient is unable to return to the site prior to the initiation of new treatment, a follow-up phone call can be conducted by the site to collect any new safety information that occurred between discontinuation of study treatment and the initiation of the new anticancer treatment.

9.21. Survival Status Follow-up

Overall survival status will be collected during the survival follow-up period every 3 months (±2 weeks) from the patient's previous visit.

For the Phase 1 Expansion part of the study, patients should be followed for up to 12 months after the last patient enrolled in this phase of the study.

For Phase 2, patients should be followed for up to 18 months after the last patient enrolled in this part of the study.

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10. EFFICACY ASSESSMENT CRITERIA

10.1. Efficacy Assessment for Solid Tumors

The determination of antitumor efficacy will be based on objective tumor assessments made by the investigator according to the revised RECIST guidelines (version 1.1, 2009) of unidimensional evaluation.[17]

For Phase 1 Expansion, the primary endpoint is ORR (and EPR for GBM or grade III glioma) and the secondary endpoints of DOR, DCR, PFS, and OS.

For Phase 2, the primary endpoint is ORR and the secondary endpoints of DOR, DCR, PFS, PROs and OS.

Primary endpoints will be based on the independent review of images by the Core Imaging Laboratory. In addition, for the Phase 2 part of the study, sensitivity analyses for some key efficacy endpoints (eg, ORR, and PFS) will be performed based on investigators or local radiologist assessments.

The RECIST guideline (version 1.1, 2009) instructs those conducting oncology trials designed with a primary endpoint that is response-related to require confirmation of response after a minimum of 4 weeks.

10.1.1. 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 Screening and during follow-up. 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 or less 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 (e.g., 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 (e.g., 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 the revised RECIST guidelines (version 1.1, 2009)[17] specifications for standard anatomical radiological imaging, which are included in the Imaging Manual.

10.1.2. Tumor Definitions

Measurable 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 less, 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.

Only measurable lesions can be selected as target lesions.

Non-measurable lesions include:

- Small visceral metastatic lesions that have a longest dimension less than 10 mm, or if slice thickness is greater than 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 (e.g., ascites and peritoneal carcinomatosis).

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

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 (i.e., visceral lesion) target lesions. Therefore, in cases of complete response (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 time point.
- 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 that cannot be read due to technical reasons, for example:
    1. CT artifact.
    2. Patient positioning where the lesions are obstructed or cannot be seen.
    3. 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 < 10 mm are considered non-pathological and should not be recorded.

Any equivocal lesion without clear diagnosis (e.g., 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 (e.g., multiple enlarged pelvic lymph nodes or multiple liver metastases).

10.1.3. Response Criteria

On-site assessments will include the assessment of:

- Target and non-target tumor responses
- Objective response

The above assessments will be made as per the time points identified in Section 9.17, Solid Tumor Assessments/Scans.

10.1.3.1. Target and Non-Target Response Assessments

Assessments will be based on the definitions below.

TARGET LESIONS	
Lesions Response:	**Definition:**
Complete Response (CR)	The disappearance of all target lesions. Any pathological lymph nodes 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, taking as a reference 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)
Non-CR/Non-PD	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 definition below).

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 stable disease (SD) or partial response (PR) in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

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 progressive disease (PD) for measurable disease (i.e., 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]).

10.1.3.1.1. Additional Criteria to Consider When Making Tumor Response Assessments

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 (e.g., 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.

10.1.3.2. Objective Response Assessment

Assessments will be based on the definitions provided in Table 13 and Table 14.

Table 13: 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	Not evaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

Table 14: 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	Not evaluable
Unequivocal PD	Yes or No	PD
Any	Yes	PD

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

10.1.4. Best Objective Response Assessment for Solid Tumors

The best objective response for solid tumors will be assessed as defined in the Statistical Analysis Plan (SAP) per RECIST guideline (version 1.1, 2009). To be assigned a status of PR or CR for Phase 1 Expansion and Phase 2, changes in tumor measurements in patients with responding tumors must be confirmed by repeat studies that should be performed at 4 weeks after the criteria for response are first met. On the other hand, confirmation is not required for Phase 1 Dose Escalation. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks across the phases.

10.2. Efficacy Assessment for Brain Tumors

10.2.1. Method of Imaging

Patients with brain tumors will be evaluated for response by contrast MRI (e.g., Gd-MRI). All MRIs should be performed when the patient is on a stable dose of steroids. Gd-MRI will be performed at screening, end of every 2 cycles (up to + 2 weeks) in the first 4 cycles and every 3 cycles (± 7 days) thereafter and at study completion for tumor measurements. For patients who discontinued treatment for reasons other than disease progression, tumor assessments should be continued until radiologic disease progression or initiation of new anticancer therapy (whichever occurs first).

10.2.2. Tumor Definitions

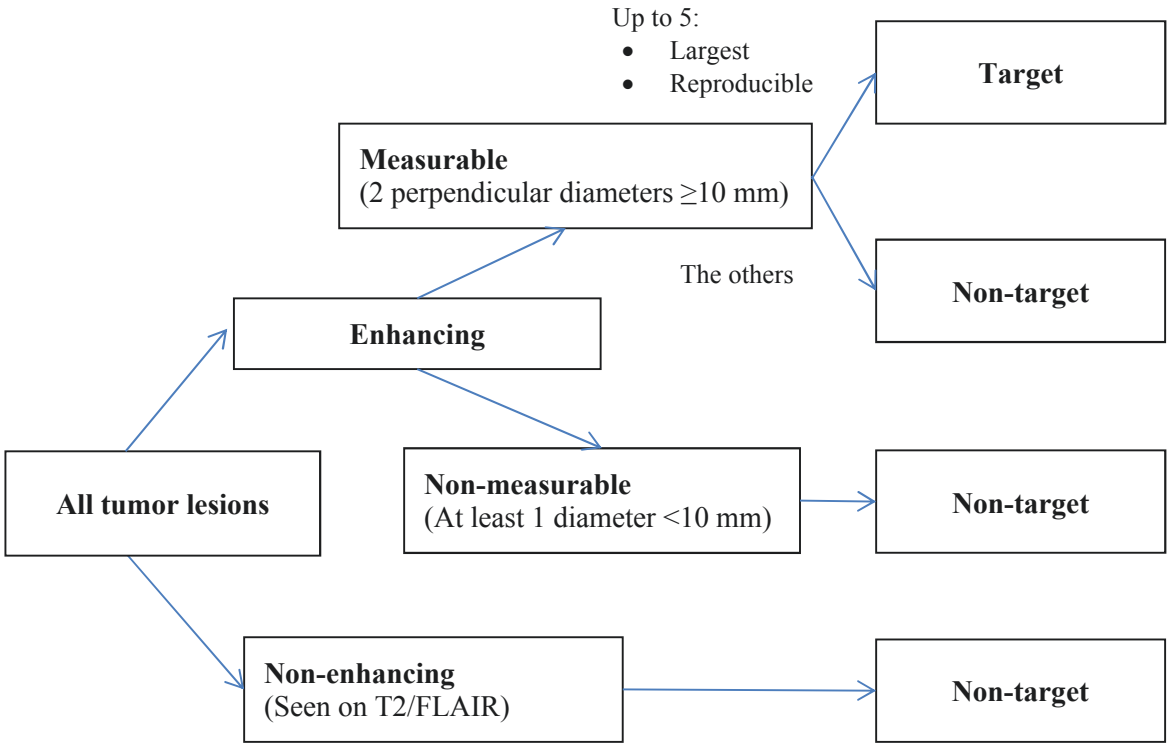
10.2.2.1. Measurable and Non-measurable Contrast Enhancing Lesions

Measurable Lesions/Target Lesions

To evaluate changes in brain tumors using the RANO criteria, weighted images will be measured and monitored for response over time for up to 5 enhancing lesions identified on baseline T1 (T1 relaxation time constant). In general, the largest enhancing lesions that lend themselves to repeated measurements will be selected as target lesions (see Figure 4). Selected target lesions will demonstrate contrast enhancement, have clearly defined margins, have two perpendicular diameters of at least 10 mm, and be visible on two or more axial slices that are at most 5 mm apart with no interslice gap. If slices were thicker than 5 mm, the selected lesions should measure two times the slice thickness on the baseline scan. To perform the size measurement, the

maximal tumor diameter will be obtained with a second diameter obtained at a right angle to the first. The product of these measurements will be used for purposes of comparison between imaging time points.

Figure 4: Algorithm for Selection of Target Lesions: RANO Criteria



Non-measurable Lesions

Non-measurable lesions are generally those that do not meet the above criteria. Tumors around a cyst or surgical cavity will also be considered non-measurable unless a nodular component measuring 10 mm or greater in diameter is present.

10.2.2.2. Non-enhancing Lesions

Non-enhancing lesions visualized with T2-weighted fluid-attenuated inversion recovery (T2/FLAIR) will also be assessed when evaluating tumor response. Non-enhancing lesions will not be measured, but instead will be monitored for changes in size. It is important to note that the extent of the non-enhancing component of the tumor can be difficult to determine since localized swelling and damage caused by radiation have a similar radiographic appearance. Changes in T2/FLAIR signal that suggest presence of an infiltrating tumor include mass effect, infiltration of the cortical ribbon, and location outside of the radiation field.

10.2.3. Response Definitions

Brain tumor response to therapy will be categorized into one of four categories: complete response, partial response, stable disease, or progression.

Complete Response

Complete response (CR) will be achieved if all enhancing (measurable and non-measurable) lesions have disappeared for at least 4 weeks, there are no new lesions, and non-enhancing lesions have either improved or remain stable. Clinically, subjects must be off corticosteroids (or be receiving only physiological replacement doses) and show stable or improved clinical symptoms.

Partial Response

Partial response (PR) will be achieved when all of the following requirements are met: the sum of the products of perpendicular diameters of all enhancing lesions is reduced by 50% or more (from baseline) for at least 4 weeks, there are no new lesions, there is no progression in non-measurable lesions, and non-enhancing lesions have either improved or remain stable. Clinically, subjects must be on a corticosteroid dose no greater than the dose they were receiving at the time of the baseline scan and they must show stable or improved clinical symptoms.

Stable Disease

A subject will be considered to have stable disease (SD) if all of the following are met: the subject does not qualify for complete response, partial response, or progressive response (described below), and non-enhancing T2/FLAIR lesions are stable. Subjects must be on either a lower dose of corticosteroids or be maintaining the same dose level as baseline. Clinical symptoms must also be stable.

Progressive Disease

Progressive disease (PD) will be defined by the occurrence of any of the following:

- The sum of the products of perpendicular diameters of enhancing lesions is increased by 25% or more compared with the smallest tumor measurement obtained either at baseline or the time point with the best response for patients receiving either stable or increasing doses of corticosteroids.
- There is a significant increase in T2/FLAIR non-enhancing lesions compared to baseline or best response scans for patients receiving either stable or increasing doses of corticosteroids. The increase in T2/FLAIR non-enhancing lesions should not be attributable to other non-tumor causes (e.g., radiation therapy, demyelination, ischemic injury, etc.).
- Appearance of new lesions.
- Clear progression of non-measurable lesions.
- There is clear clinical deterioration that is not attributable to other causes apart from the tumor (e.g., seizures, medication adverse effects, complications of therapy, cerebrovascular events, etc.) or changes in corticosteroid use.
- Failure to return for evaluation as a result of death or deteriorating condition.

A summary of brain tumor response definitions (RANO) is shown in Table 15.

Table 15: Summary of RANO Response Criteria

Criterion	Complete Response	Partial Response	Stable Disease	Progressive Disease
T1 enhancing disease	None	≥ 50% ↓	< 50% ↓ but <25% ↑	≥ 25% ↑[1]
T2/FLAIR	Stable or ↓	Stable or ↓	Stable or ↓	↑[1]
New lesion	None	None	None	Present[1]
Corticosteroids	None	Stable or ↓	Stable or ↓	NA[2]
Clinical status	Stable or ↑	Stable or ↑	Stable or ↑	↓[1]
Requirement for response	All	All	All	Any[1]

Abbreviations: NA=not applicable, RANO = Response Assessment in Neuro-Oncology

[1] Progression occurs when this criterion is present.

[2] Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

11. REPORTING SAFETY INFORMATION

11.1. Adverse Events/Serious Adverse Events

11.1.1. Adverse Events

An AE is any untoward medical condition that occurs in a patient from the time the ICF is signed and does not necessarily have a causal relationship with the use of the product.

A complete and specific clinical diagnosis should be provided for the AE verbatim term. If a diagnosis is not available, then signs and symptoms should be reported. The CTCAE (version 4.03) terms are to be used to assess severity and provide the grade for each AE that is reported.

For definitions and reporting of pregnancy, overdose, and medication errors, refer to Section 11.1.5, Pregnancy, Section 11.1.6, Overdose, and Section 11.1.7, Medication Errors, respectively.

Any untoward medical event that occurs outside the period of patient follow-up (30 days after the last dose of study drug or until the start of new antitumor therapy, (whichever is earlier) is not considered an AE.

Symptoms or laboratory or instrumental (e.g., electrocardiographic) abnormalities of a pre-existing disease, such as cancer or other diseases, should not be considered an AE. However, occurrences of new symptoms as well as worsening of pre-existing medical conditions are considered AEs. In addition, **a new laboratory or instrumental abnormality that has a clinical impact on a patient (e.g., resulting in study drug dose reduction, treatment delay, treatment discontinuation) is considered an AE, unless it is considered part of clinical manifestations to a clinical diagnosis that is already reported as an AE**.

All AEs will be reported from the time the main study ICF is signed through the period of patient follow-up (30 days after the last dose of study drug or until the start of new antitumor therapy, whichever is earlier). For the Phase 2 part of the study, any AEs that occur after the signing of pre-screening consent and are directly associated with a pre-screening procedure (i.e., fresh tumor biopsy) should be reported. 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. Documentation should include onset and resolution/stabilization dates, severity/grade, relationship to study drug, and outcome of the event. All AEs should be entered in the eCRF within 10 business days from the time the investigator first becomes aware of the AE.

Causal relationship is assessed based on the following:

1. Select "Related" if the event follows a reasonable temporal sequence from administration of study medication and 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.

The circumstance that a causal relationship can sometimes not be ruled out is not sufficient to determine that the event is "related". Instead, "related" should mean that there is evidence to suggest a causal relationship between the drug and the AE. A reasonable possibility is provided by the following example that would suggest a causal relationship between drug and the event: A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, Stevens-Johnson syndrome).

2. Select "Not related" if there is no **reasonable** possibility that the study medication caused the event, or if the event does not follow a reasonable temporal sequence from administration of study medication 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 drug and the AE.

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

- AE has resolved.
- AE has stabilized.
- The AE reporting process is provided in the eCRF Completion Guidelines.

11.1.2. Serious Adverse Events

An SAE is an AE that falls into one or more of the following categories:

a. Results in death.
b. Is life threatening (e.g., an event that, in the view of the investigator, places the patient at immediate risk of death from the event as it occurred [it does not include an event, which hypothetically might have caused death if it were more severe]).
c. Requires inpatient hospitalization or prolongation of existing hospitalization. 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.
d. Results in persistent or significant disability or 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.
e. Is a congenital anomaly/birth defect (if exposure to product just before conception or during pregnancy resulted in an adverse outcome in the child).
f. Is any other important medical event (e.g., may not result in death, be life-threatening, or require hospitalization), but based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the points above. 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.

Serious AEs must be reported to TOI Pharmacovigilance or designee **within 24 hours** from the time the investigator first becomes aware of the SAE by completing a Serious Adverse Event Form and faxing or emailing it to Taiho Pharmacovigilance or designee. 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 for reporting the SAE are provided on the SAE Form Completion Guidelines.

After the initial SAE reporting to TOI Pharmacovigilance or designee, follow-up SAE information will be submitted, by faxing or emailing an updated Serious Adverse Event Form, each time that important follow-up information (e.g., diagnosis, outcome, causality assessment, results of specific investigations) becomes available.

All SAEs **within** the follow-up window (e.g., within 30 days after the last dose of study drug or until the start of new antitumor therapy, whichever is earlier) established in the protocol will be reported to TOI Pharmacovigilance or designee.

If serious medical occurrences including deaths **outside** the follow-up window established by the protocol are reported to or observed by the investigator that he/she believes are related to the administration of TAS-120, it is the investigator's responsibility to report this occurrence to TOI Pharmacovigilance or designee.

11.1.3. Reporting of Deaths

All deaths including death due to clinical disease progression occurring through the 30-day follow-up period must be reported as an SAE within 24 hours:

- 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 of death:

- Toxicity caused by study drug.
- Radiologic disease progression.
- Clinical disease progression.
- Other causes.

11.1.4. Disease Progression

How to report events related to nonfatal disease progression:

- Disease progression is not an acceptable AE term. In cases of nonfatal disease progression, the relevant signs, symptoms and complications that led to the diagnosis of clinical disease progression should be reported as an AE. If the relevant signs, symptoms and complications meet any of the serious criteria, they should be reported as SAEs. In both cases it should be indicated whether the signs, symptoms and complications are related to clinical disease progression.

How to report events related to fatal disease progression:

- In cases of death due to clinical disease progression, the relevant signs, symptoms, and complications that led to the diagnosis of clinical disease progression should be reported as SAE terms. Clinical disease progression may only be reported as an SAE term if none of the relevant signs or symptoms supports a fatal outcome.

11.1.5. Pregnancy

If a patient becomes pregnant while in the study, the study treatment must be immediately discontinued. Pregnancy information in a female patient or in 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 Pregnancy Form and faxing or emailing it to TOI Pharmacovigilance or designee.

New and/or corrected information regarding the pregnancy obtained after submitting the Pregnancy Form must be submitted by faxing an updated Pregnancy Form to TOI Pharmacovigilance or designee.

If outcome of the pregnancy is a stillbirth, congenital anomaly/birth defect, or a serious event in the mother, report as an SAE to TOI Pharmacovigilance or designee.

11.1.6. Overdose

An overdose with TAS-120 for this clinical trial is defined as taking a dose beyond the protocol-defined dose (taking into account any dose reductions / re-escalations) in 1 day.

An overdose of TAS-120 must be reported to TOI Pharmacovigilance or 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). This should be performed by completing a Serious Adverse Event Report Form and faxing or emailing it to TOI Pharmacovigilance or designee).

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 overdose. Overdose should be managed aggressively with close monitoring and administration of prophylactic and symptomatic therapies to prevent or correct potential side effects.

11.1.7. Medication Errors

A medication error for this clinical trial is defined as an accidental, incorrect administration of a medicinal product. The error can be related to the administration of a wrong medication, nature of the medication, route of administration, dosage, or frequency of the treatment (including omission of one or more administrations).

The following types of medication errors, whether or not they meet the serious criteria, should be reported to TOI Pharmacovigilance Operations **within 24 hours of first awareness**, by completing the Serious Adverse Event Report Form and faxing or emailing it to TOI Pharmacovigilance or designee.

- 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

**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 an SAE, but will be identified through the recording of study drug accountability data in the eCRF.

11.1.8. Breaking the Study Blind

This is an open-label study.

11.2. Laboratory Evaluations

11.2.1. Reporting and Evaluation of Laboratory Test Results

Laboratory tests will be performed as required per protocol. All laboratory values that are out of the normal range will be evaluated for their clinical significance before exposing the patient to the next dose of TAS-120.

The laboratory must provide normal reference ranges.

Any laboratory abnormality that has a clinical impact on the patient (e.g., results in delay of TAS-120 dosing, study discontinuation) must be reported as an AE, unless it is considered a supporting lab to a clinical diagnosis that is already reported as an AE. Febrile neutropenia must be reported as an AE and is defined as an ANC < 1 000/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. All laboratory data will be analyzed using NCI CTCAE grade criteria (version 4.03).

11.2.2. 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 new anticancer treatment, surgery, or radiotherapy is given.

11.3. Physical Examination and Performance Status

Physical examinations and performance status evaluations will be performed as described in the Study Procedures section of the protocol. If changes are observed, the investigator will determine whether they meet the definition of an AE. All observations and evaluations will be documented.

11.4. Vital Signs and Body Weight

Vital signs and body weight will be verified and documented. If a clinically significant change is observed, the measurement will be repeated as clinically indicated and evaluated for its clinical relevance and whether it meets the definition of an AE.

12. STATISTICS

This section outlines the statistical methodology to be used to summarize the study results. A SAP will be prepared as a separate document. The SAP will include a more technical and detailed description of the planned statistical summaries and will be finalized prior to closing of the database.

12.1. Study Populations

The study populations include safety, DLT-evaluable, PK, pharmacodynamic, and efficacy populations.

Safety Population

The safety population will include all patients who received at least 1 dose of TAS-120. This population will be the primary population for safety evaluation.

DLT Evaluable Population (Phase 1 Dose Escalation only)

The DLT evaluable population was defined for Phase 1 Dose Escalation only; Phase 1 Dose Escalation has been completed as of Amendment 6.

PK and Pharmacodynamic Population

The PK and pharmacodynamic population will consist of all patients who received TAS-120 and have TAS-120 evaluable plasma and/or urine data. All such patients will be evaluated for PK and pharmacodynamics unless significant protocol deviations have impacted the data or key dosing information is missing. Changes to the procedures, which may impact the quality of PK and pharmacodynamic data, will be considered "PK and pharmacodynamics relevant protocol deviations." Examples include sample processing errors that lead to inaccurate bioanalytical results and/or inaccurate dosing on the day of PK and pharmacodynamic sampling.

Efficacy Population

The efficacy population is defined for each portion of the study as follows:

- Phase 1 Dose Escalation: All treated patients (safety population)
- Phase 1 Expansion: All treated patients (safety population)
- Phase 2: All treated iCCA patients with confirmed FGFR2 gene fusions

12.2. Statistical Analysis

12.2.1. Patient Disposition, Baseline and Treatment Characteristics

12.2.1.1. Patient Disposition

The number of patients in each study population and the reasons for exclusion will be summarized. In addition, patients' status with regard to study treatment and follow-up will also be summarized, along with the reasons for study discontinuation.

12.2.1.2. Patient Baseline Characteristics

Patient disease and baseline characteristics will be summarized using frequency distribution or descriptive statistics as appropriate.

12.2.1.3. Study Treatment

The TAS-120 administration profile will be summarized with respect to number of cycles taken, the dose intensity, dose modifications, and reasons for deviations from the planned regimen.

12.2.2. Efficacy Analysis

Tumor assessments will be performed as per Section 9.17, Tumor Assessments/Scans. For the Phase 1 Expansion, the primary endpoint is ORR (and EPR for primary CNS tumors), and secondary endpoints are DCR, DOR, PFS, OS.

For Phase 2, the primary endpoint is ORR and the secondary endpoints are DOR, DCR, PFS, PROs and OS (response evaluations based on independent review of images by the Core Imaging Laboratory). In addition, sensitivity analyses for some key efficacy endpoints (notably ORR and PFS) will be performed based on assessments by the investigator or local radiologist.

Response assessments will be made based on RECIST guidelines (version 1.1, 2009) for solid tumors (see Section 10.1, Efficacy Assessment for Solid Tumors) or RANO for brain tumors (see Section 10.2).

12.2.2.1. Objective Response Rate

Objective response rate (ORR) is defined as the proportion of patients with objective evidence of CR or PR. The evaluation of ORR will be based on investigator assessment and/or central independent review of the images as follows:

- Phase 1 dose escalation: Local CT/MRI assessment and collect CT scans or MRI for future central independent review, if warranted.
- Phase 1 expansion: Local CT/MRI assessment and collect CT scans or MRI for future central independent review, if warranted.
- Phase 2: Central independent CT/MRI image assessments (primary analysis) and local CT/MRI image assessments (sensitivity analysis).

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.

12.2.2.2. Disease Control Rate

The assessment of DCR will parallel that of ORR, with DCR defined as the proportion of patients with objective evidence of CR, PR, or SD, except that there is no requirement for a confirmation of an SD response, if it is maintained for at least 6 weeks post treatment initiation.

Disease control rate will be analyzed using the same methodology as ORR.

12.2.2.3. Duration of Response

Duration of response (DOR) is derived for those patients with objective evidence of PR or CR. Duration of response is defined as 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. 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 cancer 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. This endpoint will only be evaluated in patients with objective response of CR or PR.

Duration of response will be analyzed as a time-to-event endpoint with the median (Kaplan-Meier estimate) and associated 95% CI (Brookmeyer-Crowley methodology) reported.

12.2.2.4. Progression-free Survival

Progression-free survival (PFS) is defined as the time from the day of the first dose to the date of first objectively documented disease progression or death (any cause), whichever occurs first. 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. Early progression rate (EPR) for the GBM or Grade III glioma cohort will be assessed as the progression-free rate at the end of Cycle 2.

Progression-free survival will also be analyzed as a time-to-event endpoint with the median (Kaplan-Meier estimate) and associated 95% CI (Brookmeyer-Crowley methodology) reported, along with the Kaplan-Meier estimates for PFS rates at 3, 6, 9 and 12 months and associated 95% CIs (log-log transformation methodology of Kalbfleisch-Prentice).

12.2.2.5. Overall Survival

Overall survival (OS) is defined as the time (in months) from the date of the first dose to the death date, in the safety population for the Phase 1 Dose Escalation and Phase 1 Expansion parts of the study and the efficacy population for the Phase 2 part of the study. 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 study follow-up, or the cut-off date, whichever is earlier.

Overall survival will be analyzed similar to PFS.

12.2.2.6. Patient-Reported Outcomes

The analyses of EQ-5D and EORTC QLQ-C30 will be performed in all treated patients who have an assessment at baseline and at least one subsequent assessment.

EQ-5D

Patient's overall health state on a visual analog scale (EQ-VAS) at each assessment time point will be summarized using descriptive statistics. Proportion of patient's reporting problems for the 5 EQ-5D dimensions at each assessment time point will be summarized by level of problem. Percentages will be based on number patients assessed at each assessment time point.

A by-patient listing of EQ-5D with the problem levels for each of the 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), health state (5 dimensions digits combined in a 5-digit number) and EQ-VAS will be provided.

EORTC QLQ-C30

All scales and single items are scored on a categorical scale and linearly transformed to 0-to-100 scales with higher scores for a functional scale representing higher levels of functioning, higher scores for the global health status/quality of life representing higher levels of global health status/quality of life, and higher scores for a symptom scale representing higher level of symptoms.

Baseline and change from baseline in EORTC QLQ-C30 global health status/quality of life (QoL) composite scale data and the remaining EORTC QLQ-C30 scale data will be summarized by time point using descriptive statistics for each cohort. In addition, the percentage of patients demonstrating a clinically meaningful deterioration (defined as a 10-point change from baseline) will be presented for each scale at each assessment time point. Percentages will be based on number patients assessed at each assessment time point.

12.2.3. Safety

The safety evaluations will focus on the AEs and laboratory assessments. All patients included in the safety population will be evaluated in the safety analysis.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) terminology and the severity of the toxicities will be graded according to the NCI CTCAE (version 4.03) where applicable. Concomitant medications will be coded according to World Health Organization (WHO) Drug Dictionary for Concomitant Medication.

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

Hematological and chemistry laboratory parameters will be graded according to the NCI CTCAE (version 4.03) 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.

12.2.4. Pharmacokinetic Analysis

For Phase 1, the PK parameters in plasma and urine will be calculated by standard noncompartmental methods. In addition, the accumulation ratio will be also calculated for the last Wednesday of Cycle 1 (QOD arm) or Day 21 (QD arm) after repeated administrations, as applicable. Dose-proportionality of TAS-120 will be evaluated based on linear, power regression analyses, and 1-way analysis of variance. The detailed analytical method will be specified in the

Statistical Analysis Protocol. When further exploratory analyses are performed, the methods and the results may be reported in the Pharmacokinetic Analysis Report prepared separately.

- C_{max} Maximum concentration in plasma
- T_{max} Time to reach maximum concentration in plasma
- AUC_{0-24} Area under the concentration-time curve up to 24 hours (QD arm)
- AUC_{0-48} Area under the concentration-time curve up to 48 hours (QOD arm)
- AUC_{0-last} Area under the concentration-time curve up to the last observable concentration
- AUC_{0-inf} Area under the concentration-time curve up to infinity
- $T_{1/2}$ Elimination half-life time

The following parameters will be calculated only on Day 1.

- MRT Mean residence time
- CL/F Oral clearance
- Vd/F Volume of distribution
- Ae% Urinary excretion rate as % of dose (QOD arm)
- CLr Renal clearance (QOD arm)

The PK parameters will be calculated by noncompartmental method or population PK analysis method using Phoenix® WinNonlin (version 6.1 or later, Pharsight Corporation) or NONMEM® (version 7.2 or later, ICON Development Solutions).

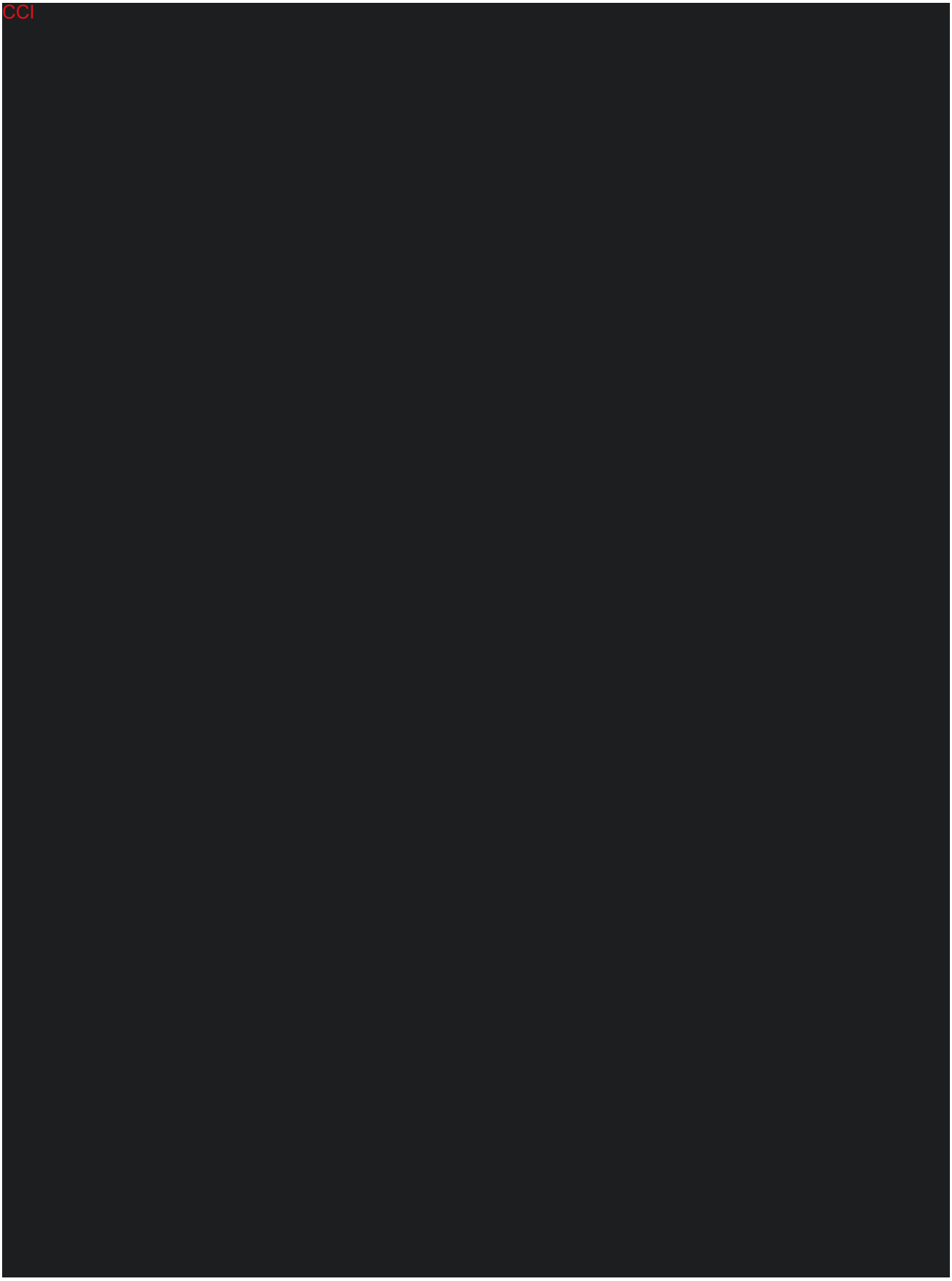
In addition, the TAS-120 concentration ratio of CSF to plasma will be calculated.

12.2.5. Pharmacodynamic Analysis (Phase 1 Dose Escalation only)

Pharmacodynamic data (FGF23 and phosphorus in serum, and phosphorus and calcium in urine) for individual time data will be summarized descriptively by dose level and schedule. Where possible, relationship between plasma PK parameters or concentration of TAS-120 will be evaluated by correlation analysis or visual inspections. When further exploratory analyses are performed, the methods and the results may be reported in the Pharmacodynamic Analysis Report.

CCI

CCI



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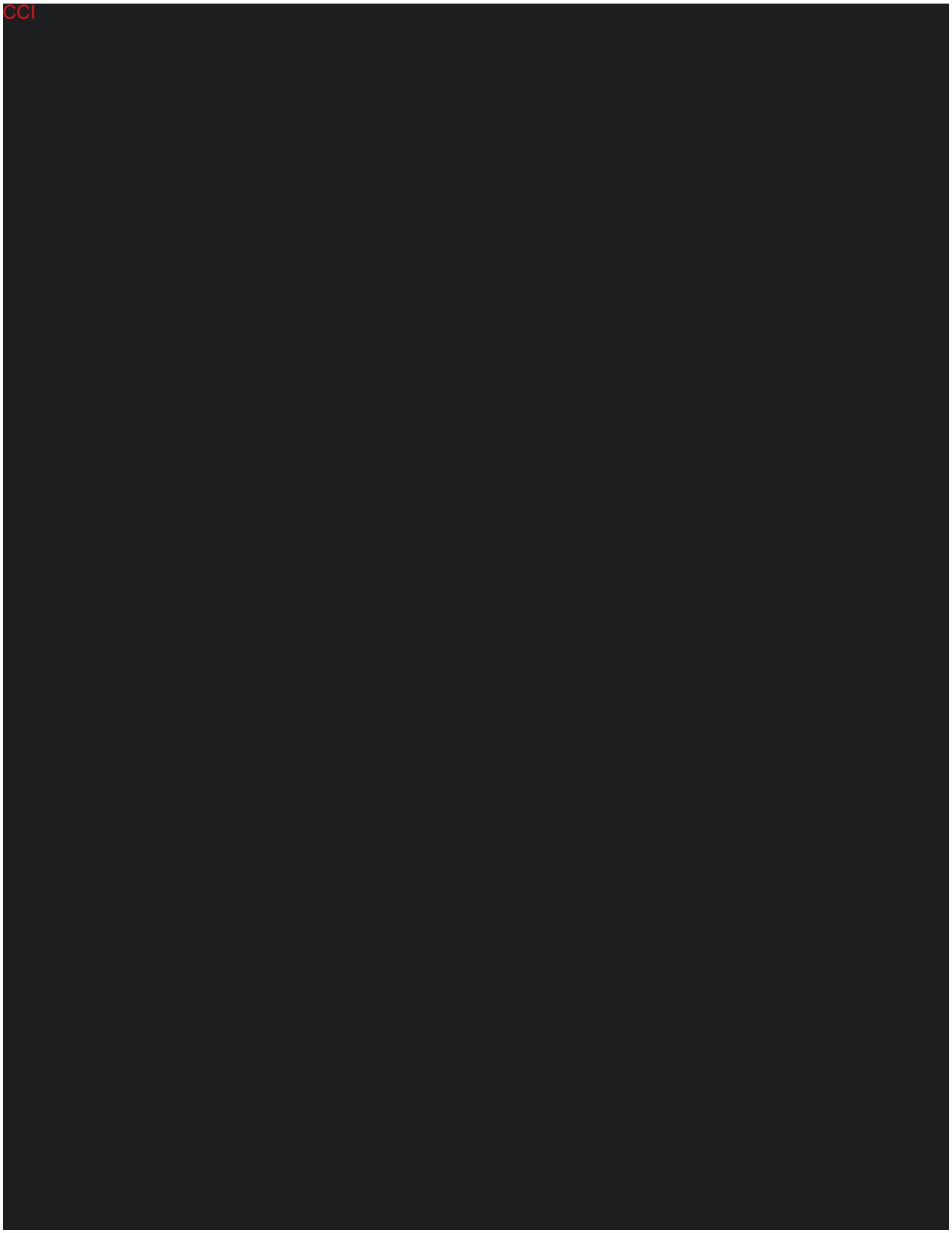

12.3.3. Phase 2

Approximately 100 iCCA patients with *FGFR2* gene fusions or other *FGFR2* rearrangements will be treated. CCI

[redacted]

CCI

[redacted]

12.4. Interim Analyses

Interim reviews of safety data from the Phase 2 portion will be performed approximately every 3 months throughout the study, until the interim analysis cut-off. These interim reviews will be performed by a Safety Review Committee (SRC), comprising, at minimum:

- 1 independent investigator and 1 independent statistician, neither of whom are directly involved in the conduct or analysis of the study; and
- A total of 5-6 study investigators representing each country/region in which patients are enrolled.

A complete description of the composition of the SRC and details on the interim analysis process will be provided in a separate safety review plan.

In addition to these reviews, the Sponsor will share safety data from the trial with all primary investigators throughout the conduct of the study.

A formal interim analysis will be performed when approximately 70% all treated patients had 6 months of follow-up. Two-sided 95% CI and 99% CI will both be provided for the primary efficacy analysis. A safety analysis will also be performed at this time, and the results will be shared with the SRC.

13. ETHICS

13.1. Ethical Considerations

It is mandatory that all considerations regarding the protection of human subjects be carried out in accordance with the protocol, Good Clinical Practice (GCP), ICH Guidelines, the ethical principles that have their origin in the Declaration of Helsinki, and all applicable regulatory requirements.

13.2. Informed Consent and Patient Information

Obtaining informed consent must be done according to the guidelines provided in the Declaration of Helsinki, ICH E6 Guideline for GCP, and local regulations.

The investigator (according to applicable regulatory requirements) or a person designated by the investigator and under the investigator's responsibility should fully inform patients of all pertinent aspects of the clinical trial. All participants should be informed to the fullest extent possible about the study in a language and in terms they are able to understand.

Prior to participation in the trial, the written ICF is to be signed and personally dated by the patient or by the patient's legal representative and by the person who conducted the ICF discussion. A copy of the signed and dated ICF will be provided to the patient. The ICF used must have had prior approval by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

13.3. Institutional Review Board/Independent Ethics Committee Approval

The study must be approved by an appropriately constituted IRB/IEC, as required in Chapter 3 of the ICH E6 Guidelines, applicable local regulations, and, for studies conducted under an Investigational New Drug (IND) application, the United States of America (USA) Code of Federal Regulations (CFR) Title 21 Part 56.

The IRB/IEC must provide written approval of the study. The written approval/favorable opinion should include protocol (title, number and version number), list of documents reviewed (e.g., protocol, ICF, IB, curriculum vitae), and the date of the review.

The investigator is required to submit a copy of the written and dated IRB/IEC approval/favorable opinion to the sponsor or its representative prior to initiation of this study.

Investigational product will not be released to the trial site and the investigator will not start the trial until this written IRB/IEC approval/favorable opinion is received by the sponsor or its representative.

The investigator is responsible for obtaining renewal of approval throughout the duration of the study. Timeframes for renewal will be based on IRB/IEC requirements but renewal at least annually is required by regulations.

At the end of the trial, the IRB/IEC will be notified of the conclusion of the trial and its outcome.

13.4. Post-study Provisions

After the completion of the study, if a patient still requires administration of study drug which has been assessed as beneficial per the investigator, the Sponsor and investigator will discuss the post-study provisions for the patient's access to study drug. At that time, patients will follow the procedures described in the Study Schedules for the EOT Visit and Safety Follow-up procedures. Subsequently, with the exception of SAEs and treatment-related AEs, data will not be collected in the electronic data capture (EDC) system.

14. ADMINISTRATIVE CONSIDERATIONS

14.1. Protocol Amendments

No change to the protocol may be made without the joint agreement of both the investigator and sponsor. Any amendment to the original protocol will be made by sponsor and will be signed by both parties and submitted to the IRB/IEC and appropriate regulatory authorities for approval or notification.

14.2. Curriculum Vitae

All investigators and any subinvestigator(s) must provide sponsor with current (within 2 years) signed and dated copies of their own curriculum vitae listing the experience, qualifications, and training prior to the beginning of the study.

14.3. Administrative Structure

The administrative structure of the study (e.g., CROs) will be provided to all sites.

In addition to ongoing safety monitoring during the study, a more comprehensive evaluation of the ongoing study safety profile will take place when key study milestones are met, such as completion of the DLT period in a specific cohort. At the end of each DLT period, the sponsor will review and discuss specific DLTs with the corresponding investigators, and the selection or rejection of particular doses as MTDs will be communicated directly to all active investigators.

14.4. Monitoring Procedures

14.4.1. Investigator's Responsibilities

The investigator agrees to conduct the study in accordance with the Clinical Trial Protocol, ICH guidelines E6 – GCP, Section 4 – investigator's obligations and the applicable regulatory requirements.

The investigator is required to ensure compliance with the protocol and other procedures provided by the sponsor. The investigator agrees to provide reliable data and all information required by the protocol, eCRF, SAE forms, and Data Resolution Forms or any other appropriate instrument. This information must be accurate, legible, and according to instructions provided.

The investigator must ensure that the sponsor, sponsor's representatives, and regulatory agencies will have access to such documentation.

The investigator may appoint subinvestigators to assist in the conduct of the trial. All subinvestigators shall be appointed and listed in a timely manner. They will be supervised and work under the responsibility of the investigator.

14.4.2. Sponsor's Responsibilities

The sponsor is responsible to health authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial protocol with regard to ethics, protocol compliance, and integrity and validity of the data recorded in the eCRFs. Thus, the main duty of the monitor is to

help the investigator and the sponsor maintain a high level of ethical, scientific, technical, regulatory, and quality in all aspects of the trial.

At regular intervals during the trial, the site will be contacted, through monitoring visits, letters or telephone calls by the sponsor or its representatives to review study progress, investigator and patient's compliance with requirements, and follow up on any issues to be addressed. During the monitoring visits, source documents, informed consent, recruitment, SAE documentation and reporting, investigational product accountability, concomitant medications, AEs, eCRFs, and queries will be reviewed with the investigator.

14.4.3. Source Documents

According to ICH guidelines the monitor will check the eCRF entries against the source documents. Source documents are original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, patient's evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, and records kept at the pharmacy, at laboratories, and at medical-technical departments involved in the clinical trial).

The Informed Consent will include a statement by which the patient allows the sponsor's duly authorized personnel, the IRB/IEC, and regulatory authorities to have direct access to original records supporting eCRF data.

14.4.4. Case Report Form

Investigators will be provided with detailed eCRF Completion Guidelines that will identify the required data points to be collected, how to document them, and when the data should be documented.

It is the responsibility of the investigator to maintain adequate and accurate eCRFs to record (according to the eCRF Completion Guidelines) all observations and other data pertinent to the clinical trial obtained during scheduled or unscheduled visits. All eCRFs should be fully completed to ensure accurate data interpretation.

The computerized handling of the data by the sponsor after receipt of the eCRFs may generate additional requests via paper queries or other means to which the investigator is obliged to respond by confirming or modifying the data questioned. These requests with their responses will be appended to the eCRFs held by the investigator and sponsor.

14.4.5. Sponsor's Audits and Regulatory Inspections

For the purpose of ensuring compliance with the protocol, GCP and applicable regulatory requirements, the investigator will permit auditing by the sponsor or its representative and inspections by regulatory authorities.

The investigator agrees to allow the auditors and inspectors to have direct access to the study records for review. The people performing these activities will not disclose any personal identity or personal medical information assessed.

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 trial. As soon as the investigator is notified of a planned inspection by the regulatory authorities or IRB/IEC, the investigator will inform the sponsor. Any results arising from such inspections will be immediately communicated by the investigator to the sponsor. The investigator shall take appropriate measures required by the sponsor to take corrective actions for all problems found during audits and/or inspections.

14.5. Archiving of Records

The investigator is responsible for the retention of all study documents according to institutional policies, local laws, ICH Parts 4.9.4 and 4.9.5 and, for studies conducted under an IND application, the USA CFR Title 21 Part 312.62. For more information on USA requirements and ICH Guidelines, please go to www.fda.gov and www.ema.europa.eu.

The investigator agrees to inform sponsor in writing of the intention to remove or destroy any study-related records. Prior to contacting sponsor, the investigator must ensure that institutional and local requirements (for example, ICH Guidelines) have been satisfied. Taiho Oncology, Inc. Regulatory Affairs will evaluate the investigator's request. The sponsor will provide authorization for destruction of such records to the investigator in writing.

In the event that all retention of records requirements have been fulfilled, but sponsor requests that the investigator maintain the records for a longer period of time, additional arrangements will be made.

14.6. Final Report

Whether the study is completed or prematurely terminated, a final report of the study will be written by the sponsor or its designee and submitted to the regulatory agency(ies), as required by the applicable regulations.

The final study report will be retained by the sponsor, or by any other subsequent owner of this drug, for 5 years beyond the lifetime of the product.

14.7. Use and Publication of Study Results

All unpublished documentation (including the protocol, eCRF, and IB) given to the investigator is strictly confidential. All recipients must agree not to disclose the information contained herein to any person without the prior written authorization of the sponsor. The submission of these documents to the IRB/IEC is permitted. The investigator agrees that 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.

The results of the study may be presented during scientific symposia 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.

14.8. Financial Disclosure

Financial disclosure for clinical investigators and record keeping of financial records will be in accordance with local regulatory requirements.

14.9. Termination of the Study

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 to notice). The new investigator must accept the responsibility in writing and be approved by the sponsor and the IRB/IEC.

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 reasons at any time. The investigator will be reimbursed for reasonable expenses incurred, if it is necessary to terminate the study or an individual patient's participation. The sponsor will not reimburse the investigator for the evaluation of patients if the evaluations are not conducted in compliance with the final protocol.

A supplemental Pharmaceuticals and Medical Devices Agency (PMDA) appendix (for Japan only) is provided in Appendix G.

15. CONFIDENTIALITY AND DATA PROTECTION

All information provided to the investigator by the sponsor or sponsor's representatives, information produced during the clinical trial including, but not limited to, the protocol, eCRF, IB, and the results obtained during the course of the trial are confidential. The members of the research team agree not to discuss such information in any way without prior written permission from the sponsor.

However, the submission of the protocol and necessary documentation to the IRB/IEC is permitted. The IRB/IEC members have the same obligation of confidentiality.

The patient's personal data 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 or 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.

16. SIGNATURES OF SPONSOR AND INVESTIGATOR

PHASE 1/2 STUDY OF TAS-120 IN PATIENTS WITH ADVANCED SOLID TUMORS HARBORING FGF/FGFR ABERRATIONS

a. Declaration of Sponsor

This study protocol was subject to critical review and has been approved by the appropriate protocol review committee of the sponsor. The information it contains is consistent with:

- The current risk-benefit evaluation of TAS-120.
- The moral, ethical, and scientific principles governing clinical research as set out in the protocol, GCP, ICH Guidelines, the ethical principles that have their origin in the Declaration of Helsinki, and all applicable regulatory requirements.

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

Date: PPD Signature PPD

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

b. Declaration of Investigator

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, the ethical principles that have their origin in the Declaration of Helsinki, 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

Date: _____ Signature: _____

Name (block letters): _____

17. REFERENCES

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APPENDIX A. LIST OF FGFR MUTATIONS

List of FGFR Mutations				
FGFR1	**AA (isoform 1)[a] change**	**AA (isoform 2)[b] change**	**AA (isoform 3)[c] change**	**Reference**
FGFR1	N546K	N544K	N577K	Sci Signal. 2009 Feb 17;2(58)
FGFR1	K656E	K654E	K687E	Oncogene. 2000 Jul 6; 19(29):3309-20.
FGFR2	**AA (IIIc) change[d]**	**AA (IIIb) change[e]**		**Reference**
FGFR2	R203C	R203C		PLoS One. 2013; 8(3):e60264.
FGFR2	S252W	S252W		Proc Natl Acad Sci U S A. 2008 Jun 24; 105(25):8713-7.
FGFR2	P253L	P253L		Nat Genet. 1995 Feb; 9(2):165-72.
FGFR2	P253R	P253R		Biochem J. 2008 Feb 15; 410(1):205-11.
FGFR2	W290C	W290C		Cancer Res. 2013 Aug 15; 73(16):5195-205.
FGFR2	K310R	K310R		TAIHO's in house data.
FGFR2	NA	S320C		Cancer Res. 2013 Aug 15; 73(16):5195-205.
FGFR2	Y375C	Y376C		Proc Natl Acad Sci U S A. 2008 Jun 24; 105(25):8713-7.
FGFR2	C382R	C383R		Proc Natl Acad Sci U S A. 2008 Jun 24; 105(25):8713-7.
FGFR2	C382T	C383T		Nature. 2013 May 2; 497(7447):67-73.
FGFR2	M537I	M538I		Neoplasia. 2013 Aug; 15(8):975-88.
FGFR2	I547V	I548V		Neoplasia. 2013 Aug; 15(8):975-88.
FGFR2	N549S	N550S		Neoplasia. 2013 Aug; 15(8):975-88.
FGFR2	N549H	N550H		Cancer Discov. 2017 Mar; 7(3):252-263.
FGFR2	N549K	N550K		Cancer Discov. 2017 Mar; 7(3):252-263.
FGFR2	K641R	K642R		PLoS One. 2013; 8(3):e60264.
FGFR2	K659E	K660E		Neoplasia. 2013 Aug; 15(8):975-88.
FGFR2	K659N	K660N		PLoS One. 2013; 8(3):e60264.
FGFR2	L763fs	L764fs		Oncogene. 2007 Nov 1; 26(50):7158-62.
FGFR2	T764fs	T765fs		Oncogene. 1997 Aug 14; 15(7):817-26.
FGFR3	**AA (IIIc) change[f]**	**AA (IIIb) change[g]**		**Reference**
FGFR3	R248C	R248C		Cell Cycle. 2014 May 15; 13(10): 1551-1559.
FGFR3	S249C	S249C		Oncogene. 2007 Aug 30; 26(40):5889-99.
FGFR3	H349Y	NA		Anticancer Res. 2011 Jan; 31(1):113-22.
FGFR3	G370C	G372C		J Bone Miner Res. 2002 May; 17(5):860-8.
FGFR3	S371C	S373C		J Bone Miner Res. 2002 May; 17(5):860-8.
FGFR3	Y373C	Y375C		Anticancer Res. 2011 Jan; 31(1):113-22.

List of FGFR Mutations			
FGFR3	G380R	G382R	PLoS One. 2012; 7(4):e34808.
FGFR3	A391E	A393E	Nat Genet. 2009 Nov; 41(11):1247-52.
FGFR3	N540K	N542K	Oncotarget. 2016 Apr 26; 7(17):24252-68.
FGFR3	K650E	K652E	Blood. 2001 Feb 1; 97(3):729-36.
FGFR3	K650M	K652M	FEBS J. 2007 Jun; 274(12):3078-93. Epub 2007 May 17.
FGFR3	K650N	K652N	Am. J. Hum. Genet. 67:1411–1421, 2000.
FGFR3	K650Q	K652Q	Am. J. Hum. Genet. 67:1411–1421, 2000.
FGFR3	K650T	K652T	Am. J. Hum. Genet. 67:1411–1421, 2000.
FGFR4	**AA (isoform 1)[h] change**	**AA (isoform 2)[i] change**	**References**
FGFR4	Y367C	NA	Cancer Res. 2007 Dec 1; 67(23):11368-76.
FGFR4	N535K	N495D	J Clin Invest. 2009 Nov; 119(11):3395-407.
FGFR4	N535D	N495D	J Clin Invest. 2009 Nov; 119(11):3395-407.
FGFR4	V550E	V510E	J Clin Invest. 2009 Nov; 119(11):3395-407.
FGFR4	V550L	V510L	J Clin Invest. 2009 Nov; 119(11):3395-407.
FGFR4	V550M	V510M	J Clin Invest. 2009 Nov; 119(11):3395-407.
FGFR4	K645E	K605E	Oncogene. 2000 Jul 6; 19(29):3309-20.

Criteria for selecting mutations

- Found in cancer as somatic mutation
- Reported to be active mutation by biological experiment
- Speculated oncogenic mutations in consideration of AA position or bioinformatic analysis without biological experiment were NOT listed

[a] Amino acid change of FGFR1 splice variant isoform 1

[b] Amino acid change of FGFR1 splice variant isoform 2

[c] Amino acid change of FGFR1 splice variant isoform 3

[d] Amino acid change of FGFR2 splice variant IIIc

[e] Amino acid change of FGFR2 splice variant IIIb

[f] Amino acid change of FGFR3 splice variant IIIc

[g] Amino acid change of FGFR3 splice variant IIIb

[h] Amino acid change of FGFR4 splice variant isoform 1

[i] Amino acid change of FGFR4 splice variant isoform 2

APPENDIX B. FGFR3 MUTATIONS

FGFR3	AA (IIIc) change[a]	AA (IIIb) change[b]	Major Reference
FGFR3	R248C	R248C	Cell Cycle. 2014 May 15; 13(10): 1551-1559.
FGFR3	S249C	S249C	Oncogene. 2007 Aug 30; 26(40):5889-99.
FGFR3	H349Y	NA	Anticancer Res. 2011 Jan; 31(1):113-22.
FGFR3	G370C	G372C	J Bone Miner Res. 2002 May; 17(5):860-8.
FGFR3	S371C	S373C	J Bone Miner Res. 2002 May; 17(5):860-8.
FGFR3	Y373C	Y375C	Anticancer Res. 2011 Jan; 31(1):113-22.
FGFR3	G380R	G382R	PLoS One. 2012; 7(4):e34808.
FGFR3	A391E	A393E	Nat Genet. 2009 Nov; 41(11):1247-52.
FGFR3	N540K	N542K	Oncotarget. 2016 Apr 26; 7(17):24252-68.
FGFR3	K650E	K652E	Blood. 2001 Feb 1; 97(3):729-36.
FGFR3	K650M	K652M	FEBS J. 2007 Jun; 274(12):3078-93. Epub 2007 May 17.
FGFR3	K650N	K652N	Am. J. Hum. Genet. 67:1411–1421, 2000.
FGFR3	K650Q	K652Q	Am. J. Hum. Genet. 67:1411–1421, 2000.
FGFR3	K650T	K652T	Am. J. Hum. Genet. 67:1411–1421, 2000.

Criteria for selecting mutations

- Reported to be active mutation by biological experiment
- Speculated oncogenic mutations in consideration of AA position or bioinformatic analysis without biological experiment were NOT listed

[a] Amino acid change of FGFR3 splice variant IIIc

[b] Amino acid change of FGFR3 splice variant IIIb

APPENDIX C. 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, e.g., 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 D. NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION

The Stages of Heart Failure NYHA Classification

In order to determine the best course of therapy, physicians often assess the stage of heart failure according to the NYHA functional classification system. This system relates symptoms to everyday activities and the patient's quality of life.

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

APPENDIX E. 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 **phos**phate
- Disodium **phos**phate
- **Phos**phoric acid
- Monopotassium **phos**phate
- Sodium acid pyro**phos**phate
- Sodium tripoly**phos**phate

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, such as 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 F. 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[a] or ≥ 80% decrease in AUC**	**Moderate Inducers[b] 50 – 80% decrease in AUC**
CYP3A	Carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort[c]	Bosentan, efavirenz, etravirine, modafinil

a. A strong inducer is a drug that decreases the AUC of sensitive index substrates of a given metabolic pathway by ≥80%.
b. A moderate inducer is a drug that decreases the AUC of sensitive index substrates of a given metabolic pathway by ≥50% to <80%.
c. 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[a]**	**Moderate Sensitive Substrates[b]**
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

a. 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.
b 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[a]	*ABCB1*	Amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil
BCRP[b]	*ABCG2*	Curcumin, cyclosporine A, eltrombopag

a. P-gp: (1) AUC fold-increase of digoxin ≥2 with co-administration and (2) in vitro inhibitor.
b. 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[a]	*ABCB1*	Dabigatran, digoxin, fexofenadine
BCRP[b]	*ABCG2*	Rosuvastatin, sulfasalazine

a. 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.
b. 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.

APPENDIX G. SUPPLEMENTAL REQUIREMENTS FOR JAPAN ONLY

CLINICAL STUDY ORGANIZATION

The study organization details (Administrative Structure) will be maintained in the study Trial Master File.

GCP COMPLIANCE AND ETHICAL IMPLEMENTATION OF THE CLINICAL STUDY

This protocol has been established in accordance with an ethical principle based on the Helsinki Declaration, Pharmaceutical and Medical Device Act, a Pharmaceutical and Medical Device Act implementation ordinance, "the departmental order (GCP) about the criterion of the implementation of the clinical trials of medical supplies."

In this clinical study, this protocol and ICH and local GCP must be followed.

ITEMS FOR EXPLANATION TO PATIENTS BY INFORMED CONSENT FORM

For informed consent by patients, the following items are explained using the informed consent form:

1. That this is a clinical trial.
2. The purpose of this clinical study.
3. Study methodology.
4. Expected study period for the patient.
5. Planned patient number to participate in the clinical study.
6. Expected benefit by investigational product for the subject's physical/mental health (if it is not expected, the reason is explained) and, expected disadvantage to the subject.
7. Existence or non-existence of treatment options other than investigational product, and expected important benefit and risk of the treatment options, as the clinical study subject is a patient.
8. Compensation and treatment that the subject can receive if health damage related to the study occurs.
9. Participation in the study is of the subject's free-will and the subject can refuse or withdraw from participation in the study at any time. The subject is not to be treated unfavorably or lose any advantage that he/she would receive when not participating in the study by refusing to participate or withdrawing from the study.
10. The fact that if information is obtained that may affect the subject's decision regarding continued participation in this study, that information will promptly be conveyed to the subject.
11. Condition and reason that participation in the study was discontinued.

12. The monitor, auditor, IRB, and the regulatory authorities can review the original medical records. In such a case, the subject's privacy is to be preserved. In addition, by applying his/her seal or signing the consent form, the subject permits such access.
13. Even if the results of the study are made public, the confidentiality of the subject's identity will be preserved.
14. The details when it is necessary for the subject to bear the burden of expense.
15. The details when the subject is to be paid in money, etc.
16. The names, positions, and contact information for the primary investigator and the sub-investigator.
17. The implementing medical institution's consultation service for reference or to make contact if the subject would like to obtain further information regarding the study and the subject's rights if health damage related to the study occurs.
18. Items that patients must follow:
    - A concrete antifertility method (condom and diaphragm, condom and spermicidal jelly, spermicide or film, diaphragm and spermicidal jelly, spermicide or film or intrauterine contraceptives).
19. The fact that when the subject is receiving treatment from another physician, the primary investigator or sub-investigator will notify said physician that the subject is participating in the study.
20. Matters related to the type of IRB that reviews and discusses eligibility, etc. for said study and the reviews and discussions held in each IRB and other matters related to IRB regarding said study.
21. About the publication of the synopses of the record of procedure of the IRB, committee name list and the conference.

THE IDENTIFICATION OF ANY DATA TO BE RECORDED ON THE CRFS, AND TO BE CONSIDERED TO BE SOURCE DATA

The following data will be recorded directly into the CRFs and will be considered source data:

- Reasons for concomitance, concomitant medication/therapy prescribed at other hospitals
- Presence or absence of AEs, name of AEs, serious/non-serious, treatment on study therapy, causal relationship with study drug, and reasons for terminating follow-up.
- Reasons for admission and discharge from the hospital, reasons for discontinuation or termination from the study, and reasons for death.

SAMPLE SIZE FOR JAPAN

Expected sample size for Japan: 15 - 20 cases in total.

CLINICAL STUDY PERIOD

Planned clinical study schedule: From May 2018 to April 2021.

APPENDIX H. SUMMARY OF PROTOCOL AMENDMENTS

Amendment 1 Key Changes:

- Added language "who have failed all standard therapies or for whom standard therapy does not exist" in order to clarify study rationale, study objectives, study design, and inclusion criteria (Phase 1 Dose Escalation)
- Revised "Definitions of Dose-limiting Toxicity and Maximum Tolerated Dose" criteria for hyperphosphatemia and increase of creatinine.
- Revised inclusion criteria to include serum phosphorus and serum calcium
- Revised exclusion criteria to include QT interval
- Added information to management of hyperphosphatemia
- Added ophthalmological examination visits per local requirement or as clinically indicated

Amendment 2 Key Changes:

- Updated visit schedules in Table 1A and Table 1B (serum chemistry only)
- Added information to the exclusion criteria for noninvestigational anticancer therapy
- Expanded the list of concomitant medications and therapies
- Revised "Definitions of Dose-limiting Toxicity and Maximum Tolerated Dose" criteria for hyperphosphatemia and creatinine increase.
- Added serum phosphorus and serum calcium to inclusion criteria
- Added information to the QT interval exclusion criteria
- Clarified management of hyperphosphatemia
- Revised dose reduction requirements
- Clarified Screening criteria
- Clarified fractionation of CK into isoforms
- CCI [redacted]
- CCI [redacted]
- Clarification of study phase to solid tumor assessments/scans
- Expanded method of capturing and reporting medication errors.

Amendment 3 Key Changes:

- Removed references to NSCLC, gastric, and breast cancers and multiple myeloma population from sections throughout the protocol amendment as appropriate
- Added information to timing of initiating the QD arm in relation to QOD dosing schedule
- Updated the language on women of childbearing potential and effective contraception inclusion criteria to comply with Clinical Trials Facilitation Group (CTFG) Guidelines
- Added change to include tablets (i.e., number of tablets, description of packaging and storage information) about 4 mg and 20 mg TAS-120 tablets.
- Updated information on assessment of overall response rate
- Revised section on determination of sample size
- Updated guidelines for management of hyperphosphatemia
- Added additional electrocardiogram (ECG) evaluations as appropriate

Amendment 4 Key Changes:

- Updated clinical information for 2 clinical trials TAS-120-101 Phase 1/2 Trial TPU-TAS-120-101 [US/EU/Australia] and Phase 1 trial 10059010 [Japan]
- Added rationale for the selection of QD dosing schedule
- Added a new intermediate dose level of 20 mg QD to enable a more precise determination of the Recommended Phase 2 Dose (RP2D).

Amendment 5 Key Changes:

- Added specific cohorts of patients to be enrolled in the 4 groups in the Phase 1 Expansion
- Updated study endpoints for the Phase 1 Expansion and Phase 2 parts of the study including early progression rate (EPR) as a primary endpoint and added Response Assessment in Neuro-Oncology (RANO) as the guidelines for efficacy assessment for patients with glioblastoma multiforme (GBM) or grade III glioma, PFS and OS.
- Added efficacy and tumor assessments for brain tumors and added RANO tumor assessment criteria for brain tumors.
- Updated the inclusion and exclusion criteria to further define patients included in Phase 1 Expansion and Phase 2
- Revised guidelines for serum phosphorus monitoring and management of hyperphosphatemia
- Provided the procedure for screening and identifying iCCA patients with tumors that have FGFR gene fusions in the Phase 2 part of the study.
- CCI [redacted]
- Clarification of evaluations at visit schedules
- Updated definitions of populations in statistical methods in both the Phase 1 Expansion and Phase 2
- Revised section on determination of sample size to further specify the sample size justification for the specific cohorts of patients to be enrolled in the Phase 1 Expansion and to provide sample size justification for patients enrolled in the Phase 2 part of the study.

Amendment 6 Key Changes:

- Added an additional 4 cohorts of patients to be enrolled in the Phase 1 Expansion.
- Added information that established 20 mg QD as the RP2D
- Clarified Phase 2 primary objective, added a key secondary objective, other secondary objectives CCI [redacted]
- Updated the inclusion and exclusion criteria to further define patients in Phase 1 Expansion and Phase 2
- Provided methods for prescreening testing of tumor samples for FGFR2 gene fusion before enrollment into Phase 2
- Removed TAS-120 capsule formulation as it is no longer applicable
- Updated information on timing and fasting requirements to study drug administration procedures
- Updated guidelines on Dose Hold, Dose Modifications and Dose Resumption
- Clarification of evaluations in visit schedules

- Updated information on statistical analysis of disease control rate (DCR), duration of response (DOR), PFS
- Added assessments of and statistical analysis of Patient-Reported Outcome assessments.
- Updated determination of sample size information to further specify the sample size justification for the specific cohorts of patients to be enrolled in the Phase 1 Expansion and to further specify sample size justification for patients enrolled in the Phase 2 part of the study.

Amendment 7 Key Changes:

Global

- Reformatted and clarified study events tables to ensure consistency throughout the protocol.
- Altered inclusion requirement for bilirubin to allow for serum or plasma assessment of bilirubin and to include patients with Gilbert's syndrome and bilirubin up to 3 x upper limit of normal.
- Clarified requirements for pregnancy testing of women of childbearing potential throughout the study.
- Throughout the document, editorial changes, including elimination of errors or minor rewordings to improve clarity, were made as necessary. The administrative alterations do not affect the planned conduct or analysis of the study.

Phase I Expansion

- Added brief rationale for the design of the Phase I expansion portion of the study.
- Enrollment suspended into Phase I expansion Groups 1, 3, 4, 6, and 8.
- Refined criteria for enrollment into other groups in Phase I expansion, including:
    - Changing the FGFR requirement for Group 7 from "FGF9 or FGF19 amplifications" to "FGFR2 amplifications."
    - Changing the requirement for Group 5 from "grade III glioma" to "primary CNS tumors."
- Changes were made to study objectives, statistical methods, and other sections of the protocol as necessary for consistency with the revised population of each subgroup in the Phase I expansion portion of the study.

Phase 2

- Expanded eligibility requirements to allow all patients with FGFR2 rearrangements, rather than patients with FGFR2 gene fusions only.
- Clarified requirements for tumor testing to determine and/or confirm study eligibility on the basis of FGFR2 gene fusion status.
- Clarified requirements for prior therapy (patients must have received at least one prior systemic gemcitabine-platinum therapy and have documented progression following the most recent prior therapy.
- Added planned interim reviews of safety to be performed approximately every 3 months throughout the study, including brief description of the SRC that will perform these reviews.

Amendment 8 Key Changes:

- Guidelines for management of hyperphosphatemia were updated to reflect analysis of most current available data.