Statistical Analysis Plan

Sponsor Name:	Taiho Oncology, Inc.
Protocol Number and Title:	TPU-TAS-120-101 PHASE 1/2 STUDY OF TAS-120 IN PATIENTS WITH ADVANCED SOLID TUMORS HARBORING FGF/FGFR ABERRATIONS
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Version: 3.3, Phase 1 Dose Escalation Only

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Version: __3.3_____ **Version Date:** __12MAR2018_____

I confirm that I have reviewed this document and agree with the content.

APPROVALS	
INC Research	
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Taiho Oncology Inc.	
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1. GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Description
λ_z	Elimination rate constant
β-HCG	Beta-human chorionic gonadotropin
Ae%	Urinary excretion rate as % of dose
AE	Adverse Event
ALT (SGPT)	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
APTT	Activated partial thromboplastin time
AST (SGOT)	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC_{0-24}	Area under the concentration-time curve up to 24 hours
AUC_{0-48}	Area under the concentration-time curve up to 48 hours
AUC_{0-last}	Area under the concentration-time curve up to the time of last quantifiable concentration
AUC_{0-inf}	Area under the concentration-time curve up to infinity on C1D1
BUN	Blood urea nitrogen
CI	Confidence Interval
CL/F	Oral (or fractional) Clearance
CLr	Renal clearance
C_{max}	Maximum observed plasma concentration
CK	Creatine kinase
CK-MB	Creatine kinase (isoform heart muscle)
CK-MM	Creatine kinase (isoform skeletal muscle)
CR	Complete Response
CRF	Case Report Form
CRP	C-reactive protein

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Abbreviation	Description
CSF	Cerebral Spinal Fluid
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DCR	Disease Control Rate
DLT	Dose Limiting Toxicity
DR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFF	Efficacy Population
FGF/FGFR	Fibroblast growth factor / Fibroblast growth factor receptor
FLC	Free light chain
GnRH	Gonadotropin-releasing hormone
ICH	International Conference on Harmonization
IMP	Investigational Medicine Product
IMWG	International Myeloma Working Group
INR	International normalized ratio
IU	International Units
LH-RH	Luteinizing hormone-releasing hormone
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MRT	Mean residence time up to infinity
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association

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Abbreviation	Description
ORR	Objective response rate
PD	Progressive Disease
PFS	Progression-free survival
PGx	Pharmacogenomics
PK	Pharmacokinetic(s)
PR	Partial Response
PT	Preferred Term
QC	Quality Control
QD	Once daily (continuous) dosing
QOD	3 times a week (Monday, Wednesday, and Friday) dosing
QTc	Corrected QT Interval
QTcB	Bazett's Correction of QT Interval
QTcF	Fridericia' Correction of QT Interval
RAUC	Accumulation ratio calculated based on AUC0-last
RBC	Red Blood Cell
RCmax	Accumulation ratio calculated based on Cmax
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
RSQ	R-Square
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sCR	Stringent complete response
SD	Stable Disease
SE	Standard Error
SFLC	Serum free light chain
SI	Standard International System of Units

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Abbreviation	Description
SOC	System Organ Class
SOP	Standard Operating Procedure
SPEP	Serum Protein Electrophoresis
TEAE	Treatment Emergent Adverse Event
TLF	Table, Listing and Figure
TOI	Taiho Oncology Inc.
TPC	Taiho Pharmaceutical, Co., Ltd.
$T_{1/2}$	Half-life time
T_{max}	Time to reach maximum concentration in plasma
ULN	Upper Limit of Normal
UPEP	Urine Protein Electrophoresis
Vd/F	Apparent volume of distribution
WBC	White blood cell
WHO	World Health Organization

Statistical Analysis Plan

2. PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure that the summary tables, data listings and figures (TLFs) which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. RESPONSIBILITIES

INC Research Biostatics Group will perform the statistical analyses and are responsible for the production and quality control of all tables, listings and figures (TLFs). INC Research Biostatics Group will perform PK analysis following this SAP with the guidance and the preliminary result supplied by Taiho Oncology, Inc. The preliminary result Taiho will provide are the ones associated with plasma samples only. CCI

2.2. TIMINGS OF ANALYSES

In this study, patients will receive the study medication according to the proposed treatment schedule until disease progression (PD), occurrence of intolerable side effects, decision to discontinue treatment by the Investigator, withdrawal of consent by patient, or other criteria for discontinuation are met (see protocol Section 6.3, Discontinuation Criteria). A patient is considered discontinued from study treatment when TAS-120 is discontinued.

For the purpose of the final analyses for dose escalation phase, the dose escalation phase will be considered completed when all patients in phase 1 dose escalation have discontinued from treatment or have sufficient follow-up (more than 6 months) from the date of the first treatment with TAS-120 of the last patient enrolled, whichever occurs first.

3. STUDY OBJECTIVES

3.1. PHASE I DOSE ESCALATION

3.1.1. Primary Objective

- To investigate the safety and to determine the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D) of TAS-120 and its associated dosing schedule (3 times a week [Monday, Wednesday, and Friday] [QOD]) or once daily [QD]) in patients with advanced solid tumors with or without FGF/FGFR abnormalities who have failed all standard therapies or for whom standard therapy does not exist.

3.1.2. Secondary Objectives

- To investigate the clinical pharmacokinetics (PK) of TAS-120.
- To investigate the clinical pharmacodynamics of TAS-120.
- To determine any preliminary antitumor activity observed with TAS-120.

4. STUDY DESIGN

4.1. BRIEF DESCRIPTION

This is a phase 1/2 study of TAS-120 in patients with advanced solid tumors harboring FGF/FGFR aberrations. TAS-120 is administered once a day, in the morning (Phase 1 Dose Escalation only), orally, 3 times a week (i.e., QOD, Monday, Wednesday, and Friday) or everyday (i.e., QD) in patients. The study will be conducted in 3 parts: a Phase 1 Dose-Escalation part to determine the MTD and RP2D of TAS-120 in 2 dose schedules (QOD or QD), a Phase 1 Expansion part and a Phase 2 part to further evaluate the efficacy and safety of the RP2D of TAS-120 and dose schedule. Phase 1 expansion and Phase 2 will be planned in a separate SAP.

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 of TAS-120 until at least one of the discontinuation criteria is met (see Protocol Section 6.3).

Phase 1 Dose-Escalation

TAS-120 is administered to cohorts of patients with advanced solid tumors at up to 10 escalating dose levels (Table 1). At all dose levels, 3 to 6 patients with advanced solid tumors is to enrolled in each cohort sequentially. Dose escalation begins with QOD dosing. When QOD dose escalation reaches Dose Level 5, Dose Level 1 of QD dosing is to be initiated. For the QD arm, TAS-120 is administered at up to 11 escalating dose levels in 21- day treatment cycles.

At Dose Level 1 (for both arms), the patients start TAS-120 treatment sequentially at intervals of a minimum of 1 week. Beginning with Dose Level 5 in both arms, patient eligibility criteria is restricted only to patients with an FGF/FGFR abnormality.

Escalation to each subsequent dose level occur only after the current dose level is found to be safe according to the protocol criteria ("3 + 3" design). Intrapatient dose escalation is not allowed.

The MTD is defined as the highest dose level at which less than 33% of the patients experience a dose-limiting toxicity (DLT) during Cycle 1 (See 4.1.1. Definitions of DLT and MTD). At least 6 evaluable patients is to be enrolled at the MTD level. The RP2D is equal to or less than the MTD, and its associated dosing schedule is selected based on the safety, PK, pharmacodynamic, and preliminary efficacy data observed during Phase 1 Dose Escalation.

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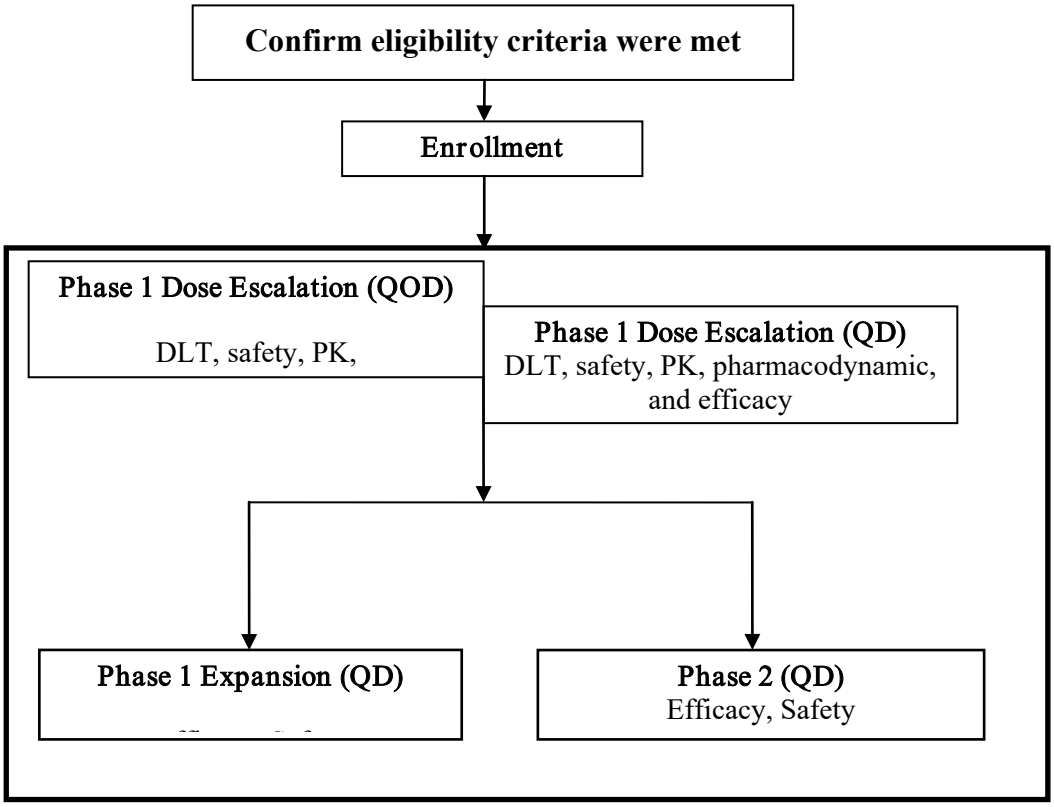
Based on investigator and sponsor assessment, if further clinical evaluation is required, additional 3 to 6 patients may be added to any cohort.

Table 1: Dose Levels

QOD Dose Level	*Dose in mg (QOD)*	*Patient population*	*QD Dose Level*	*Dose in mg (QD)*	*Patient population*
1	*8*	*With or without FGF/FGFR abnormalities*	---	---	---
2	*16*	*With or without FGF/FGFR abnormalities*	---	---	---
3	*24*	*With or without FGF/FGFR abnormalities*	---	---	---
4	*36*	*With or without FGF/FGFR abnormalities*	---	---	---
5	*56*	*With FGF/FGFR abnormalities*	*1*	*4*	*With or without FGF/FGFR abnormalities*
6	*80*	*With FGF/FGFR abnormalities*	*2*	*8*	*With or without FGF/FGFR abnormalities*
7	*120*	*With FGF/FGFR abnormalities*	*3*	*16*	*With or without FGF/FGFR abnormalities*
			3.5	*20*[a]	*With FGF/FGFR abnormalities*
8	*160*	*With FGF/FGFR abnormalities*	*4*	*24*	*With or without FGF/FGFR abnormalities*
9	*200*	*With FGF/FGFR abnormalities*	*5*	*36*	*With FGF/FGFR abnormalities*
10	*240*	*With FGF/FGFR abnormalities*	*6*	*56*	*With FGF/FGFR abnormalities*
-	-	---	*7*	*80*	*With FGF/FGFR abnormalities*
-	-	---	*8*	*120*	*With FGF/FGFR abnormalities*
-	-	---	*9*	*160*	*With FGF/FGFR abnormalities*
-	-	---	*10*	*200*	*With FGF/FGFR abnormalities*
-	-	---	*11*	*240*	*With FGF/FGFR abnormalities*

Abbreviations: QD = once daily; QOD = 3 times a week (Monday, Wednesday, and Friday); FGF = fibroblast growth factor; FGFR = fibroblast growth factor receptor.
[a] Intermediate dose level added for dose optimization in Amendment 4.

Overall Study Design



4.1.1. Definitions of DLT and MTD

Only drug-related toxicities during the Cycle 1 are considered in the assessment of DLTs.

A DLT is defined as the following:

a) ≥ Grade 3 nonhematologic toxicity (excluding nausea/vomiting, diarrhea)

b) ≥ Grade 3 nausea/vomiting lasting > 48 hours and uncontrolled by aggressive antiemetic therapy, including serotonin 5-HT3 receptor antagonists (e.g., ondansetron)

c) ≥ Grade 3 diarrhea lasting > 48 hours and unresponsive to antidiarrheal medication

d) Grade 4 neutropenia lasting > 7 days

e) Febrile neutropenia (absolute neutrophil count [ANC] < 1 000/mm3 with a single body temperature of > 38.3°C [101°F] or a sustained temperature ≥ 38°C [100.4°F] for more than 1 hour).

f) Grade 4 thrombocytopenia or Grade 3 thrombocytopenia associated with bleeding and requiring blood transfusion

g) Corneal disorder worsening by 1 grade or more

h) Hyperphosphatemia: any increase of phosphorus ≥ 9mg/dL or an increase of phosphorus ≥ 7mg/dL lasting for 7 days or more despite phosphate -lowering therapy for 7 days as outlined in Appendix C or according to institutional guidelines.

i) Increase of creatinine (> 1.5 × upper limit of normal [ULN]) lasting for 7 days or more associated with serum phosphorus > 5.5 mg/dL despite phosphate-lowering therapy for 7 days and/or calcium × phosphorus > 55 mg/dL despite phosphate-lowering therapy for 7 days.

j) Grade 2 hypercalcemia for > 7 days or Grade 3 hypercalcemia

k) Ectopic de novo calcification in soft tissues, as determined by the investigator

l) Any > Grade 2 drug-related toxicity that prevents completion of Cycle 1 (> 80% administration of intended dose of TAS-120)

m) Inability to start Cycle 2 within 2 weeks of schedule due to a > Grade 2 drug-related toxicity.

The MTD of TAS-120 is defined as the highest dose level at which less than 33% of the patients experience a DLT during Cycle 1. At least 6 evaluable patients will be enrolled to establish the MTD.

4.1.2. Dose Escalation Scheme

A “3 + 3” design scheme is used for dose escalations. A minimum of 3 patients is treated at each dose level prior to escalation to the next cohort. If none of the initial 3 patients treated at the first dose level experience a DLT during Cycle 1 of therapy, the dose is to

be escalated to the next level. If a DLT is observed in 1 of the first 3 patients, then 3 additional patients is to be enrolled at the same dose level. If none of the 3 additional patients have DLTs after they all complete Cycle 1 of treatment, the dose is to be escalated to the next level. If ≥ 1 of the additional 3 patients develop a DLT, then dose escalation ceases and at least a total of 6 evaluable patients is to be enrolled in the previous dose level to establish the MTD. If 2 of the first 3 patients in a cohort experience DLTs, then dose escalation ceases and at least a total of 6 evaluable patients is to be enrolled in the previous dose level to establish the MTD. No intrapatient dose escalation is allowed.

Based on investigator and sponsor assessment, if further safety evaluations are required, additional 3 to 6 patients may be added to any cohort for a total of up to 12 patients per cohort.

4.1.3. Replacement Criteria

During Phase 1 Dose Escalation, patients who do not complete Cycle 1 of therapy because of a DLT will be considered evaluable and will not be replaced. Patients who withdraw for any reason other than a DLT during Cycle 1, and who have not received at least 80% of the intended TAS-120 dosage, is considered inevaluable and is to be replaced.

4.2. SUBJECT SELECTION

4.2.1. 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 of age.

3. Phase 1 Dose Escalation:

   Patients with histologically or cytologically confirmed advanced, measurable or non-measurable (as defined by Response Evaluation Criteria in Solid Tumors [RECIST] guidelines [version 1.1, 2009]) metastatic solid tumor(s) who have failed all standard therapies or for whom standard therapy does not exist. Starting with Dose Level 5 of each dosing schedule, only patients with locally diagnosed amplification, mutation, translocation or other associated abnormalities of FGF/FGFR will be enrolled (see Protocol Section 8.12, Pharmacogenomic (FGF/FGFR) Analysis).

4. May have received any number of prior therapies for advanced or metastatic disease.

5. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 on Day 1 of Cycle 1 (see Protocol Appendix A, ECOG Performance Status).

6. Able to take medications orally (e.g., no feeding tube).

7. Adequate organ function as defined by the following criteria:

8. 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.
    a. Total serum bilirubin ≤ 1.5 × ULN.
    b. Absolute neutrophil count ≥1 500/mm^3 (i.e., ≥ 1.5 × 10^9/L by International Units [IU]) (excluding measurements obtained within 7 days after administration of granulocyte colony-stimulating factor [G-CSF]).
    c. Platelet count ≥ 100 000/mm^3 (IU: ≥ 100 × 10^9/L) (excluding measurements obtained within 7 days after a transfusion of platelets).
    d. Hemoglobin ≥ 8.0 g/dL (excluding measurements within 4 weeks of a transfusion of packed red blood cells [RBCs] or whole blood).
    e. Serum phosphorus ≤ ULN.
    f. Serum calcium ≤ ULN.
    g. Creatinine < 1.5 × ULN.

9. Women of child-bearing potential must have a negative pregnancy test (urine or serum) within 7 days prior to administration of the first dose of TAS-120. Both males and females of reproductive potential must agree to use adequate birth control during the study and for 6 months after the last dose of TAS-120. Female patients are not considered to be of child bearing potential if they have a history of tubal ligation or hysterectomy or are post-menopausal with a minimum of 1 year without menses.

10. Willing and able to comply with scheduled visits and study procedures.

4.2.2. 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 endocrine alteration of calcium-phosphorus homeostasis.

2. History and/or current evidence of ectopic mineralization/calcification including

but not limited to soft tissue, kidneys, intestine, or myocardia and lung with the exception of calcified lymph nodes and asymptomatic arterial calcification.

3. Current evidence of corneal disorder/keratopathy including but not limited to bullous/band keratopathy, corneal abrasion, inflammation/ulceration, keratoconjuctivitis, etc., confirmed by ophthalmologic examination.

4. History or current evidence of cardiac arrhythmia and/or conduction abnormality.

5. Corrected QT interval (QTc) > 470 msec on electrocardiogram (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 prior to the first dose of TAS-120 or limited field radiotherapy within 2 weeks prior to the first dose of TAS-120.
    c. Any noninvestigational anticancer therapy within 3 weeks prior to TAS-120 administration (mitomycin within prior 5 weeks). Concomitant treatment of Gonadotropin-Releasing Hormone (GnRH) agonists or Luteinizing Hormone-Releasing Hormone (LH-RH) agonists is permitted in prostate cancer patients if they have been on therapy for more than 6 months and tolerating the therapy.
    d. Any medication administered within 7 days prior to first dose of TAS-120 that is known to affect QT interval or to be arrhythmogenic such as, but not limited to, the following drugs (http://crediblemeds.org/pdftemp/pdf/CompositeList.pdf):
        i. Ondansetron
        ii. Erythromycin
        iii. Droperidol
        iv. Halofantrine
    e. Any investigational agent received either concurrently or within the previous 30 days.

7. A serious illness or medical condition(s) including, but not limited to, the following:
    a) Known brain metastasis unless patient is clinically stable and off corticosteroids for ≥ 2 months.
    b) Known leptomeningeal metastasis.
    c) Known acute systemic infection.

d) Myocardial infarction, severe/unstable angina, symptomatic congestive heart failure (New York Heart Association [NYHA] Class III or IV (see protocol Appendix B, New York Heart Association [NYHA] Classification) within the previous 6 months; if > 6 months cardiac function must be within normal limits and the patient must be free of cardiac-related symptoms.
e) Chronic nausea, vomiting, or diarrhea considered to be clinically significant in the opinion of the investigator.
f) Known human immunodeficiency virus or acquired immunodeficiency syndrome-related illness, or a history of serum positivity to hepatitis B or C.
g) Congenital long QT syndrome, or any known history of torsade de pointes, or family history of unexplained sudden death.
h) Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or TAS-120 administration, or may interfere with the interpretation of study results, and in the judgment of the investigator would make the patient inappropriate for entry into this study.

8. Known hypersensitivity to TAS-120 or any drugs similar to it in structure or class.

9. Pregnant or lactating female.

4.3. DETERMINATION OF SAMPLE SIZE

CCI [redacted]

[redacted] Approximately 60 to 120 evaluable patients is to be enrolled in Phase 1 Dose Escalation, including replacements for patients not meeting the DLT-evaluable criteria assuming that all cohorts are filled. In addition, based on investigator and sponsor assessment, if further safety evaluations are required an additional 3 to 6 patients may be added to any cohort.

4.4. TREATMENT ASSIGNMENT & BLINDING

This is an open-label, non-randomized study. Treatment for patients is assigned according to the study design for sequential dose escalation phase.

4.5. ADMINISTRATION OF STUDY MEDICATION

Each treatment cycle is 21 days in duration. During Phase 1 Dose Escalation, TAS-120 is given to patients in each cohort of escalating doses to determine the MTD.

All patients receive TAS-120 at the assigned dose, orally, once a day, 3 times a week (Monday, Wednesday, and Friday) [QOD] or continuously (once daily dosing [QD]) in 21-day treatment cycles. TAS-120 is taken with a glass of water on an empty stomach (2 hours after and 1 hour before a meal).

4.6. STUDY PROCEDURES AND FLOWCHART

The study assessments are summarized in Table 2A. 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 and on the last Wednesday of Cycle 1 (QOD) or Day 21 of Cycle 1 (QD). A window of ± 7 days is allowable for computed tomography (CT) scans and follow-up visits. These windows are not applicable during Screening. If any Screening assessments are repeated on Day 1 of Cycle 1.

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Table 2A: Study Schedule for Phase 1 Dose Escalation

	Screening Period		On-Treatment Period								End-of-Treatment Visit[a]
	Screening Day		Cycle 1 (21 days) Day of Cycle				Subsequent Cycles (21 days) Day of Cycle				30-Day Safety Follow-up Visit[b]
Procedure	-28 to -1	-7 to -1	1	8	15	Last Wednesday of Cycle 1 (QOD) or Day 21 (QD)[c]	1	8	15	21	
Sign ICF	X										
Review inclusion/exclusion criteria	X										
Medical history	X										
ESS		X									
Physical examination		X					X[d]				X
Vital signs[e] and weight		X					X[d]				X
Ophthalmological examination[f]	X							X[f]			
Neurological examination[g]	X										
Height		X									
ECOG Performance Status	X		X				X[d]				X
Electrocardiogram	X		X[h]			X[h]	X[h]				X
Hematology and coagulation[i]		X	X	X	X		X	X[i]	X		X
Serum chemistry[j]		X	X	X	X		X	X[j]	X		X
Urinalysis		X					X[d]				X
Pregnancy test		X									
PK/pharmacodynamic blood sampling[k]			X			X					
PK urine sampling (QOD only)[l]			X								
Pharmacodynamic urine sampling[m]			X			X					
Prior and concomitant medications[n]	X	→	→	→	→	→	→	→	→	→	X
AE/toxicity assessment[o]			X	→	→	→	→	→	→	→	X
Tumor assessment/scans[p]	X									X	X
TAS-120 treatment[q]			X	→	→	→	X	→	→	→	

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	Screening Period		On-Treatment Period								End-of-Treatment Visit[a]
	Screening Day		Cycle 1 (21 days) Day of Cycle				Subsequent Cycles (21 days) Day of Cycle				30-Day Safety Follow-up Visit[b]
Procedure	-28 to -1	-7 to -1	1	8	15	Last Wednesday of Cycle 1 (QOD) or Day 21 (QD)[c]	1	8	15	21	
Tumor tissue sampling for PGx analysis	X[r]										

Abbreviations: AE = adverse event; ECOG = Eastern Cooperative Oncology Group; ESS = existing signs and symptoms; ICF = informed consent form; PGx = pharmacogenomic; PK = pharmacokinetic; QD = once daily (continuous) dosing; QOD = 3-times-a-week (Monday, Wednesday, Friday) dosing.

[a] End of treatment (EOT) Visit (optional): If the decision to discontinue TAS120 is made for reasons other than radiologic disease progression, an EOT visit should be considered to capture the status of the patient at the time of discontinuation. At the EOT visit, serum chemistry, hematology, and coagulation testing will be performed along with any other test deemed clinically indicated by the investigator (e.g., electrocardiogram, ophthalmological examination, neurological examination). The EOT visit should occur within 3 days of the decision to discontinue treatment. The EOT visit does not replace the 30-day safety follow-up visit.

[b] 30-Day Safety Follow-up Visit: If the patient starts new anticancer therapy within 30 days of the last dose of TAS-120, the 30-day safety follow-up visit should be performed before the start of new anticancer therapy. See Section 10.17, 30-Day Safety Follow-up.

[c] Last Wednesday of Cycle 1 (QOD) or Day 21 (QD): only for patients enrolled in Phase 1 Dose Escalation but not required for patients enrolled in Phase 1 Expansion and Phase 2.

[d] Physical Exam, Vital Signs, Weight, ECOG Performance Status, and Urinalysis: Beginning with Cycle 2 and for all subsequent cycles, obtain within 24 hours prior to Day 1 TAS-120 administration.

[e] Vital Signs: Heart rate, blood pressure, body temperature, and respiration rate.

[f] Ophthalmological Examination: Obtain at Screening, at 4 to 6 weeks after starting treatment with TAS-120, and repeat if clinically indicated using the same testing methods. For further details on the scope of the examination, see Section 10.8, Ophthalmological Examination.

[g] Neurological Examination: Obtain at Screening and repeat if clinically indicated using the same testing methods employed at Screening, in addition to any other clinically indicated examinations. For further details on the scope of the examination, see Section 10.9, Neurological Examination.

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[h] Electrocardiogram (ECG) Evaluation: On Day 1 and on the last Wednesday of Cycle 1 (Phase 1 Dose Escalation only, QOD arm), obtain 2 hours after the TAS-120 dose. On Day 1 and Day 21 of Cycle 1 (Phase 1 Dose Escalation only, QD arm), obtain at 2 hours after the TAS-120 dose. For all subsequent cycles starting with Cycle 3 (Phase 1 Dose Escalation) or Cycle 2 (Phase 1 Expansion and Phase 2), ECG should be performed on Day 1 (± 3 days) of each cycle obtained 2 at hours after the TAS-120 dose, see Section 10.7, Electrocardiogram (ECG) Evaluation.

[i] Hematology and Coagulation: Obtain within 24 hours prior to TAS-120 administration on Day 1 of each cycle, and anytime on Day 8 and Day 15 of Cycle 1 and Cycle 2 (± 3 days). Starting with Cycle 3, the Day 8 assessment is no longer required, unless deemed clinically indicated by the investigator. For more details, see Section 10.10.1, Hematology and Coagulation.

[j] Serum Chemistry: Obtain within 24 hours prior to TAS-120 administration on Day 1 of each cycle, and anytime on Day 8 and Day 15 of Cycle 1 and Cycle 2 (± 3 days). For more details, see Section 10.10.2. Starting with Cycle 3, the Day 8 assessment is no longer required, unless deemed clinically indicated by the investigator or if previous serum chemistries showed an elevation of phosphorus that required action as specified Section 9.1.1.1.1 .

[k] PK/Pharmacodynamic Blood Sampling: During Phase 1 Dose Escalation, collect PK/pharmacodynamic blood samples at the following time points on Day 1 and on the last Wednesday of Cycle 1 (QOD) or on Day 1 and Day 21 of Cycle 1 (QD): immediately prior to dosing (0 hour) and postdose at 30 minutes and 1, 2, 3, 4, 6, 8, 12, 24 (QOD and QD), and 48 hours (QOD only). The 48-hour postdose sample (QOD) and the 24-hour postdose sample (QD) must be collected prior to TAS-120 administration on that day. See Section 10.13.1, Pharmacokinetic/Pharmacodynamic Blood Sample Collection.

[l] PK Urine Sampling (QOD only): During Phase 1 Dose Escalation, PK urine samples will be collected predose on Day 1 of Cycle 1 and from 0 to 12, 12 to 24, and 24 to 48 hours postdose. The 24- to 48-hour postdose sample (QOD) must be collected prior to TAS-120 administration on Day 3 of Cycle 1. See Section 10.13.2, Pharmacokinetic Urine Sample Collection (QOD Arm Only).

[m] Pharmacodynamic Urine Sampling: During Phase 1 Dose Escalation, collect pharmacodynamic urine samples at the following time points on Day 1 and the last Wednesday of Cycle 1 (QOD) or on Day 1 and Day 21 of Cycle 1 (QD): predose and from 0 to 12, 12 to 24, and 24 to 48 hours (QOD arm only) postdose. The 24- to 48-hour postdose sample (QOD) must be collected prior to TAS-120 administration on Day 3 and the last Friday of Cycle 1. The 12- to 24-hour postdose sample (QD) must be collected prior to TAS-120 administration on Day 2 and Day 22 of Cycle 1. See Section 10.13.4, Pharmacodynamic Urine Sample Collection, for detailed description of the pharmacodynamic urine sampling schedule.

[n] Prior and Concomitant Medications: Collect from the time the ICF is signed through 30 days after administration of the last dose of TAS-120.

[o] Adverse Event Assessment: Collect from the time of the first dose of TAS-120 through 30 days after administration of the last dose of TAS-120.

[p] Tumor Assessments/Scans for Solid Tumors: Perform the same tumor assessments/scans obtained at Screening at the end of every 2 cycles (± 7 days) up to Cycle 4. Thereafter tumor assessments and scans may be performed every 3 cycles, or as clinically indicated. See Section 10.16.1 , Solid Tumor Assessment/Scans Section 10.16.2 for details. Computed tomography scans obtained before the ICF is signed may be used as the screening tumor scan if done within 28 days of the first dose of TAS-120. A CT scan must be performed within 2 weeks of discontinuation of TAS-120 treatment, if the patient discontinued for reasons other than radiological disease progression. For scheduled tumor assessments thereafter, see Section 10.16.1 , Solid Tumor Assessment/Scans, Section 10.16.2 and Section 11.1, Efficacy Assessment for Solid Tumors.

[q] TAS-120 Treatment: QOD arm: TAS-120 will be administered orally, once daily, in the morning (Phase 1 Dose Escalation only) with a glass of water on an empty stomach, 3 times a week (Monday, Wednesday, and Friday) between Days 1 through 21 of each cycle. See Section 9.1.1, Treatment Regimen, for TAS-120 dose levels. QD arm: TAS-120 will be administered orally, once daily, in the morning (Phase 1 Dose Escalation only) with a glass of water on an empty stomach, continuously on Days 1 through 21 of each cycle. See Section 9.1.1, Treatment Regimen, for TAS 120 dose levels.

[r] Tumor Tissue Sampling for PGx Analysis: Previously collected archived tumor tissue samples (PGx samples) from patients with solid tumors must be shipped to the central PGx laboratory designated by the sponsor, after patients have provided informed consent. For Phase 1 Dose Escalation and Phase 1 Expansion, patients can be enrolled before central PGx laboratory confirmation of FGF/FGFR abnormality has been obtained; however, if available, the archived PGx tissue sample should be collected and shipped to the central laboratory after the signing of the ICF. For Phase 2, refer to the Pharmacogenomic Operation Procedure Manual provided by the sponsor.

5. ENDPOINTS

This study is to evaluate safety, tolerability, PK, pharmocodynamic, and antitumor activity of the TAS-120 in patients with advanced solid tumors. The efficacy, safety, pharmacokinetic and other endpoints in the study are listed below. The detailed information regarding collections and analysis methods is presented in Sections 9, 10, 11, and 12.

5.1. SAFETY ENDPOINTS

5.1.1. Adverse Events

An adverse event (AE) is any untoward medical condition that occurs in a patient while participating in this clinical study. Treatment-Emergent AEs (TEAEs) are those AEs that occur from the initiation of TAS-120 administration to 30 days after the last dose of study medication, and do not necessarily have a causal relationship to the use of the study medication. The TEAEs will be summarized.

5.1.2. Laboratory Evaluations

Safety laboratory test results will be collected. All applicable hematological and chemistry laboratory parameters will be graded using computer algorithm per numeric ranges defined in the NCI Common Terminology Criteria for Adverse Events (CTCAE), v4.03. The related endpoints include the worst severity grade will be summarized.

5.1.3. Vital Signs and Body Weight

Vital signs (blood pressure, heart rate, body temperature, and respiration rate) and body weight will be collected.

5.1.4. ECG

The 12-lead resting electrocardiogram (ECG) will be performed. ECG findings including QT Interval, QTcB, QTcF and RR interval will be recorded and described in Section 10.7.

5.1.5. Physical Examination

The physical examination will also be performed in the study.

5.2. PHARMACOKINETIC ENDPOINTS

For Phase 1 Dose Escalation, the PK parameters in blood 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.

- 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
- $T_{1/2}$ Terminal half-life time
- R_{Cmax} Accumulation ratio calculated based on C_{max}
- R_{AUC} Accumulation ratio calculated based on AUC_{0-last}

The following parameters will be calculated on only 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)

5.3. PHARMACODYNAMIC ENDPOINTS

For pharmacodynamics evaluations in blood, serum phosphorus and FGF23 will be determined. For the urine pharmacodynamics evaluation, phosphorus and calcium in urine will be determined.

5.4. EFFICACY ENDPOINTS

Tumor measurements using radiological imaging studies will be collected. The investigator will evaluate the imaging studies for tumor response and/or progression. Response assessment will be made based on the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (version 1.1, 2009).

Statistical Analysis Plan

The efficacy endpoints in the study are Best Overall Response, overall response rate (ORR), disease control rate (DCR), and duration of response (DR). In addition, time to radiological progression and/or progression-free survival may be explored as appropriate.

6. ANALYSIS SETS

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

6.1. SAFETY POPULATION

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

6.2. DLT EVALUABLE POPULATION

The DLT evaluable population will include all patients in Phase 1 Dose Escalation who either experience a DLT during the first cycle of treatment or who complete the first cycle of with at least 80% of planned study medication (TAS-120) administered. MTD determination will be based on this population.

6.3. PK AND PHARMACODYNAMIC POPULATION

The PK and pharmacodynamic population in Phase 1 Dose Escalation 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.

6.4. EFFICACY POPULATION

The efficacy population will include all patients in the safety population.

6.5. PROTOCOL DEVIATIONS

The protocol deviations may include: informed consent errors, not meeting an eligibility criterion, study drug overdose or other incompliance. The details will be included in TPU-TAS-120-101 Protocol Deviation Definition Document. The major protocol deviations may be summarized while the minor protocol deviations will only be listed.

7. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

7.1. GENERAL METHODS

All relevant data will be presented in patient data listings.

All categorical (binary and ordinal) data will be summarized using frequency counts and percentages of patients. Percentage will be calculated using the corresponding treatment group in the study population as the denominator. The continuous variables will be summarized using number of non-missing observation (n), mean, standard deviation (SD), median, minimum and maximum unless otherwise specified. For example, the numbers of events and censorings will be reported for time-to-event analysis. All estimations will include a point estimate and the corresponding 95% confidence interval.

Summary tables will be presented by dosing schedule (i.e., QOD and QD), dose level and overall. Data listings will be ordered by assigned dosing schedule, dose level and patient ID. The dose levels presented in tables and listings for Phase 1 Dose Escalation are:

8 mg QOD, 16 mg QOD, 24 mg QOD, 36 mg QOD, 56 mg QOD, 80 mg QOD, 120 mg QOD, 160 mg QOD, 200 mg QOD, 240 mg QOD;

4 mg QD, 8 mg QD, 16 mg QD, 20 mg QD, 24 mg QD, 36 mg QD, 56 mg QD, 80 mg QD, 120 mg QD, 160 mg QD, 200 mg QD, and 240 mg QD if applicable.

For concomitant medications and adverse events, the cycles are determined based on their start/onset dates. For other collected data, the cycles are determined based on their visit dates.

When there are multiple laboratory records for a scheduled visit, the one closest to the target date (relative to the Day 1 in that cycle) will be used for analysis. If there are two or more records with the same time period to the target date, the later one will be used for analysis. However, the baseline for laboratory test is the defined as the latest laboratory result prior to the first dose of study medication.

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

CCI [redacted]

7.2. KEY DEFINITIONS

7.2.1. First Dose Date

First dose date in the study is defined as the first dose of TAS-120 in Cycle 1.

7.2.2. Cut-Off Date of Final Analysis

For the purpose of final analysis, the cut-off date is defined as the date which all patients either discontinue from the treatment or have sufficient follow-up (more than 6 months) from the date of the first day of treatment with TAS-120 of the last patient enrolled, whichever occurs first.

7.2.3. Last Dose Date

For the purpose of analysis, the last dose date is defined as the last dose date of TAS-120 for the patient or the cut-off date of final analysis, whichever occurs first.

7.2.4. Study Day

The study day in the study is the days relative to the first dose date in the study, while the cycle day is the days relative to the first dose date in that cycle.

7.2.5. Treatment Duration

The overall treatment duration is defined as last dose date – first dose date+1.

7.3. MISSING DATA

Missing data will not be imputed. Complete missing or partial date will be presented in the listings as reported on CRFs.

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

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

Table 4: Partial Date Imputation for TEAE Determination

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

The above rule is also used for determining the cycles of adverse events and concomitant medications.

The derived date is only used for determining TEAEs, cycle of adverse events and concomitant medications. The collected partial dates will be reported in the listings.

8. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

8.1. SUBJECT DISPOSITION AND WITHDRAWALS

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

8.2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographics and baseline characteristics (age, gender, ethnicity, race, weight, and height) will be summarized by dose level and overall for Phase 1 Dose Escalation.

8.3. MEDICAL HISTORY

Medical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA 17.0). Medical history will be listed by dose level or disease type, patient number, start date and end date. There is no imputation for dates for medical history.

8.4. OTHER BASELINE DISEASE CHARACTERISTICS

The cancer type (NSCLC, breast cancer, gastric cancer and other solid tumor), FGF/FGFR status (FGFR1 amplification, FGF19 amplification etc) by local genotyping assay) will be summarized by dose level and overall by dosing schedule .

Pre-study surgery and prior radiation therapy will be summarized by dose level and overall by dosing schedule. For pre-study surgery, the number and percentage of patients with biopsy, primary tumor removal, metastatic tumor removal, and other surgeries will be reported. For prior-radiation therapy, the number and percentage of patients with palliative and therapeutic radiation therapies will be presented in the summary table.

All prior anticancer therapies (adjuvant therapies, neoadjuvant therapies, therapies for advanced/metastatic disease, and maintenance therapies including prior FGFR inhibitor) will be summarized by dose level and overall by dosing schedule. The number of patients with 1, 2, 3 and >=4 prior regimens will be summarized for all anticancer therapies and for advanced/metastatic disease only.

All collected information for cancer diagnosis, pre-study surgery, prior-radiation therapy, and prior anti-cancer therapy will also be listed.

8.5. MEDICATION

Prior or concomitant medications will be collected from the time of informed consent through 30 days after administration of last dose of study medication.

Medications which started and stopped prior to the first dose of TAS-120 are considered as prior medications. Medications which started prior to the first dose of TAS-120 and continued into the treatment period are considered as prior and concomitant medications.

Medications with a start date from first dose of TAS-120 to 30 days after administration of the last dose of TAS-120 will be considered as concomitant medications.

Prior and concomitant medications will be coded according to World Health Organization (WHO) Drug Dictionary (WHODrug version March 2014) for Concomitant Medication. The concomitant medications will be summarized by ATC level 2 (Therapeutic Main Group) and ATC level 4 (Chemical/Therapeutic Subgroup) using the number and percentage of patients by dose level and overall. Medications will be sorted in descending order of frequency of ATC level 2 and ATC level 4 within ATC level 2 in the total column. A patient will be counted only once within each level of summation if the patient has taken a medication more than once.

All prior and concomitant medications will be listed.

9. EFFICACY

Solid Tumor Assessments

Tumor assessments/imaging studies of the chest, abdomen, and pelvis (as clinically indicated) will 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 (± 7 days), up to Cycle 4.
- Following Cycle 4, at least after every 3 cycles or as clinically indicated.
- Within 2 weeks after 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 for target lesions, non-target lesions and overall responses are provided in the following Tables 5, 6, 7 and 8.

Table 5: Assessments for Target Lesions

TARGET LESIONS	
Lesion 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.

Table 6: Assessments for Non-Target Lesions

NON-TARGET LESIONS	
Lesion 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).

Table 7: Overall Response Assessment with Target Lesions

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

Table 8: Overall Response Assessment without Target Lesions

Non-target Lesions	New Lesions	Overall 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

For Phase 1 Dose Escalation, only on-site tumor assessments will be conducted.

9.1. BEST OVERALL RESPONSE

The best overall response is the best response recorded from the start of treatment until progressive disease or the start of subsequent anticancer treatment.

Statistical Analysis Plan

For patients with solid tumors, according to RECIST guideline (Version 1.1, 2009), to be assigned a status of PR or CR, changes in tumor measurements in patients with responding tumors must be confirmed at least 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.

At the analysis stage, the best overall response will be assigned for each patient as the best response recorded from all time point responses recorded from the start of treatment. Confirmation of partial response and complete response will follow the confirmation process contained in the following table where the best two consecutive time points are considered. Best overall response both with confirmation of partial response and complete response and without confirmation of partial response and complete response will be summarized.

Earlier Response (not yet confirmed)	**Later Response (confirmation)**	**Confirmed Response**
Complete Response	Complete Response	Complete Response
Complete Response	No Complete Response or missing	Stable Disease
Partial Response	Complete Response or Partial Response	Partial Response
Partial Response	Stable Disease or Progressive Disease or missing	Stable Disease
Partial Response	Stable disease and then partial response (only one SD in between)	Partial Response
Stable Disease	n/a – no confirmation needed	Stable Disease
Progressive Disease	n/a – no confirmation needed	Progressive Disease

9.2. OBJECTIVE RESPONSE RATE

The objective response rate (ORR) is defined as the proportion of patients who achieved best overall response of ≥ partial response (PR) in the Efficacy Population (CR or PR for solid tumor patients. ORR based on the Investigator's assessments will be summarized by disease type (for example NSCLC with FGFR1 amplification, breast cancer with FGFR1 amplification, gastric cancer with FGFR2 amplification, and other solid tumors with other alternative FGF/FGFR abnormality) by dosing schedule and overall. The corresponding 90% and 95% confidence intervals will be presented.

9.3. DURATION OF RESPONSE

Duration of response 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 progressive disease (PD) or death due to any cause.

After the first documentation of response, patients who are alive and progression free during the treatment period and follow-up will have their event time censored on the last tumor assessment date in the study treatment. For the purpose of final analyses for dose escalation phase, the last assessment date should be prior to the cut-off date of final analysis for which all patients either discontinue from the treatment or have sufficient follow-up (more than 6 months) from the date of the first day of treatment with TAS-120 of the last patient enrolled, whichever occurs first. For patients who start another anticancer treatment, their events should be censored at the last tumor assessment prior to the new treatment.

Time to response and Duration of response will be listed for Efficacy Population for Phase 1 Dose Escalation.

10. SAFETY

The population used for safety analyses will be the Safety Population. Safety will be assessed on the basis of adverse event (AE) reports, clinical laboratory data, ECG parameters, physical examinations, vital signs and body weight, performance status, ophthalmological examination, and neurological examination.

10.1. EXTENT OF EXPOSURE

The actual dosage in the study for TAS-120 will be calculated for capsules and dosage. Since the patients may have different treatment periods, the average daily dose is defined as the dosage divided by actual dose duration, which is the sum of all cycle treatment period prior to the cut-off date of final analysis.

The cycles initiated and completed, extent of exposure (treatment duration), and total dosage for TAS-120 will be summarized by dose level and overall for Phase 1 Dose Escalation by dosing schedule.

Relative dose intensity (RDI) is defined as the ratio of the amount of drug actually administered to the amount planned in the study for TAS-120. The relative dose intensity from Day 1 of Cycle 1 is calculated in the following steps:

1. For each cycle, calculate the actual total dose administered in mg for TAS-120.

2. The total dose administered in mg is the sum of all cycle total doses administered in mg in the study.

3. Total treatment duration in weeks for dose intensity calculation = (last dose date – first dose date +1) for QD; or (last dose date – first dose date +2) for QOD .

4. Weekly Dose Intensity = Total dose administered in mg divided by total treatment duration in weeks.

5. Relative Dose Intensity = Weekly Dose Intensity divided by the planned weekly dose in mg, which is the planned dose level in mg/day multiplied by 3.5 for QOD and multiplied by 7 for QD. The Relative Dose Intensity will be expressed in percentage.

Relative dose intensity will be summarized by dose levels and dosing schedule for cycle 1 and for all cycles.

In addition, patients with TAS-120 dose reductions from the previous cycle, patients with dose reductions due to AEs, patients with dose held/delays due to AEs, and patients with treatment discontinuations due to AEs will be summarized for the entire study.

All recorded information for study medication administration and accountability for TAS-120 will be listed.

10.2. DOSE LIMITING TOXICITY

The dose limiting toxicity in the first cycle of Phase 1 Dose Escalation will be presented by dose level and overall for Safety Population by dosing schedule. The compliance to the 3+3 design scheme for dose escalation rules will be shown in the table.

10.3. ADVERSE EVENTS

An adverse event (AE) is any untoward medical condition that occurs in a patient while participating in this clinical study. 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, v4.03, where applicable.

Treatment-Emergent Adverse Events (TEAEs) are those adverse events that occur from the initiation of TAS-120 medication administration to 30 days after the last dose of study medication, and do not necessarily have a causal relationship to the use of the study medication. Treatment-Emergent Adverse Events (simply referred to as adverse events in summary tables) will be summarized.

A Serious Adverse Event (SAE) is an AE which falls into one or more of the following categories:

a. Results in death
b. Is life-threatening
c. Requires inpatient hospitalization or prolongation of existing hospitalization
d. Results in persistent or significant disability or incapacity
e. Is a congenital anomaly/birth defect
f. Is any other important medical event

All deaths occurring through the 30-day follow-up period is reported as outcomes of SAEs. Signs, symptoms and complications related to disease progression should be reported as AE or SAEs. Clinical disease progression may only be reported as an SAE term if none of the relevant signs or symptoms supports a fatal outcome. While those

severe AEs are classified into Grade 3 AEs, those life-threatening AEs are classified into Grade 4 AEs.

Adverse Events will be summarized by dose level and overall for Phase 1 Dose Escalation. AEs will be presented by system organ class in the overall column in decreasing order. Within each system organ class, the AEs will be displayed by preferred term (PT) in decreasing order in the overall column.

The following adverse event summary tables will be generated:

1) An overall summary with the number and percentage of patients reporting AEs, serious AEs, grade 3 or higher AEs, treatment-related AEs, Dose Limiting Toxicities, AEs leading to study treatment (TAS-120) discontinuation and AEs with outcome of deaths. Summary with combined groups will also be generated.

2) AEs overall and by system organ class and preferred term.

   In the summary, a patient is counted once at the system organ class and once at each preferred term within the system organ class. Additional summary by system organ class, preferred term and grade (including Total and >= grade 3 categories) will also be generated.

3) Study-treatment-related AEs overall and by system organ class and preferred term. Additional summary by system organ class, preferred term and grade (including Total and >= grade 3 categories) will also be generated.

   All those AEs with relationship to TAS-120 marked as “Related” or missing will be reported in the table.

4) AEs by highest grade (worse severity) overall and by system organ class and preferred term.

   In the summary, a patient is counted once at the highest grade for which the event occurred in the system organ class and the highest grade for each unique preferred term within that system organ class. Therefore, patients may only contribute once to each preferred term and once to each system organ class. The missing severity grade will be reported in a separate category.

5) Serious AEs, overall and by system organ class and preferred term. Additional summary by system organ class, preferred term and grade (including Total and >= grade 3 categories) will also be generated.

6) Grade 3 or higher AEs, overall and by system organ class and preferred term

7) Study-treatment related AEs by grade (severity) , overall and by system organ class and preferred term

8) AEs leading to study treatment termination, overall and by system organ class and preferred term. Additional summary by system organ class, preferred term and grade (including Total and >= grade 3 categories) will also be generated.

9) AEs with outcome of deaths, overall and by system organ class and preferred term

In addition, the time to onset of some special AEs of interest in the study may be summarized if appropriate.

Dose limiting toxicity list will be provided based on the DLT evaluable population.

10.4. LABORATORY EVALUATIONS

Blood samples for hematology, coagulation and serum chemistry assessments are collected and measured at baseline (within 7 days prior to study medication administration on Day 1 of Cycle 1), within 24 hours prior to Day 1 study drug administration of each cycle, anytime on Day 8 and Day 15 of Cycle 1 and Cycle 2, the end of treatment visit and 30-day safety follow-up visit. Starting with Cycle 3, the Day 8 assessment is not required, unless deemed clinically indicated by the investigator. Creatine kinase needs to be repeated on Day 1 of Cycle 2. Fractionation of CK into its isoforms must be performed in case of an elevation of CK (unless the isoform CK [isoform skeletal and heart muscle] [CK-MM and CK-MB] was tested, in which case a fractionation is no longer needed). If CK is abnormally elevated at Screening (Day -7 to -1), the results of the fractionation must be available prior to starting TAS-120 treatment for that patient.

Hematology and coagulation parameters that will be measured include: RBC count, Hemoglobin, Hematocrit, Platelets, INR, APTT, White blood cell (WBC) count with differential, Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils. Serum chemistry parameters that will be measured include: ALT (SGPT), AST (SGOT), Alkaline phosphatase, Total bilirubin, Albumin, Creatinine, Blood urea nitrogen (BUN), Phosphorus, Calcium, Chloride, Sodium, Potassium, Bicarbonate, Glucose, CK, and CRP and ß2-microglobulin for multiple myeloma only. Fractionation of bilirubin (direct/indirect bilirubin or conjugated/unconjugated) must be performed in case of an elevation of total bilirubin.

Urine sample for qualitative analysis are only collected at baseline (within 7 days prior to study medication administration on Day 1 of Cycle 1), within 24 hours prior to study medication administration on Day 1 beginning with Cycle 2, the end of treatment visit and 30-day safety follow-up visit. The following parameters will be measured: protein, glucose, and urine density.

The website http://www.globalrph.com/conv_si.htm provides conversion factors between SI units and Conversion units.

The CTCAE grades of Hemoglobin, Platelet, INR, APTT, White blood cell (WBC) count with differential, Neutrophils, Lymphocytes, Fibrinogen, ALT (SGPT), AST (SGOT), Alkaline phosphatase, Bilirubin, Albumin, Creatinine, Calcium, Sodium, Potassium, and Glucose will be determined using computer algorithm only based on the numerical component of CTCAE v4.03 grading scale. For the parameters with uni-directional criteria, the CTCAE grade will be derived from 0 to 4. For the parameters with bi-directional criteria, the CTCAE grade will be derived from both low and high direction. Grade 0 is defined for a non-missing value which doesn't meet any criteria and within the normal range.

The worst severity grade during the treatment and 30 days follow-up will also be summarized descriptively. For the parameter with bi-directional criteria, both highest and lowest grade will be summarized. The worst grade in cycle 1 also will also be summarized in same way.

The shift in CTCAE grades from baseline to the worst grade in Cycle 1, and Entire Study for bi-directional parameters and unidirectional parameters will be presented. For all lab tests, a shift table in normal range from baseline to the worst grade in Cycle 1, and Entire Study will also be presented.

All collected laboratory hematology, coagulation, serum chemistry and urinalysis results will be listed. The normal laboratory ranges provided by laboratory will be also listed.

10.5. VITAL SIGNS AND BODY WEIGHT

Vital signs (blood pressure, heart rate, body temperature, and respiration rate) and body weight are collected at baseline (within 7 days prior to study medication administration on Day 1 of Cycle 1), within 24 hours prior to study drug administration on Day 1 beginning with Cycle 2, the end of treatment visit and 30-day safety follow-up visit.

The observed values of vital sign and weight and their changes from baseline at these scheduled visits will be summarized descriptively by cohort and overall. When the

multiple results recorded at the same visit, the last valid result will be used for the summary. All values for vital sign and weight collected on eCRFs will be listed.

10.6. ECG

The 12-lead resting electrocardiogram (ECG) are performed at screening (within 28 days prior to the study medication administration on Day 1 of Cycle 1), 2 hours after the dose on Day 1 of Cycle 1 and the last Wednesday of Cycle 1 (QOD arm) or 2 hours after study medication administration on Day 1 and Day 21 of Cycle 1 (QD arm) for patients enrolled in Phase 1 Dose Escalation, and the end of treatment visit and 30-day follow-up visit. For UK Protocol version, the 12-lead resting ECG is also performed at Day 1 ± 3 days beginning with Cycle 3 (Phase 1 Dose Escalation).

A summary table reported the counts and percentage of Normal and Abnormal (CS, NCS) ECG will be presented for safety population and UK safety subgroup.

For QT Interval, and its Fridericia's correction, the absolute QT/QTc interval prolongation are defined in three different ways as: (1) QT (QTc) interval>450 ms; (2) QT (QTc) interval>480 ms; (3) QT (QTc) interval>500 ms. The change from baseline in QT (QTc) interval are defined in two different categories as: (1) QT(QTc) interval increases from baseline >30 ms; (2) QT(QTc) interval increases from baseline >60 ms. The number and percentage of patients meeting the above different categories will be summarized by dose level and overall for safety population and UK safety subgroup. A graph for QT interval and its Fridericia's correction may also be presented.

10.7. PHYSICAL EXAMINATION

Physical examination are performed at baseline (within 7 days prior to study medication administration on Day 1 of Cycle 1), within 24 hours prior to study drug administration on Day 1 beginning with cycle 2, the end of treatment visit and 30-day safety follow-up visit. The physical examination data is presented in a data listing.

10.8. PERFORMANCE STATUS

ECOG performance status is recorded at baseline (within 28 days prior to study medication administration on Day 1 of Cycle 1), Day 1 of cycle 1 prior to first dose, within 24 hours prior to study drug administration on Day 1 beginning with Cycle 2, the end of treatment visit and 30-day safety follow-up visit.

ECOG Performance Status scores have 6 different grades from 0 to 5 and described in the following table:

Table 10: Eastern Cooperative Oncology Group

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

The change from Day 1 in Cycle 1 in the ECOG Performance Status scores will be presented in a shift table by cohort and overall.

10.9. OPHTHALMOLOGICAL EXAMINATION

Ophthalmological examination will be performed at baseline (within 28 days prior to study medication administration on Day 1 of Cycle 1) and 4-6 weeks after the first dose. The examination will be repeated, if clinically indicated, and the repeat examination will include the same testing employed at baseline in addition to any other clinically indicated examination. Ophthalmological examination result will be listed.

10.10. NEUROLOGICAL EXAMINATION

Neurological examination will be performed at baseline (within 28 days prior to study medication administration on Day 1 of Cycle 1). The basic neurologic examination 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 baseline in addition to any other clinically indicated examination. Neurological examination result will be listed.

10.11. PREGNANCY TEST

If the patient is female and of child bearing potential, a serum or urine ß-HCG pregnancy test will be performed 7 days prior to the first administration of the study drug. Pregnancy test result will be listed.

11. PHARMACOKINETICS

INC Research Biostatics Group is responsible for the calculation of pharmacokinetic parameters statistical analysis, production and quality control of TLFs of the PK data.

11.1. SAMPLE COLLECTION

During Phase 1 Dose Escalation, blood samples for pharmacokinetic analysis will be collected at the following time points on Day 1 of Cycle 1 (C1D1) and on the last Wednesday of Cycle 1 (C1LW) (QOD arm) or on Day 1 of Cycle 1 (C1D1) and Day 21 of Cycle 1 (C1D21) (QD arm):

pre-dose (-0.5hr) and after the morning dose at 0.5 hr (± 0.1 hr), 1 hr (± 0.1 hr), 2 hr (± 0.2 hr), 3 hr (± 0.2 hr), 4 hr (± 0.5 hr), 6 hr (± 0.5 hr), 8 hr (± 0.5 hr), 12 hr (± 2 hr), 24 hr (± 2 hr) (QOD and QD arms), and 48 hr (± 2 hr) (QOD only).

The 48-hour postdose sample (QOD arm) and the 24-hour postdose sample (QD arm) must be collected prior to TAS-120 administration on that day.

During Phase 1 Dose Escalation, urine samples for pharmacokinetic analysis of TAS-120 will be collected on Day 1 of Cycle 1 (QOD arm) at the following time points:

pre-dose, 0 to 12 hr (±2 hr), 12 to 24 hr (±2 hr), and 24 to 48 hr (±2 hr).

The 24 to 48 hours postdose sample must be collected prior to TAS-120 administration on Day 3 and the last Friday of Cycle 1.

11.2. PK PARAMETERS TO BE CALCULATED

The following PK parameters will be calculated for Day 1 of Cycle 1 (C1D1) and the last Wednesday of Cycle 1 (C1LW) in QOD arm, and for C1D1 and Day 21 of Cycle 1 (C1D21), according to the non-compartment method. $AUC_{0\text{-}inf}$, MRT, CL/F and Vd/F will be calculated only for C1D1. Urine PK parameter will be calculated for only C1D1 in QOD arm. The calculated PK parameters will be summarized by study arm, dose levels and study periods.

Plasma PK parameters:

- C_{max} (ng/mL): Maximum concentration in plasma
- T_{max} (hr): Time to reach maximum concentration in plasma
- $AUC_{0\text{-}last}$ (ng·hr/mL): Area under the concentration-time curve up to the last observable concentration

- $AUC_{0\text{-}inf}$ (ng·hr/mL): Area under the concentration-time curve up to infinity on C1D1 calculated as follows:

  $AUC_{0\text{-}inf} = AUC_{0\text{-}last} + C_{last}/\lambda z$

  where C_{last} is the last measurable plasma concentration and λz is the elimination rate constant after the AM dose estimated using log-linear regression during the elimination phase. The points used in the λz calculation will be determined by visual inspection of the data describing the elimination phase and at least three time points will be used in λz calculations.

- $AUC_{0\text{-}24}$ (ng·hr/mL): Area under the concentration-time curve up to 24 hours estimated as partial area (QD arm)

- $AUC_{0\text{-}48}$ (ng·hr/mL): Area under the concentration-time curve up to 48 hours estimated as partial area (QOD arm)

- $T_{1/2}$ (hr): Terminal half-life time = ln(2)/ λz

- MRT (hr): Mean residence time = $AUMC_{0\text{-}inf}/AUC_{0\text{-}inf}$

  where $AUMC_{0\text{-}inf}$ is the area under the first moment curve (AUMC) extrapolated to infinity.

- CL/F (L/hr): Oral clearance = Dose/$AUC_{0\text{-}inf}$

  where the dose will be the actual dose per body of TAS-120.

- Vd/F (L): Apparent volume of distribution = (CL/F)/λz

- R_{Cmax}: Accumulation ratio calculated based on C_{max}
  = C_{max} (C1LW or C1D21)/ C_{max} (C1D1)

- R_{AUC}: Accumulation ratio calculated based on $AUC_{0\text{-}last}$
  = $AUC_{0\text{-}last}$ (C1LW or C1D21)/$AUC_{0\text{-}last}$ (C1D1)

Urine PK parameters:

- Ae% (%): Urinary excretion rate as % of dose = Ae(total amount of excretion)/dose
- CLr (mL/min): Renal clearance = Ae(total amount of excretion)/$AUC_{0\text{-}48}$

11.3. PLASMA AND URINE CONCENTRATION DATA

Plasma and urine concentration data will be assayed at Covance Laboratories Inc. as per the sample analysis outline of the bioanalytical study below.

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[redacted]

11.4. PK SAMPLE COLLECTION TIME

The calculation of PK parameter in plasma will be based on the actual time after the dosing. The values will be calculated as "actual clock time of blood collection" – "actual clock time of dosing" to obtain actual hours after dose. The actual time after dose will be summarized by study arm, dose levels and study periods according to nominal collection time. The urine PK parameters will be summarized according to nominal collection period, without any corrections with actual sampling time. The concentration data out of the time window will not be excluded from analysis unless the time point is overlapped with adjacent time points.

11.5. CALCULATION OF PLASMA PK PARAMETERS

Estimation of pharmacokinetic parameters in plasma will be performed using Phoenix™ WinNonlin® (Certara, L.P.), Version 6.4 or later software.

The PK parameters of interest are C_{max}, T_{max}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$ (C1D1 only), $AUC_{0\text{-}24}$, $T_{1/2}$, MRT (C1D1 only), R_{Cmax}, R_{AUC}, CL/F (C1D1 only), and Vd/F (C1D1 only). The C_{max} and T_{max} are obtained from experimental observations. If the maximum plasma concentration occurs at 2 or more time points, the T_{max} is assigned to the time of the earliest occurrence. In determining the T_{max}, the actual time of the plasma sample relative to the dosing time will be used.

The BLQ value will be handled as follows for the calculation of plasma PK parameters:

- The time of collection of the pre-dose sample will be set to zero;
- Actual post-dose sampling times are expressed relative to the time of dosing;
- Plasma concentrations below the LLOQ in the pre-dose sample(s) and in early time-points (lag-time) will be treated as zero, if applicable;

- Plasma concentrations below the LLOQ appearing in terminal samples will be treated as missing values;
- Plasma concentrations below the LLOQ in the middle of the curve that are flanked by measurable concentrations will be treated as missing values.

At the first dosing (C1D1), if the predose concentration is ≤ 5 percent of C_{max} value in that subject, the subject's data without any adjustments can be included in all pharmacokinetic measurements and calculations. If the predose value is > than 5 percent of C_{max}, the subject will be dropped from all PK evaluations.

The AUCs are calculated using noncompartmental analysis. The actual time of the plasma sample relative to the dosing time is used to calculate the AUCs. In calculating the AUCs a linear trapezoidal method is used for all portions of the plasma concentration-time curve. The $AUC_{0\text{-}inf}$ is calculated as the $AUC_{0\text{-}last}$ + $C_{last}/\lambda z$ where $AUC_{0\text{-}last}$ is the area under the curve from 0 to the last quantifiable concentration, C_{last} is the last quantifiable concentration observed and λz is the absolute value of the slope of the terminal log-linear phase.

The λ_z will be calculated using the log-linear regression. Visual inspection and improvement in the adjusted RSQ will be used to determine those time points prior up to but not including the C_{max}. The elimination half-life ($T_{1/2}$) is calculated as ln(2)/ λz.

The parameter estimates for $T_{1/2}$, $AUC_{0\text{-}inf}$, MRT, CL/F and Vd/F will not be calculated if ANY of the following conditions are met:

- Insufficient number of time points (less than 3) are available for calculating the slope of the log-linear regression line

- The adjusted RSQ is less than 0.81

- The percent of area extrapolated (time of last quantifiable plasma concentration to infinity) accounts for more than 20% of the $AUC_{0\text{-}inf}$ ($AUC_{0\text{-}last}$ / $AUC_{0\text{-}inf}$ is less than 0.80).

11.6. CALCULATION OF URINE PK PARAMETERS

The urine PK parameters will be determined for TAS-120 on C1D1. The amount of TAS-120 excreted in each urine collection will be calculated by multiplying the volume (in mL) by the concentration. Total amount of urinary excretion from time zero to 48 hours postdose (Ae mg) for TAS-120 will be calculated by summing the excretion values over all urine collections following a dose of study drug. Urinary excretion will be reported as a percentage of the administered dose of study drug (Ae%).

Renal clearance of TAS-120 will be calculated as below.

- CLr (Renal clearance) = Ae(Total amount of excretion)/AUC_{0-48} × 10^6 × 60

The urine volume, urinary concentration, Ae (mg) Ae% and CLr of TAS-120 will be summarized by study arm and dose levels according each urine collection period.

11.7. PK PARAMETERS SUMMARIZATION

Individual plasma concentrations will be listed and summarized by dose level and collection timepoint/ schedule, including number of observations (N), arithmetic mean, SD, CV, minimum, median, and maximum.

Individual PK parameters will be listed and summarized by dose level and collection timepoint/ schedule, including N, arithmetic mean, SD, CV, minimum, median, and maximum.

11.8. DOSE PROPORTIONALITY

Dose-proportionality of TAS-120 will be evaluated based on linear, power regression analyses, and one-way analysis of variance (ANOVA).

Regression analysis using linear model

Dose proportionality of TAS-120 PK parameters (C_{max}, AUC_{0-inf} and AUC_{0-last}) will be analyzed by regression analysis for both single dose (C1D1) and multiple doses (C1LW or C1D21) , C_{max} and AUC_{0-last} using linear model as below.

(AUC or C_{max}) = a×(dose)+ b

This model will be used to investigate the null hypothesis (H0: b=0) with calculating 90% confidence intervals for the intercept (b).

Regression analysis using power model

Dose proportionality of TAS-120 PK parameters (C_{max}, AUC_{0-inf} and AUC_{0-last}) will be analyzed by regression analysis for both single dose (C1D1) and multiple doses (C1LW or C1D21, C_{max} and AUC_{0-last}) using power model as below.

log(AUC or C_{max}) = α+ ß log(dose)

This model will be used to investigate the null hypothesis (H0: ß=1) with calculating 90% confidence intervals for the power constant (ß).

One-way ANOVA

Prior to the analysis, dose-dependent parameters (C_{max}, $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}last}$) will be normalized with dose. All PK parameters will be log-transformed prior to the analysis, and then the differences in the means of dose levels will be tested by one-way ANOVA.

11.9. ACCUMULATION RATIO

Besides the calculation of individual accumulation ratio, the mean accumulation ratio at RP2D or MTD will be estimated by paired t-test. TAS-120 PK parameters (C_{max}, and $AUC_{0\text{-}last}$) will be log-transformed and the mean ratio will be estimated for C1LW (C1LW/C1D1) and C1D21 (C1D21/C1D1).

12. PHARMACODYNAMICS

A secondary objective of Phase 1 Dose Escalation in this study is to investigate the clinical pharmacodynamics of TAS-120.

12.1. PD ENDPOINTS

For pharmacodynamics evaluations in blood, serum phosphorus and FGF23 will be collected. For the urine pharmacodynamics evaluation, phosphorus and calcium in urine will be collected. Urine creatinine levels will also be analyzed as controls and phosphorus and calcium level will be normalized by creatinine concentration.

Exploratory statistical analyses may be performed as appropriate.

12.2. SAMPLE COLLECTION

During Phase 1 Dose Escalation, blood samples for pharmacodynamic analysis will be collected at the following time points on C1D1 and on C1LW (QOD arm) or on C1D1 and C1D21 (QD arm):

pre-dose (-0.5hr) and after the morning dose at 0.5 hr (± 0.1 hr), 1 hr (± 0.1 hr), 2 hr (± 0.2 hr), 3 hr (± 0.2 hr), 4 hr (± 0.5 hr), 6 hr (± 0.5 hr), 8 hr (± 0.5 hr), 12 hr (± 2 hr), 24 hr (± 2 hr) (QOD and QD arms), and 48 hr (± 2 hr) (QOD only).

The 48-hour postdose sample (QOD arm) and the 24-hour postdose sample (QD arm) must be collected prior to TAS-120 administration on that day.

During Phase 1 Dose Escalation, urine samples for pharmacodynamic analysis of TAS-120 will be collected on C1D1 and on the C1LW (QOD arm) or on C1D1 and C1D21 (QD arm) at the following time points:

pre-dose, 0 to 12 hr (±2 hr), 12 to 24 hr (±2 hr), and 24 to 48 hr (±2 hr) (QOD arm only).

The 24 to 48 hours postdose sample (QOD arm) must be collected prior to TAS-120 administration on Day 3 and the last Friday of Cycle 1. The 12 to 24 hours postdose sample (QD arm) must be collected prior to TAS-120 administration on Day 2 and Day 22 of Cycle 1.

Statistical Analysis Plan

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13. PHARMACOGENOMICS

Cancer patients with or without FGF/FGFR abnormalities is enrolled into the first 4 cohorts of the QOD arm and QD arm during Phase 1 Dose Escalation. The pharmacogenomic FGF/FGFR analysis need to be done to obtain FGF/FGFR abnormality confirmation.

The FGF/FGFR gene abnormalities include genetic amplifications, mutations, and translocations. For Phase 1 Dose Escalation, patients is enrolled before central pharmacogenomics (PGx) laboratory confirmation of FGF/FGFR abnormality has been obtained.

The number and percentage of patients with and without FGF/FGFR abnormality will be summarized by dose level and overall.

All collected information for pharmacogenomic analyses from local and central laboratories will be listed. Other summaries and statistical analyses may be performed as appropriate.

14. INTERIM ANALYSES

No formal interim analysis is planned with respect to stopping the trial early or for lack of efficacy purpose.

15. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

There are no changes from the analysis planned in the protocol.

16. REFERENCE LIST

1. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

2. Durie BGM, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia. 2006 Sep; 20(9):1467-73.

17. PROGRAMMING CONSIDERATIONS

The following conventions are some recommended approaches for the study.

All tables, data listings, figures (TLFs), and statistical analyses will be generated using SAS® 9.3 or later (SAS® Institute Inc., Cary, NC, USA). The computer-generated table, listing and figure output will adhere to the following specifications.

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17.1. GENERAL CONSIDERATIONS

- A separate SAS program will be created for each output.
- Each output will be stored in a separate file.
- Output files will be delivered in Word format.

17.2. TABLE, LISTING, AND FIGURE FORMAT

17.2.1. General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8
- The data displays for all TLFs will have a 1.5-inch binding margin on top of a landscape oriented page and a minimum 1-inch margin on the other 3 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

17.2.2. Headers

- All output should have the following header at the top left of each page:
  <Sponsor Name> Protocol XXX (INC Research study number xxx)
  Draft/Final Run <date>
- All output should have Page n of N at the top or bottom right corner of each page. TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date (date output was generated) should appear along with program name and location as the last footer on each page.

17.2.3. Display Titles

- Each TLF should be identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is will be used. A decimal system (x.y and x.y.z) should be used to identify TLFs with related contents. The title is centered. The analysis set should be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
As Treated Population

17.2.4. Column Headers

- Column headings should be displayed immediately below the solid line described above in initial upper-case characters.
- For numeric variables, include “unit” in column or row heading when appropriate.
- Analysis set sizes will be presented for each cohort in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of patients in the analysis set.

17.2.5. Body of the Data Display

17.2.5.1. General Conventions

Data in columns of a table or listing should be formatted as follows:

- alphanumeric values are left-justified;
- whole numbers (e.g., counts) are right-justified; and
- numbers containing fractional portions are decimal aligned.

17.2.5.2. Table Conventions

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n=0 for all dose levels in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so any counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more dose levels should be included.
- An Unknown or Missing category may be added to any parameter for which information is not available for 1 or more patients.
- Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more significant digit than the original values, and standard deviations should be printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX

Maximum XXX

- Percentage values should be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Pre-determine how to display values that round down to 0.0. A common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of patients in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% should be presented as 100%, without any decimal places.
- Tabular display of data for medical history, and all tabular displays of adverse event data should be presented by SOC with the highest occurrence in the overall in decreasing order, assuming all terms are coded. Within SOC, medical history and adverse events (by preferred term) should be displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics which cannot be estimated should be reported as "-".
- The percentage of patients is normally calculated as a proportion of the number of patients assessed in the relevant dose level (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of patients exposed. Describe details of this in footnotes or programming notes.

- For categorical summaries (number and percentage of patients) where a subject can be included in more than one category, describe in a footnote or programming note if the subject should be included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

17.2.5.3. Listing Conventions

- Listings will be sorted for presentation in order of dose level, patient number, visit/collection day, and visit/collection time.
- Dates should be printed in SAS® DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates should be represented on subject listings as dashes (--JUL2000).

- All observed time values must be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available

17.2.5.4. Figure Conventions

- Unless otherwise specified, for all figures, study visits and time points will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

17.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with “Note:” if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line where possible.
- Footnotes will be present on the page where they are first referenced and thereafter on each page of the table, unless the footnote is specific only to certain pages. Subject specific footnotes should be avoided.
- Footnotes will be used sparingly and must add value to the table, figure, or data listing. If more than six lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., ‘Program : myxxxxxx.sas Listing source: 16.x.y.z’).

18. QUALITY CONTROL

SAS programs are developed to produce clinical trial output such as analysis data sets, summary tables, data listings, figures or statistical analyses. INC Research SOP CCI provide an overview of the development of such SAS programs.

INC Research SOP CCI describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the proper clinical trial output by checking for their logic, efficiency and commenting and by review of the produced output."

For all data sets, tables and listings generated by SAS, INC Biostatistics will create SAS codes independently, and then use SAS PROC COMPARE procedure to perform 100% electronic comparison for all numerical and character values. In addition, the Lead Biostatistician, Lead Programmer and Senior Statistical Reviewer will review all TLFs for consistency and accuracy.

STATISTICAL ANALYSIS PLAN

VERSION: 2.0

DATE OF PLAN: 25 OCT 2019

PROTOCOL NUMBER:

TPU-TAS-120-101

STUDY TITLE:

PHASE ½ STUDY IN PATIENTS WITH ADVANCED SOLID TUMORS HARBORING FGF/FGFR ABERRATIONS (PHASE I EXPANSION)

SPONSOR:

Taiho Oncology, Inc.

101 Carnegie Center

Princeton, NJ USA 08540

+1 (609) 750-5300

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

STATISTICAL ANALYSIS PLAN

APPROVAL PAGE

PHASE ½ STUDY IN PATIENTS WITH ADVANCED SOLID TUMORS HARBORING FGF/FGFR ABERRATIONS (PHASE I EXPANSION)

Protocol TPU-TAS-120-101
Version 2.0

Prepared by:

PPD

	Signature	Date

Approved by:

PPD

	Signature	Date

PPD

	Signature	Date

TABLE OF CONTENTS

LIST OF TABLES

1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
BUN	Blood urea nitrogen
CCA	Cholangiocarcinoma
Ccr	Calculated creatinine clearance
CI	Confidence interval
CK	Creatine kinase
CK-MB	Creatine kinase (isoform heart muscle)
CR	Complete response
CSF	Cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CYP	Cytochrome P450
DCR	Disease control rate
DOR	Duration of response
eCCA	Extra-hepatic cholangiocarcinoma
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	End-of-treatment
EP	Early progression
EPR	Early progression rate
FFPE	Formalin fixed paraffin embedded
FGF	Fibroblast growth factor
FGFR	Fibroblast growth factor receptor
GBM	Glioblastoma multiforme
GCP	Good Clinical Practice
Gd-MRI	Gadolinium-based magnetic resonance imaging
iCCA	Intra-hepatic cholangiocarcinoma
ICH	International Council for Harmonisation
INR	International normalized ratio
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging

Abbreviation	Term
ms	Milliseconds
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PR	Partial response
PROs	Patient-Reported Outcomes
PT	Preferred term
QD	Once daily (continuous) dosing
QTcF	Fridericia's corrected QT interval
R	Response
RANO	Response Assessment in Neuro-Oncology
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SOC	System Organ Class
WHO	World Health Organization
WOCBP	Women of child-bearing potential

2. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and data displays to be included in the Clinical Study Report (CSR) for Protocol TAS-120-101.

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.

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 fusions have been identified as an early driver of oncogenic events. These gene 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.

The Phase I Expansion part of the study included a total of 8 disease 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.

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.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objectives

- 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
- 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

3.1.2. Secondary Objectives

- To investigate the safety of TAS-120
- To evaluate Disease Control Rate (DCR), Duration of Response (DOR) and PFS

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3.2. Study Endpoints

3.2.1. Primary Endpoints

- Objective response rate (ORR, according to RECIST 1.1 and EPR for primary CNS tumors). Objective response rate is defined as the proportion of patients who had best overall response (BOR) of CR or PR.

3.2.2. Secondary Endpoints

- Duration of response (DOR)

Duration of response is defined as the time from the first documented response (CR or PR) to the first documented objective progressive disease (PD) or death due to any cause.

- Disease control rate (DCR)

Disease control rate is 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.

- Progression-free survival (PFS)

PFS is defined as the time from the first dosing date to the date of the first documented progression or death due to any cause, whichever occurs first.

- Overall survival (OS)

OS is defined as the time between the first dosing date and the date of death.

- Safety and Tolerability of TAS-120

Safety will be analyzed through the incidence of death, adverse event, concomitant medications, physical examination, vital sign measurements, clinical laboratory results, ECG results, ECOG performance status, and other safety observations at the time points indicated in the Study Schedule of Assessments (Table 1) will be monitored and recorded. The data will be summarized.

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4. STUDY DESCRIPTION

4.1. Summary of Study Design

This is an open-label, nonrandomized, and Phase I Expansion study of TAS-120, evaluating the efficacy, safety, and antitumor activity of the RP2D 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.

As of Amendment 6, the Phase 1 Dose Escalation Phase is completed and MTD/RP2D of 20 mg QD was established.

TAS-120 will be administered orally at 20 mg, QD in 21-day cycles. Approximately 185 patients will be enrolled. Patients will be assigned to one of 8 disease groups based on diagnosis, prior therapy, and FGFR aberration:

- Group 1 (Enrollment suspended as of Amendment 7): Patients with intrahepatic or extrahepatic CCA harboring FGFR2 gene fusions or rearrangements.
- Group 2: Patients with intrahepatic or extrahepatic CCA harboring FGFR2 gene fusions or rearrangements 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): CCA (iCCA or eCCA) with FGFR2 gene fusions or rearrangements treated with prior FGFR inhibitors
- Group 4 (Enrollment suspended as of Amendment 7): CCA (iCCA or eCCA) with other FGFR abnormalities, i.e., gene 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).
- 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

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				
		1	4 (±1d)	8 (±3d)	15 (±3d)	1 (±3d)	End of Tx (+0-7 days)	30 (±3) days After Last		
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.
ECOG performance status	X	X				X	X	X		

	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)				
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 protocol Section 10.13.1.
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 protocol Section 10.1.1.
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	End of Tx (+0-7 days)	30 (±3) days After Last		
		Day				Day				
		1	4 (±1d)	8 (±3d)	15 (±3d)	1 (±3d)				
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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 protocol Section 10.17. 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	End of Tx (+0-7 days)	30 (±3) days After Last		
		Day 1	Day 4 (±1d)	Day 8 (±3d)	Day 15 (±3d)	Day 1 (±3d)				
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 protocol Section 9.1.1

4.2. Treatment Assignment and Blinding/Unblinding

After the patient's initial eligibility is established and informed consent has been obtained, the 20 mg QD of TAS-120 will be administered orally in patients with tumors harboring specific FGF/FGFR aberration. The treatment of TAS-120 will be continued with 21-day treatment cycle until at least one of the criteria for study discontinuation criteria is met.

This is an open label study. The blinding/unblinding is not applicable in this study.

Primary endpoints for CCA and CNS patients, ORR will be based on the independent review of images by the Core Imaging Laboratory according to the RECIST 1.1. For the other tumor types, ORR will be based on investigators assessment.

4.3. Determination of Sample Size

For this Phase I Expansion study, up to approximately 185 patients will be enrolled among the different tumor types as outlined below:

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

5.1. Study Periods

The study periods are defined in the table 4 below.

Table 4. Definition of Study Periods for Analysis

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

Abbreviations: ICF=informed consent form.

5.2. Treatment Groups

There are 8 disease groups in this Phase I Expansion study as described in section 4.1 of this SAP. 20 mg QD of TAS-120 has been selected as the dose for each of the 8 disease groups.

In addition, in early portion of the Phase I Expansion study, a small number of patients were treated with 16 mg DQ and then followed by 20 mg QD.

5.3. Populations for Analysis

- **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.
- **Pharmacokinetics and Pharmacodynamics 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.
- **Efficacy Population:** all treated Patients (Safety Population).

5.4. Timing of Analysis

The final analysis will be performed when at least 90% of all treated patients had 4 months of follow-up.

The timing of the interim analysis please referred to Section 4.3 Determination of Sample Size of this SAP.

6. STATISTICAL ANALYSIS

6.1. General Methods

All relevant data will be presented in patient level data listings.

All categorical (binary and ordinal) data will be summarized by tumor type groups using frequency counts and percentages of patients. Percentage will be calculated based on groups in the study population as the denominator. The continuous variables will be summarized using number of non-missing observation (n), mean, standard deviation (SD), median, minimum and maximum unless otherwise specified. The number of events and censorings will be reported for time-to-event analysis. All estimations will include a point estimate and the corresponding 95% confidence interval.

Summary tables will be presented by the disease type. Data listings will be presented with the groups and patient ID. The tables by sub-groups such as: age groups, gender, races, ECOG categories, and will be also summarized.

Analysis Cohort based on disease type (disease group 1 through group 8) are assigned as follows. Unless otherwise specified, by-cohort analysis will be included in tables and figures.

- Cohort 1: Patients with Cholangiocarcinoma (CCA). It combines disease group 1 to 4
- Cohort 2: Patients with primary CNS tumor. It's the patients from disease group 5
- Cohort 3: Patients with advanced urothelial carcinoma. It's the patients from disease group 6
- Cohort 4: Patients with breast cancer or gastric cancer. It's the patients from disease group 7
- Cohort 5: Patients with the tumor types in disease group 8, harboring FGFR gene fusions or activating mutations
- Cohort 6: Patients not included in cohort 1 to cohort 5

For concomitant medications and adverse events, the cycles are determined based on their start/onset dates. For other collected data, the cycles are determined based on their visit dates. When there are multiple laboratory records for a scheduled visit, the one closest to the target date (relative to the Day 1 in that cycle) will be used for analysis. If there are two or more records with the same time period to the target date, the later one will be used for analysis.

Time to event distribution (e.g. progression free survival, overall survival, time to response, and duration of response) will be estimated using Kaplan Meier techniques. When appropriate, the median along with the corresponding log-log transformed 95% CI will be estimated. Rates at fixed time points will be derived from the Kaplan Meier estimate and corresponding confidence interval will be derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function S(t). Confidence intervals for binomial proportions, ORR and DCR, will be derived using the Clopper-Pearson method.

For patients who were also treated with 16 mg QD during early portion of the Phase I Expansion of the study, separate analysis will be presented.

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

6.2. Study Conduct

6.2.1. Accrual

The accrual will be summarized on the enrolled population separately for each cohort. The number of patients accrued by region and investigational site will be summarized for all enrolled patients. A patient level listing of accrual will also be produced.

6.2.2. Protocol Deviations

Important protocol deviation is defined as a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect the patient's rights, safety or well-being.

Important protocol deviations will be included in the Clinical Study Report (CSR). These include: Important ICF issues, inclusion/exclusion criteria not met, withdrawal criteria not followed; wrong treatment, incorrect dose/ overdose based on protocol definitions, important deviations based on protocol design, and other important GCP deviations. All protocol deviations will be tracked and corrective actions implemented.

6.3. Study Population

6.3.1. Patient Disposition

The number of patients in all treated population will be summarized by analysis Cohorts along with the reason for exclusion from the population. In addition, patients' status with regard to study treatment and follow-up will also be summarized, along with the reasons for study discontinuations.

In addition, summary tables will also be provided for the iCCA patients: with FGFR2 rearrangement, without FGFR2 rearrangement, with FGFR2 rearrangement with GEM/CIS and without FGFRi Prior Treatment, with FGFR2 rearrangement with FGFRi prior treatment.

6.3.2. Demographic and Other Baseline Characteristics

The following baseline characteristics will be summarized by Cohort, as well as by these 4 categories for the iCCA patients: with FGFR2 rearrangement, without FGFR2 rearrangement, with FGFR2 rearrangement with GEM/CIS and without FGFRi Prior Treatment, with FGFR2 rearrangement with FGFRi prior treatment. Listings will also be provided:

- Age (descriptive statistics)
- Age category (<65, >=65)

- Gender (male, female)
- Race groups (Caucasian/white, Black, Asian/Oriental, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Ethnicity (Hispanic/Latino, Not Hispanic/Latino)
- ECOG Performance Status (1, 0)
- Baseline Weight (kg)
- Baseline Height (cm)
- Prior surgical resection of primary tumor
- Locally advanced disease only
- Metastatic disease
- Region of enrollment (Asia (excluding Japan), Japan, Rest-of-the-World)

6.3.3. Medical History

Medical terms in medical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA 18.1). Medical history will be listed by patient number, start date and end date, and CTCAE grade. The treatment start date and end date versus the first dose date maybe listed.

6.3.4. Prior/Concomitant Therapies

Prior or concomitant medications and therapies will be collected from the time of informed consent through 30 days after administration of last dose of study medication.

Medications and therapies which started and stopped prior to the first dose of TAS-120 are considered as prior medications. Medications and therapies which started prior to the first dose of TAS-120 and continued into the treatment period are considered as prior and concomitant medications. Medications or therapies with a start date from first dose of TAS-120 to 30 days after administration of the last dose of TAS-120 will be considered as concomitant medications and therapies.

Prior and concomitant medications will be coded according to World Health Organization (WHO) Drug Dictionary (WHODrug version March 2014) for Concomitant Medication. The concomitant medications will be summarized by ATC level 2 (Therapeutic Main Group) and ATC level 4 (Chemical/Therapeutic Subgroup) using the number and percentage of patients. Medications will be sorted in descending order of frequency of ATC level 2 and ATC level 4 within ATC level 2 in the total column. A patient will be counted only once within each level of summation if the patient has taken a medication more than once.

All prior and concomitant medications and therapies will be listed in patient level.

6.3.4.1. Prior Anticancer Therapy

The baseline cancer types with number of patients with confirmed FGFR2 gene fusions or other FGF/FGFR aberrations, and prior FGFRi treatment will be summarized. A patient level listing will also be provided.

Pre-study surgery and prior radiation therapy will be summarized by tumor type groups. For pre-study surgery, the number and percentage of patients with biopsy, primary tumor removal, metastatic tumor removal, and other surgeries will be reported. For prior-radiation therapy, the number and percentage of patients with palliative and therapeutic radiation therapies will be presented in a summary table.

All prior anticancer therapies (adjuvant therapies, neoadjuvant therapies, therapies for advanced/metastatic disease, and maintenance therapies) will be summarized. The number of patients with 1, 2, 3 and >=4 prior regimens will be summarized for all anticancer therapies and for advanced/metastatic disease only. The number of patients and percent with best of response for prior anticancer therapy will also be summarized.

All collected information for cancer diagnosis, pre-study surgery, prior-radiation therapy, and prior anti-cancer therapy will be summarized and listed.

6.3.4.2. Other Prior/Concomitant Therapy

Prior/current medication will be classified by anatomic and therapeutic classes. Agents and medication will be reported using the generic name. A listing by patient will also be provided.

In addition, percentage of subjects who received concomitant medication for management of hyperphosphatemia will be reported by cohort (percentages of treated subjects by medication class and generic term).

Total duration of medications (excluding overlaps) given for management of hyperphosphatemia will be also summarized.

6.4. Efficacy Analyses

6.4.1. Primary Efficacy Analyses

The primary endpoint, Objective Response Rate (ORR), defined as the proportion of patients who achieved best overall response of partial response (PR) or complete response (CR) in the Efficacy Population for solid tumor patients. It will be calculated from the best of overall response recorded from the start of treatment until progression disease or start of subsequent new anticancer treatment. The overall response can be derived based on target lesion response, non-target response as well as the emergence of new lesion for patients with measurable disease at baseline. Rules for Overall Response derivation is summarized in Table 5.

A minimum of 4-week interval between two tumor measurements is required to confirm PR or CR. A minimum of 6-week interval between initial of treatment (first dose date) and tumor measurement is required for SD. The confirmation rule is shown in Table 5.

The 95% confidence interval (binomial proportion confidence interval) for ORR will be constructed with Clopper-Pearson 95% CI.

The ORR summary based on Independent Review will be presented for iCCA patients by the 4 categories of: with FGFR2 rearrangement, without FGFR2 rearrangement, with FGFR2 rearrangement with GEM/CIS and without FGFRi Prior Treatment, with FGFR2 rearrangement with FGFRi prior treatment.
In addition, ORR will be presented based on data from the Investigator Review.

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

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

6.4.2. Secondary Efficacy Analyses

The Duration of Response (DOR) is defined as the time between the date of first response and the subsequent date of objectively documented progression of disease or death. The CR or PR will be derived based on investigators or local radiologist assessment, as well as independent review. The censoring rule is shown in Table 6.

Overall survival (OS) is defined as the time between the first dosing date and the date of death. Progression free survival (PFS) is defined as the time from the first dosing date to the date of the first documented progression or death due to any cause, whichever occurs first. The censoring rule is illustrated in Table 7.

Duration of response (DOR) and PFS will be analyzed using Kaplan–Meier product-limit estimates. Median PFS will be presented with 2-sided 95% CI if estimable. Censoring rules (table 8, Table 9) is based on the Food and Drug Administration Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007). The cumulative PFS will be plotted over time. OS will be analyzed similarly if data is available.

DCR is 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. DCR will be calculated and a 2-sided Clopper–Pearson 95% CI will be constructed.

Summary tables and plots for the secondary endpoints based on Independent Review will be presented for iCCA patients by these 4 categories: with FGFR2 rearrangement, without FGFR2 rearrangement, with FGFR2 rearrangement with GEM/CIS and without FGFRi Prior Treatment, with FGFR2 rearrangement with FGFRi prior treatment.

Summary tables and plots will also be presented based on data from the Investigator Review.

Table 6. Censoring Rules for Progression-Free Survival

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

a. If documented PD and/or death occurs after the last dose, it is counted as a PFS event as long as the PD and/or the death occurs within 21 days since the date of the last dose of study drug and provided that it does not violate other censoring rules (e.g. start of new anticancer therapy before the PD or death). Otherwise the patient will be censored on the date of last tumor assessment before the date of last dose date + 21 days.
b. For PFS analysis, the date of last tumor assessment refers to the date of last adequate tumor assessment of CR, PR, SD, or PD.
c. This refers to patients who were still receiving study treatment at time of data cutoff.
d. Two or more missed tumor assessments is defined as having either one of the following two durations being longer than 2 cycles for the first 6 months of treatment, or thereafter 3:
- Duration between two consecutive tumor assessments
- Duration between the last tumor assessment and death or PD.

Table 7. Censoring Rules for Overall Survival (OS) Endpoint.

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

6.4.3. Other Efficacy Analyses

By-patient listing to include FGFR gene status, first dose date, duration of treatment, best overall response, duration of response, and cancer sub-type will be presented for each cohort.

For cohort 2 patients, response to therapy follows the RANO (Response Assessment in Neuro-Oncology) criteria. The criteria are shown in Table 8 below:

Table 8. Summary of RANO Response Criteria

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

Abbreviations: NA=not applicable, RANO = Response Assessment in Neuro-Oncology, T1 = T1 relaxation, T2/FLAIR = T2-weighted fluid-attenuated inversion recovery.

[a] Progression occurs when this criterion is present.

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

The response results with RANO response criteria will be compared with the response results with RECIST 1.1. The best responses with the two criteria will be used and displayed in the table output. The patient level listing will be provided.

6.5. Safety Analyses

The population used for safety analyses will be the safety population who enrolled in the study. Safety will be assessed on the basis of adverse event (AE) reports, clinical laboratory data, ECG parameters, physical examinations, vital signs and body weight, performance status, and ophthalmological examination.

6.5.1. Extent of Exposure

6.5.1.1. Administration of Study Drug

The number of cycles initiated and completed, extent of exposure (Treatment Duration), relative dose intensity in Cycle 1, relative dose intensity in all cycle and total dosage for TAS-120 will be summarized.

Relative dose intensity (RDI) is defined as the ratio of the amount of drug actually administered to the amount planned in the study for TAS-120. The relative dose intensity is calculated in the following steps:

1. Amount of drug actually administered is total number of dose administered
2. Treatment Duration = last dose date – first dose date +1
3. Amount of drug planned for the patient =Treatment Duration
4. Relative Dose Intensity = (Amount of drug actually administered / Amount of drug planned) x 100%

A by-patient listing of dosing of study medication will be also provided.

6.5.1.2. Modification of Study Drug

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

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

By-patient listings of dose interruptions and dose reductions will be also provided.

In addition, summary tables will also be provided for the iCCA patients by the categories of: with FGFR2 rearrangement, without FGFR2 rearrangement, with FGFR2 rearrangement with GEM/CIS and without FGFRi Prior Treatment, with FGFR2 rearrangement with FGFRi prior treatment.

6.5.2. Adverse Events

Summary of AEs will be performed by cohort, and by these 4 categories for the iCCA patients: with FGFR2 rearrangement, without FGFR2 rearrangement, with FGFR2 rearrangement with GEM/CIS and without FGFRi Prior Treatment, with FGFR2 rearrangement with FGFRi prior treatment.

6.5.2.1. Deaths

All deaths will be summarized. The reasons of death will also be summarized. The reasons are categorized in the following terms:

- Radiological Disease Progression
- Clinical Disease Progression
- Toxicity
- Adverse Event
- Other

A by-patient listing of all deaths will be provided for the All Treated patients population.

6.5.2.2. Serious Adverse Events

A serious Adverse Event (SAE) is an AE which falls into one or more of the following categories:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Is any other important medical event

Serious AEs will be summarized with the following categories:

- Overall summary of SAEs by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by SOC/PT.

- A summary of serious AEs, overall and by system organ class and preferred term.

6.5.2.3. Adverse Events Leading to Discontinuation of Study Drug

AEs leading to discontinuation will be summarized:

- Overall summary of AEs leading to discontinuation by worst CTC Grade (grade 1, 2, 3, 4, 5, any grade, Grade 3-5) presented by SOC/PT
- Overall summary of drug-related AEs leading to discontinuation by worst CTC grade (Grade 1, 2, 3, 4, 5, any grade, Grade 3-5) presented by SOC/PT

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

6.5.2.4. Adverse Events Leading to Dose Modification

AEs leading to dose modification (including dose interruption or reduction) will be summarized:

- Overall summary of AEs leading to modification by worst CTC Grade (grade 1, 2, 3, 4, 5, any grade, Grade 3-5) presented by SOC/PT
- Overall summary of drug-related AEs leading to discontinuation by worst CTC grade (Grade 1, 2, 3, 4, 5, any grade, Grade 3-5) presented by SOC/PT

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

6.5.2.5. Adverse Events

An adverse event (AE) is any untoward medical condition that occurs in a patient while participating in this clinical study. Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA 18.1) terminology and the severity of the toxicities will be graded according to the NCI CTCAE, v4.03, where applicable.

Adverse Events that occur from the initiation of TAS-120 medication administration to 30 days after the last dose of study medication, and do not necessarily have a causal relationship to the use of the study medication will be summarized.

Number of patients with AEs will be presented by system organ class in the overall column in decreasing order. Within each system organ class, the number of patients with AEs will be displayed by preferred term (PT) in descending order.

The following adverse event summary tables will be generated:

1) An overall summary with the number and percentage of patients reporting AEs, serious AEs, grade 3 or higher AEs, treatment-related AEs, AEs leading to study treatment (TAS-120) discontinuation and AEs with outcome of deaths.

   In the summary, a patient is counted once at the system organ class and once at each preferred term within the system organ class. Additional summary by system organ class,

preferred term and grade (including Total and >= grade 3 categories) will also be generated.

2) Study-treatment-related AEs overall and by system organ class and preferred term. Additional summary by system organ class, preferred term and grade (including Total and >= grade 3 categories) will also be generated.

   All those AEs with relationship to TAS-120 marked as "Related" or missing will be reported in the table.

3) AEs by highest grade (worse severity) overall and by system organ class and preferred term.

   In the summary, a patient is counted once at the highest grade for which the event occurred in the system organ class and the highest grade for each unique preferred term within that system organ class. Therefore, patients may only contribute once to each preferred term and once to each system organ class. The missing severity grade will be reported in a separate category.

4) Grade 3 or higher AEs, overall and by system organ class and preferred term

5) Study-treatment related AEs by grade (severity), overall and by system organ class and preferred term

6) AEs leading to study treatment termination, overall and by system organ class and preferred term. Additional summary by system organ class, preferred term and grade (including Total and >= grade 3 categories) will also be generated.

7) AEs with outcome of deaths, overall and by system organ class and preferred term

In addition, the time to onset of some special AEs of interest in the study may be summarized if appropriate.

6.5.2.6. Adverse Events of Special Interest

Incidence:

Adverse event of special interest (AESI), including hyperphosphatemia, will be summarized for each category/subcategory:

- Overall summary of AESI by worst CTC grade presented by category or subcategory / PT

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

Time to Onset:

Time-to-onset of selected AESI, including hyperphosphatemia, will be graphically displayed for each category/subcategory of AESI using the Kaplan-Meier technique:

- Time to AESI (grade 1 and above)

- Time to AESI of Grade ≥3

Time to Resolution:

Time-to-resolution of selected AESI, including hyperphosphatemia, will be summarized separately for each category / subcategory:

- Time to resolution of AESI of Grade ≥3

Time-to-resolution analyses are restricted to treated patients who experienced the specific events.

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

6.5.2.7. Multiple Adverse Events

The following summary tables will be provided:

- Total number and rate (exposure adjusted) of occurrences for all AEs.
- For AESI: number of subjects experiencing an AESI once or multiple times

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

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

Y = 365.25 for years or Y = 30.4375 for months

Listing displaying the unique instances of all AEs (that is, after duplicates have been eliminated and overlapping and contiguous occurrences of the same event (same PT) have been collapsed) will be provided.

6.5.3. Clinical Laboratory Evaluations

Clinical laboratory results will be summarized using SI units. Laboratory measurements will be summarized for all protocol scheduled time points for all patients in the safety population. Descriptive (n, mean, STD, median, min and max) statistics will be presented for all clinical chemistry, hematology and coagulation laboratory parameters at each scheduled visit. Change from baseline at each scheduled post-baseline visit will also be presented.

Patient counts and percentages of patient for each category of each urinalysis parameters will be summarized at each scheduled visit.

Shift tables will be presented for each laboratory parameter to display the shift from baseline to the maximum post-baseline CTCAE grade (v4.03). Summary tables will be provided presenting the count and percentage of patients for each laboratory test by the maximum post-baseline CTCAE grade reported. All post-baseline assessments (including unscheduled visits) will be used to determine the maximum (worst) post-baseline CTCAE grade. Time to maximum Grade 3/4 and

time to resolution (return to grade <2 or baseline grade or below) may be summarized as appropriate.

Any laboratory abnormality that has a clinical impact on the patient, eg, results in delay of study drug 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 < 1000/mm^3 with a single body temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than 1 hour. All laboratory data will be analyzed using CTCAE grade criteria (Version 4.03).

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

A baseline laboratory value will be defined as the last assessment performed on or prior to the date and time of first dose of study treatment. Laboratory test results will be categorized by CTCAE criteria V4.03.

Estimated creatinine clearance (CLcr) will be calculated using baseline creatinine value according to the following formula.

$$\text{CLcr(mL/min)} = \frac{[140 - \text{age(years)}] * \text{weight(kg)}}{72 * \text{serum creatinine(mg/dL)}} \{* 0.85 \text{ if female}\}$$

All clinical laboratory data will be presented in patient level listings.

The laboratory tests among Hematology and Coagulation, Serum chemistry, and Urinalysis are listed in table 9.

Table 9. Laboratory Tests

Assessment	Test Items
Hematology and Coagulation	Red blood cell count, hemoglobin, hematocrit, platelets, white blood cell count with differential, neutrophils, lymphocytes, monocytes, eosinophils, basophils, International normalized ratio (INR), Activated partial thromboplastin time (APTT)
Serum chemistry	Aspartate aminotransferase (AST), alanine aminotransferase (ALT), ALP, total bilirubin, glucose, creatinine clearance, blood urea nitrogen(BUN) or urea, phosphorus, calcium, chloride, sodium, potassium, creatine kinase (CK), creatinine kinase MB (CK-MB), Troponin I, Troponin T
Urinalysis	Urine protein, glucose, urine density
Other	CCI [redacted]

- Neutrophils includes both segmented and band neutrophils
- creatinine clearance includes calculated (Ccr) or measured creatinine clearance

6.5.3.1. Additional Safety Analyses

6.5.3.1.1. Ophthalmological Examination

Ophthalmological examination will be performed at screening (within 28 days prior to study medication administration on Day 1 of Cycle 1), 4-6 weeks after starting treatment with TAS-120, End of treatment visit, and 30-day safety follow-up. Ophthalmological examination results will be summarized and listed.

6.5.3.1.2. Neurological Examination

The neurological examination will be obtained at screening within 28 days prior to TAS-120 administration on Day 1 of cycle 1, other time due to local requirements or physician judgement, end of treatment visit, and 30-day safety follow-up visit. The examination results will be listed.

6.5.4. Vital Signs

Vital sign measurements including systolic blood pressure, diastolic blood pressure, pulse rate, respiration rate, and temperature at each scheduled and changes from baseline in vital sign measurements will be summarized with descriptive statistics at each scheduled time point.

Weight at each scheduled time and changes from baseline will be summarized with descriptive statistics at each scheduled time point for the safety population. Weight will be displayed in kilograms, height, collected only at baseline, will be displayed in centimeters, and temperature will be displayed in Celsius. The safety population will be used.

All vital signs data will be presented in a listing.

6.5.5. Electrocardiograms

The results of the read 12-lead ECG at each scheduled will be summarized by the categories Normal; Abnormal, not clinically significant; and Abnormal, clinical significant. If two ECG measurements are collected during one visit, the worst category will be used in the summary. The safety population will be used.

A summary of interval duration measurements at each cycle and change from baseline will be summarized with descriptive statistics at each scheduled time point. QTcF result values will be categorized as follows: <=470 msec, >470 and <=480 msec, >480 and <=500 msec, >500 msec. A summary of the frequency of QTcF interval result and change from baseline categories will be generated by visit. The change from baseline categories defined as: QTc interval increase from baseline <= 30 msec; QTC interval increases from baseline 30 - 60 msec; QTc interval increases from baseline > 60 msec: If two ECG measurements are collected during one visit, the mean measurement will be used in the summary.

The 12-lead, resting ECGs will be obtained to explore the relationship between the plasma concentration of TAS-120 and QTc prolongation.

6.5.6. Physical Examination

All physical examination will be performed 24 hours prior to TAS-120 administration on day 1 beginning with cycle 2. The baseline screening measurement of physical examination will be taken on screening within 28 days prior to TAS-120 administration on Day 1 of Cycle 1. The physical examination will also obtain at the End of Treatment Administration, and 30-day safety follow-up visit.

The physical examination data will be presented in a patient level listing.

6.5.7. ECOG Performance Status

The ECOG performance status score will be obtained at the following time points: screening, and 24 hours prior to TAS-120 on day 1 beginning with cycle 2, the End of Treatment Administration, and 30-day safety follow-up visit. The ECOG performance status scores and the grades from 0 to 5 is described in the following table:

Table 10. Grade Categories of Eastern Cooperative Oncology Group Score

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

The change from Day 1 in Cycle 1 in the ECOG performance status scores will be presented in a shift table. A patient level listing will also presented.

6.5.8. Pregnancy Test

If the patient is female and of child bearing potential, a serum or urine beta-human chorionic gonadotropin (β-HCG) pregnancy test will be performed 7 days prior to the first administration of the study drug. Pregnancy test result will be listed.

6.6. Other Analyses

The Quality of Life data is not collected in the Phase I Expansion study.

CCI

6.8. Pharmacokinetic Analyses

6.8.1. Optional Pharmacokinetic Samples

Optional blood PK samples will 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).

Kp (TAS-120 concentration ratio of CSF to plasma) will be calculated as follows:

Kp = CSF concentration / Plasma concentration at the same time.

For patients whose CSF sample was collected, the summary Table for plasma and CSF concentrations and Kp value will be provided.

A patient level listing for plasma, CSF concentrations and Kp values will be provided.

6.8.2. Pharmacokinetic Blood Samples

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 summary table and subject level listing for plasma concentration will be provided.

7. CHANGES IN PLANNED ANALYSIS

The following table summarizes substantive changes made to the SAP in the current Amendment 1;

Section	Description of Change	Brief Rationale
Section 4.1 *Summary of Study Design*	Text was amended as follows: Group 1 (Enrollment suspended as of Amendment 7): Patients with intrahepatic or extrahepatic CCA harboring FGFR2 gene fusions *or rearrangements.* Group 2: Patients with intrahepatic or extrahepatic CCA harboring FGFR2 gene fusions *or rearrangements* 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): CCA (iCCA or eCCA) with FGFR2 gene fusions *or rearrangements* treated with prior FGFR inhibitors	In order to be consistent with the protocol.
Section 5.4 *Timing of Analysis*	The following text was amended as follows: The final analysis will be performed when *at least 90% of* all treated patients had ~~approximately~~ 4 months of follow-up.	In order to be consistent with patients' follow-up time.

8. DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

8.1. Baseline Period

Baseline evaluations or events are defined as evaluations or events that occur before the date and time of first dose of study treatment.

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

- Pre-treatment AEs will be defined as AEs with an onset date prior to but not including the day of the first dose of study treatment
- Baseline evaluations (laboratory tests, vital signs) will be defined as evaluations with a date on or prior to the day of first dose of study treatment

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

8.2. Post-Baseline Period

On-treatment AEs will be defined as AEs with an onset date and time on or after the date-time of the first dose of study drug (or with an onset date on or after the day of first dose of study treatment if time is not collected or is missing). An AE will be counted as on-treatment if the event occurred within 30 days of the last dose of study treatment.

On-treatment evaluations (laboratory tests, vital signs) will be defined as evaluations taken after the day (and time, if collected and not missing) of first dose of study treatment. An evaluation will be counted as on-treatment if it occurred within 30 days of the last dose of study treatment.

8.3. AESI Definition and Conventions

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

8.4. Time-to-Onset Definition

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

If the subject did not experience an AESI (of any grade) in the category, time-to-onset will be censored at the maximum follow-up time of all subjects in their respective treatment group (that is, for subjects without an event, follow-up time is defined from first dosing date up to last dosing date +30 days if subjects are off treatment and followed for at least 30 days, otherwise it

is defined up to the last known alive date). The resulting Kaplan-Meier plot will represent the cumulative rate of the AESI (any grade) in the category over time.

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

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

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

8.5. Time-to-Resolution Definition

In order to derive the time-to-resolution, overlapping or contiguous AESI within a specific category will be collapsed into what will be termed "clustered" AESI. For example, if a subject (without pre-treatment AE) experienced an AE from 01 January to 05 January, another AE (with different PT but within same category) from 06 January to 11 January, and the same AE from 10 January to 12 January, these will be collapsed into one clustered AESI from 01 January to 12 January. Table 11 summarizes key derivation steps for each type of clustered select AEs. Algorithm for collapsing multiple records of adverse event is summarized in section 8.6.

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

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

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

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

Table 11: Derivation of Clustered AESI

Type of clustered select AE	Derivation
Any grade	Collapse any on-treatment AESI from the same category
Drug-related of any grade	Collapse any on-treatment drug-related AESI from the same category

Type of clustered select AE	Derivation
Grade 3-5	Collapse any on-treatment AESI from the same category. Resolution will be based on the onset date of the earliest Grade 3-5 records (if no Grade 3-5 record, clustered AESI is excluded)
Drug-related of Grade 3-5	Collapse any on-treatment drug-related AESI from the same category. Resolution will be based on the onset date of the earliest Grade 3-5 record (if no Grade 3-5 record, clustered AESI is excluded)

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

8.6. Multiple Adverse Events

The algorithm for collapsing multiple records of select adverse event is using the following conventions. For each patient and specified category, the corresponding adverse event records will be collapsed when:

Multiple adverse event records have the same onset date.

The onset date of an event record is either the same day or 1 day later than the resolution date of a preceding event record (contiguous events).

The onset date of an event record is after the onset date and prior to or on the resolution date of a preceding event record (overlapping events).

8.7. Other Data Handling Rules

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

If an AE has a completely missing onset date, the AE will be included in the AE summary tables. A medication with a completely missing start date is considered a prior medication. A medication with a completely missing stop date is considered a concomitant medication.

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

Table 12. Partial Date Imputation Rule for AE or Medication

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

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

The above rule is also used for determining the cycles of adverse events and concomitant medications.

The derived date is only used for determining AEs, cycle of adverse events and concomitant medications. The collected partial dates will be reported in the listings.

For the medical history, prior surgery, prior radiotherapy, and prior systemic cancer therapies:

- Missing day and month - January 1 will be assigned to the missing fields.
- Missing month only - Treat day as missing and replace both month and day according to the above procedure.
- Missing day only - Assign first of the month to the missing day.

Partially missing stop dates for the types of data listed above will be imputed as:

- year is missing, no imputation. Date left missing.
- month is missing and year is prior to year of first dose of study medication- impute 'December'.
- month is missing and year the same as the year of the first dose of study medication – impute same month as in start date of study medication.
- day is missing, impute 'last date of that month'. If results in a date ≥ the date of the first dose of study medication impute day as the day prior to the first dose of study medication.

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STATISTICAL ANALYSIS PLAN

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TPU-TAS120-101

STUDY TITLE:

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

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

STATISTICAL ANALYSIS PLAN
Version 2.0

APPROVAL PAGE

PHASE ½ STUDY IN PATIENTS WITH ADVANCED SOLID TUMORS HARBORING FGF/FGFR ABERRATIONS (PHASE 2)

Protocol TPU-TAS-120-101

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1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
BUN	Blood urea nitrogen
CCA	Cholangiocarcinoma
Ccr	Calculated creatinine clearance
CI	Confidence interval
CK	Creatine kinase
CK-MB	Creatine kinase (isoform heart muscle)
CR	Complete response
CSF	Cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CYP	Cytochrome P450
DCR	Disease control rate
DOR	Duration of response
eCCA	Extra-hepatic cholangiocarcinoma
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	End-of-treatment
EP	Early progression
EPR	Early progression rate
FFPE	Formalin fixed paraffin embedded
FGF	Fibroblast growth factor
FGFR	Fibroblast growth factor receptor
GCP	Good Clinical Practice
iCCA	Intra-hepatic cholangiocarcinoma
ICH	International Council for Harmonisation
INR	International normalized ratio
MedDRA	Medical Dictionary for Regulatory Activities
ms	Milliseconds
MTD	Maximum tolerated dose
NCI	National Cancer Institute
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PR	Partial response

Abbreviation	Term
PROs	Patient-Reported Outcomes
PT	Preferred term
QD	Once daily (continuous) dosing
QTcF	Fridericia's corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SOC	System Organ Class
WHO	World Health Organization
WOCBP	Women of child-bearing potential

2. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and data displays to be included in the Clinical Study Report (CSR) for the Phase 2 portion of Protocol TPU-TAS120-101.

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%).

Fibroblast growth factor/fibroblast growth factor receptor aberrations are a reported genetic modification in CCA. In iCCA, FGFR2 gene fusions which are present in an estimated 10% to 20% of patients,[1,2,3] have been identified as an early driver of oncogenic events. Therefore, inhibiting the FGFR pathway in patients with iCCA is a plausible therapeutic strategy for appropriately selected patients with this disease.

TAS-120 (Futibatinib) is a novel selective and irreversible small molecule FGFR inhibitor that equally inhibited all 4 subtypes of FGFR and showed high selectivity for FGFR when tested against a panel of 296 kinases, as in preclinical studies. During the Phase 1 Dose Escalation part of this study, dose levels of 4, 8, 16, 20 and 24 mg QD were evaluated, where 24 mg was determined as the DLT dose level, and 20 mg QD was determined as the maximum tolerated dose (MTD) and RP2D. The Phase 1 Expansion part of the study included a total of 8 treatment groups enrolling different patient populations, including a group of patients with iCCA. The Phase 2 portion of the study is to confirm and assess the efficacy and safety of TAS-120 on patients who have been diagnosed with iCCA harboring *FGFR2* gene fusions or other *FGFR2* rearrangements.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objective

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

3.1.2. Secondary Objectives

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

CCI [redacted]

3.2. Study Endpoints

3.2.1. Primary Endpoint

Objective response rate (ORR) according to RECIST 1.1 guidelines[4]. Objective response rate is defined as the proportion of patients who had best overall response (BOR) of CR or PR based on independent central radiology review.

3.2.2. Secondary Endpoints

- Duration of response (DOR)

Duration of response is defined as the time from the first documented response (CR or PR) to the first documented objective progressive disease (PD) or death due to any cause.

- Disease control rate (DCR)

Disease control rate is 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.

- Progression-free survival (PFS)

PFS is defined as the time from the first dosing date to the date of the first documented progression or death due to any cause, whichever occurs first.

- Overall survival (OS)

OS is defined as the time between the first dosing date and the date of death.
ORR, DOR, DCR and PFS endpoints will be calculated based on IRC and based on investigator assessment

- Safety and Tolerability of TAS-120

Safety will be analyzed through the incidence of death, adverse event, concomitant medications, physical examination, vital sign measurements, clinical laboratory results, ECG results, ECOG performance status, and other safety observations at the time points indicated in the Study Schedule of Assessments (Table 1) will be monitored and recorded. The data will be summarized.

- Patient-Reported Outcomes (PROs)

EQ-5D

The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, severe problems. Once the data have been collected and a database created, a scoring function can be used to assign a value (i.e., EQ-5D index score) to self-reported health states from a set of population-based preference weights.

The EQ VAS records the patient's self-rated health state on a 100-point vertical, visual analogue scale (0 = worst imaginable health state; 100 = best imaginable health state).

EORTC QLQ-C30

Health-related quality of life (HRQoL) will be assessed using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire Version 3. It is a 30-item instrument that has gained wide acceptance in oncology clinical studies. The EORTC QLQ-C30 is composed of multi-item and single scales. These include five functional scales (physical, role, emotional, social, and cognitive), three symptom (fatigue, nausea and vomiting, and pain) and a global health status/QOL scale and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties). All scales and single items meet the standards for reliability. The reliability and validity of the questionnaire is highly consistent across different language-cultural groups. Except for the overall health status and global quality of life items, responses for all items are 4-point categorical scales ranging from 1 (Not at all) to 4 (Very much). The overall health status/quality of life responses are 7-point Likert scales.

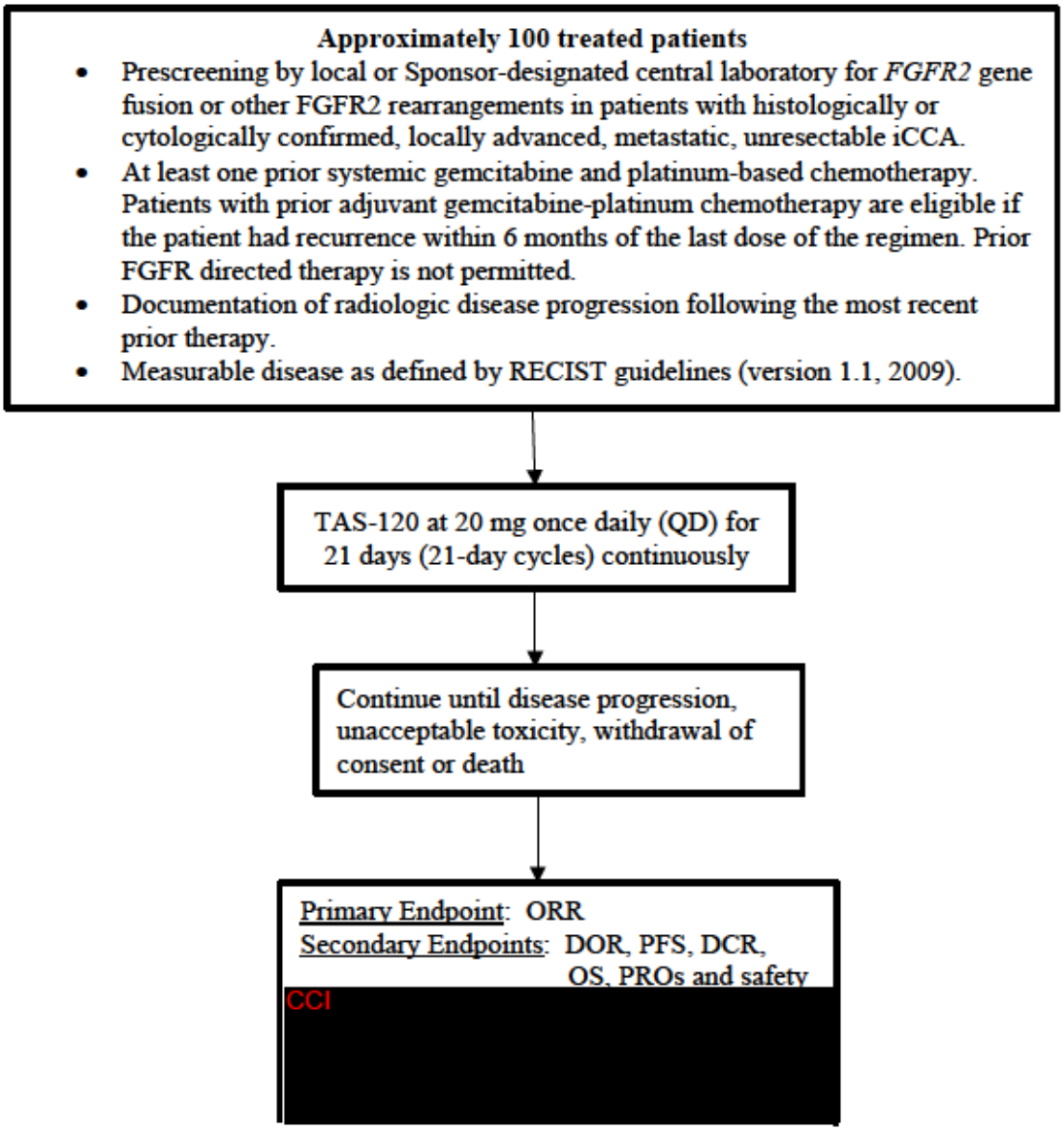
4. STUDY DESCRIPTION

4.1. Summary of Study Design

This is an open-label, nonrandomized, Phase 2 study of TAS-120 (Futibatinib), evaluating the efficacy, safety, tolerability, PK and antitumor activity of TAS-120 in patients with Intra-hepatic cholangiocarcinoma (iCCA) with *FGFR2* gene fusions or other *FGFR2* rearrangements who have failed all standard therapies or for whom standard therapy does not exist.

The overall study design is described in Figure 1. Study schedule for this phase 2 study is presented in Table 1.

Figure 1: Study Schema



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.

In this study, patients will be followed for survival for up to 18 months after the last patient enrolled. The detailed study schedule is shown in Table 1.

Table 1: 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	End of Tx (+0-7 days)	30 (±3) days After Last		
			Day 1	4 (±1d)	8 (±3d)	15 (±3d)	Day 1 (±3d)				
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, tumor tissue should be provided if available. In cases where local laboratory testing is used to determine eligibility, tissue must be submitted to central laboratory for confirmation during the study.										
Review eligibility criteria		X	X								
Demographics/medical history		X									
Review of pre-existing signs and symptoms		X	X								
Physical examination		X	X				X	X			Within 24 hours prior to dosing on D1 of each cycle.
Vital signs		X	X				X	X			Heart rate, blood pressure, body temperature, and respiration rate.
Height and Weight		X	X				X	X			Height at screening only.
Ophthalmological examination		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			As clinically indicated after screening, using same methods used at screening.
ECOG performance status		X	X				X	X			Within 24 hours prior to 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	End of Tx (+0-7 days)	30 (±3) days After L		
			Day 1	4 (±1d)	8 (±3d)	15 (±3d)	Day 1 (±3d)				
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.
ctDNA blood samples		X						(X)			Minimum of 20 mL whole blood at screening (mandatory) and EOT (optional).
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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 Protocol Section 12.1

	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 L		
			Day 1	4 (±1d)	8 (±3d)	15 (±3d)	Day 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 Protocol Section 10.17. 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 1	4 (±1d)	8 (±3d)	15 (±3d)	Day 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 protocol Section 9.1.1.

4.2. Treatment Assignment and Blinding/Unblinding

After the patient's initial eligibility is established and informed consent has been obtained, the 20 mg QD of TAS-120 (Futibatinib) will be administered orally in iCCA patients. The treatment of TAS-120 will be continued with 21-day treatment cycle until at least one of the criteria for study discontinuation criteria is met.

This is an open-label study. Blinding/unbinding is not applied.

4.3. Determination of Sample Size

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

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

5.1. Study Periods

The study periods are defined in Table 3 below.

Table 3 Definition of Study Periods for Analysis

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

Abbreviations: ICF=informed consent form.

5.2. Treatment Regimens

TAS-120 will be administered continuously once daily on a 21-day treatment cycle until at least 1 of the criteria for study discontinuation is met. TAS-120 will be administered as outlined in Study Drug Administration (Protocol amendment 9, Section 9.1.1) and Dose Reduction/Modification Procedures (Protocol amendment 9, Section 9.1.3). There are no breaks in dosing between cycles.

5.3. Populations for Analysis

- **Safety Population:** All patients who received at least 1 dose of TAS-120. This population will be the primary population for safety evaluation
- **Efficacy Population:** All Intra-hepatic cholangiocarcinoma (iCCA) patients who received at least 1 dose of TAS-120 with FGFR2 gene fusions or other FGFR2 rearrangements
- **PRO Population:** All patients who received TAS-120 treatment and had EQ-5D or EORTC QLQ-C30 assessment at baseline and at least one subsequent post-baseline assessment
- **Per-protocol Patients (Per-Protocol Population):** All treated subjects who have no relevant protocol deviations. For patients who have a relevant deviation during the study, data collected before the point of deviation can be included in the analysis preformed for this population.

5.4. Timing of Analysis

The final analysis for the primary objective will be performed when majority of patients responding to futibatinib had at least 6 months of follow-up from onset of response.

6. STATISTICAL ANALYSIS

6.1. General Methods

All relevant data will be presented in patient level data listings.

All categorical (binary and ordinal) data will be summarized using frequency counts and percentages of patients. Percentage will be calculated using the corresponding treatment group in the study population as the denominator. The continuous variables will be summarized using number of non-missing observation (n), mean, standard deviation (SD), median, minimum and maximum unless otherwise specified. The number of events and censorings will be reported for time-to-event analysis. All estimations will include a point estimate and the corresponding 95% confidence interval.

The recommended phase 2 dose (RP2D) is 20 mg daily (QD). The treatment dose level is 20 mg during the regular treatment in Phase 2 of the study.

A formal interim analysis, as well as interim analysis for safety will be performed in this Phase 2 part of the study (Section 6.8).

For concomitant medications/therapy and adverse events, the cycles are determined based on their start/onset dates. For other collected data, the cycles are determined based on their visit dates. These data include Lab test, Physical exam, Vital signs, Height and weight, Ophthalmological exam, Neurological exam, ECOG, ECG, Pregnancy test, PK, ctDNA, CCI PRO data, Scheduled tumor assessment.

When there are multiple laboratory records for a scheduled visit, the one closest to the target date (relative to the Day 1 in that cycle) will be used for analysis. If there are two or more records with the same time period to the target date, the later one will be used for analysis.

Time to event distribution (e.g. progression free survival, overall survival, time to response, and duration of response) will be estimated using Kaplan Meier techniques. When appropriate, the median along with the corresponding log-log transformed 95% CI will be estimated. Rates at fixed time points will be derived from the Kaplan Meier estimate and corresponding confidence interval will be derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function S(t). Confidence intervals for binomial proportions, ORR and DCR, will be derived using the Clopper-Pearson method.

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

6.2. Study Conduct

6.2.1. Accrual

The accrual will be summarized on the enrolled population separately with number of patients accrued by country and investigational site.

A patient level listing of accrual will also be produced.

6.2.2. Protocol Deviations

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

Important protocol deviations will be summarized and listed in the Clinical Study Report (CSR).

Relevant protocol deviations are a subset of important protocol deviations that may impact study endpoints. Relevant protocol deviation in phase 2 of this study includes patients who do not have evaluable post-baseline tumor assessment.

6.3. Study Population

6.3.1. Patient Disposition

The number of patients in each study population will be summarized in a table with 5 major analysis sets, safety population, efficacy population, per-protocol population, PK population, and PRO population. Patient disposition table will include number of patients treated at data cutoff, number of discontinued patients along with the reason for exclusion from the population. In addition, patients' status with regard to study treatment and follow-up will also be summarized, along with the reasons for study discontinuations.

6.3.2. Demographic and Other Baseline Characteristics

The following baseline characteristics will be summarized. Listings will also be provided:

- Age (descriptive statistics)
- Age category (<65, >=65)
- Gender (male, female)
- Race groups (Caucasian/white, Black, Asian/Oriental, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Regions (North America, Europe, Asia Pacific(excluding Japan), Japan)
- Ethnicity (Hispanic/latino, Not Hispanic/Latino)
- ECOG Performance Status (1, 0)
- Baseline Weight (kg)
- Baseline Height (cm)
- Baseline *FGFR* rearrangements status by local lab (commercial test provided to clinician as standard of care based on tumor tissue) and/or central lab (clinical trial assay performed on tumor tissue)
- Prior surgical resection of primary tumor (Yes/No)

- Prior (neo) adjuvant treatment (Yes, No)

FGFR2 aberration types will be summarized. A patient level listing will also be provided.

Pre-study anti-cancer surgery and prior radiation therapy will be summarized. For prior-radiation therapy, the number and percentage of patients with palliative and therapeutic radiation therapies will be presented in a summary table.

All prior systemic anticancer therapies (adjuvant therapies, neoadjuvant therapies, therapies for advanced/metastatic disease, and maintenance therapies) will be summarized. The number of patients with 1, 2, and >=3 prior regimens will be summarized for all systemic anticancer therapies and for advanced/metastatic disease only.

All collected information for cancer diagnosis, pre-study surgery, prior-radiation therapy, and prior systemic anti-cancer therapy will be summarized and listed.

6.3.3. Medical History

Medical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA 22.0). Medical history will be listed by patient number, start date and end date. The treatment start date and end date versus the first dose date maybe listed.

6.3.4. Prior/Concomitant Therapy and Therapies

Prior or concomitant medications and therapies will be collected from the time of informed consent through 30 days after administration of last dose of study medication.
Medications and therapies which started and stopped prior to the first dose of TAS-120 are considered as prior medications. Medications and therapies which started prior to the first dose of TAS-120 and continued into the treatment period are considered as prior and concomitant medications and therapies.

Medications or therapies with a start date from first dose of TAS-120 to 30 days after administration of the last dose of TAS-120 will be considered as concomitant medications or therapies.

Prior and concomitant medications will be coded according to World Health Organization (WHO) Drug Dictionary for Concomitant Medication. The concomitant medications will be summarized by ATC level 2 (Therapeutic Main Group) and ATC level 4 (Chemical/Therapeutic Subgroup) using the number and percentage of patients. Medications will be sorted in descending order of frequency of ATC level 2 and ATC level 4 within ATC level 2 in the total column. A patient will be counted only once within each level of summation if the patient has taken a medication more than once.

All prior and concomitant medications and therapies will be listed.

6.3.4.1. Prior Anticancer Therapy

Pre-study anti-cancer surgery and prior radiation therapy will be summarized. For pre-study surgery, the number and percentage of patients with biopsy, primary tumor removal, metastatic tumor removal will be reported. For prior-radiation therapy, the number and percentage of patients with palliative and therapeutic radiation therapies will be presented in a summary table.

All prior systemic anticancer therapies (adjuvant therapies, neoadjuvant therapies, therapies for advanced/metastatic disease, and maintenance therapies) will be summarized. The number of patients with 1, 2 and >=3 prior regimens will be summarized for all systemic anticancer therapies and for advanced/metastatic disease only. The number of patients and percent with best of response for prior systemic anticancer therapy will also be summarized.

All collected information for cancer diagnosis, pre-study surgery, prior-radiation therapy, and prior systemic anti-cancer therapy will be summarized and listed.

6.3.4.2. Other Prior/Concomitant Therapy

Prior/current medication will be classified by anatomic and therapeutic classes. Agents and medication will be reported using the generic name. A listing by patient will also be provided.

In addition, percentage of subjects who received concomitant medication for management of hyperphosphatemia will be reported by cohort (percentages of treated subjects by medication class and generic term).

Total duration of medications (excluding overlaps) given for management of hyperphosphatemia will be also summarized.

6.4. Efficacy Analyses

6.4.1. Primary Efficacy Analyses

The primary endpoint, Objective Response Rate (ORR), defined as the proportion of patients who achieved best overall response of partial response (PR) or complete response (CR) per RECIST 1.1 based on Independent Review Committee (IRC) in the Efficacy Population, will be summarized by a binomial response rate. ORR will be calculated from the best of overall response recorded from the start of treatment until progression disease or start of subsequent new anticancer treatment. The overall response can be derived based on target lesion response, non-target response as well as the emergence of new lesion for patients with measurable disease at baseline. Table 4 presents the rules to derive the overall response.

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

95% confidence interval (binomial proportion confidence interval) for ORR will be constructed with Clopper-Pearson 95% CI. The null hypothesis will be rejected if the 2-sided 95% CI lower

bound is greater than 10%. This translates in observing at least 17 responders out of 100 in the Efficacy Population.

The objective response rate will be created by both independent review and investigator review. The primary endpoints, ORR, assessed with RECIST 1.1, will be displayed in the efficacy tables with both independent and investigator review.

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

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

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

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

6.4.2. Secondary Efficacy Analyses

The Duration of Response (DOR) is defined as the time between the date of first response and the subsequent date of objectively documented progression of disease or death. The CR or PR will be derived based on investigators or independent radiologist assessment. The censoring rule is shown in Table 6.

Overall survival (OS) is defined as the time between the first dosing date and the date of death. Progression free survival (PFS) is defined as the time from the first dosing date to the date of the first documented progression or death due to any cause, whichever occurs first. The censoring rule is illustrated in Table 6 and Table 7.

Duration of response (DOR), PFS, and OS will be analyzed using Kaplan–Meier product-limit estimates. Median PFS and OS will be presented with 2-sided 95% CI if estimable. Censoring rules (Table 6, Table 7) is based on the Food and Drug Administration Guidance for Industry

Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007). The cumulative PFS and OS will be plotted over time.

The Disease Control Rate (DCR) is defined as the proportion of patient with objective evidence of CR, PR, or SD, except that there is no requirement for a confirmation of an SD response. DCR will be calculated and a 2-sided Clopper–Pearson 95% CI will be constructed.

Table 6. Censoring Rules for Progression-Free Survival

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

a. If documented PD and/or death occurs after the last dose, it is counted as a PFS event as long as the PD and/or the death occurs within 21 days since the date of the last dose of study drug and provided that it does not violate other censoring rules (e.g. start of new anticancer therapy before the PD or death). Otherwise the patient will be censored on the date of last tumor assessment before the date of last dose date + 21 days.
b. For PFS analysis, the date of last tumor assessment refers to the date of last adequate tumor assessment of CR, PR, SD, or PD.
c. This refers to patients who were still receiving study treatment at time of data cutoff.
d. Two or more missed tumor assessments is defined as having either one of the following two durations being longer than 2 cycles for the first 6 months of treatment, or thereafter 3:
- Duration between two consecutive tumor assessments
- Duration between the last tumor assessment and death or PD.

Table 7. Censoring Rules for Overall Survival (OS).

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

6.4.2.1. Sensitivity Analyses

The following sensitivity analyses will be performed on the key efficacy endpoints as follows:

- Primary efficacy endpoint (ORR) based on the Per-protocol Analysis Set using a similar analysis method as the primary analysis
- ORR and PFS based on assessments by the investigator or local radiologist on the Efficacy Population

6.4.3. Subgroup Analyses

To assess consistency of treatment effects in different subsets, IRC assessed ORR (primary analysis) will be summarized for the following subgroups.

- Age group (<65, >=65)
- Gender (male, female)
- Race (Caucasian/white, Black, Asian, Other)
- Baseline ECOG score (0, 1)
- Prior systemic therapy 1 line, 2 lines, and 3 or more lines for advanced/metastatic disease
- North America, Europe, Asia Pacific (excluding Japan), Japan,
- Prior surgical resection of primary tumor (Yes, No)
- Prior (neo) adjuvant treatment (Yes, No)
- Baseline *FGFR* rearrangements status by local lab (commercial test provided to clinician as standard of care based on tumor tissue) and/or central lab (clinical trial assay performed on tumor tissue)
- Patients with solid tissue sample and report

6.5. Safety Analyses

All safety analyses will be performed considering all treated patients.

6.5.1. Extent of Exposure

6.5.1.1. Administration of Study Drug

The number of cycles initiated and completed, extent of exposure (Treatment Duration) relative dose intensity in all cycle and total dosage for TAS-120 will be summarized.

Relative dose intensity (RDI) is defined as the ratio of the amount of drug actually administered to the amount planned in the study for TAS-120. The relative dose intensity is calculated in the following steps:

1. Amount of drug actually administered is total number of dose administered
2. Treatment Duration = last dose date – first dose date +1
3. Amount of drug planned for the patient =Treatment Duration
4. Relative Dose Intensity = (Amount of drug actually administered / Amount of drug planned) x 100%

A by-patient listing of dosing of study medication will be also provided.

6.5.1.2. Modification of Study Drug

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

The number and percentage of patient with at least one dose reduction and reason for the dose reduction will be summarized. Time to first dose reduction and interruption will be summarized.

By-patient listings of dose interruptions and dose reductions will be also provided.

6.5.2. Adverse Events

6.5.2.1. Deaths

All deaths including death due to disease progression occurring in screening, on treatment, 30-day safety follow-up, or survival follow-up periods will be summarized. The reasons of death will also be summarized. The reasons are categorized in the following terms:

- Radiological Disease Progression
- Clinical Disease Progression
- Toxicity
- Adverse Event
- Other

A by-patient listing of all deaths will be provided for the All Treated Patient population.

6.5.2.2. Serious Adverse Events

A serious Adverse Event (SAE) is an AE which falls into one or more of the following categories:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Is any other important medical event

Serious AEs will be summarized with the following categories:

- Overall summary of SAEs by worst CTC grade (grade 1, 2, 3, 4, 5, any grade, Grade 3-5) presented by SOC/PT.

- A summary of serious AEs, overall and by system organ class and preferred term.

Summary of treatment-related serious AE and by-patient listing of SAEs will also be provided.

6.5.2.3. Adverse Events Leading to Discontinuation of Study Drug

AEs leading to discontinuation will be summarized by treatment group:

- Overall summary of AEs leading to discontinuation by worst CTC Grade (grade 1, 2, 3, 4, 5, any grade, Grade 3-5) presented by SOC/PT
- Overall summary of treatment-related AEs leading to discontinuation by worst CTC grade (Grade 1, 2, 3, 4, 5, any grade, Grade 3-5) presented by SOC/PT

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

6.5.2.4. Adverse Events Leading to Dose Modification

AEs leading to dose modification (including dose interruption or reduction) will be summarized by treatment group:

- Overall summary of AEs leading to modification by worst CTC Grade (grade 1, 2, 3, 4, 5, any grade, Grade 3-5) presented by SOC/PT
- Overall summary of treatment-related AEs leading to discontinuation by worst CTC grade (Grade 1, 2, 3, 4, 5, any grade, Grade 3-5) presented by SOC/PT

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

6.5.2.5. Adverse Events

An adverse event (AE) is any untoward medical condition that occurs in a patient while participating in this clinical study. Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA 22.0) terminology and the severity of the toxicities will be graded according to the NCI CTCAE, v4.03, where applicable.

Adverse Events that occur from the initiation of TAS-120 medication administration to 30 days after the last dose of study medication, and do not necessarily have a causal relationship to the use of the study medication will be summarized.

Number of patients with AEs will be presented by system organ class in the overall column in decreasing order. Within each system organ class, the number of patients with AEs will be displayed by preferred term (PT) in descending order.

The following adverse event summary tables will be generated:

1) An overall summary with the number and percentage of patients reporting AEs, serious AEs, grade 3 or higher AEs, treatment-related AEs, AEs leading to study treatment (TAS-120) discontinuation and AEs with outcome of deaths.

   In the summary, a patient is counted once at the system organ class and once at each preferred term within the system organ class. Additional summary by system organ class, preferred term and grade (including Total and >= grade 3 categories) will also be generated.

2) Study-treatment-related AEs overall and by system organ class and preferred term. Additional summary by system organ class, preferred term and grade (including any grade and >= grade 3 categories) will also be generated.

   All those AEs with relationship to TAS-120 marked as "Related" or missing will be reported in the table.

3) AEs by highest grade (worse severity) overall and by system organ class and preferred term.

   In the summary, a patient is counted once at the highest grade for which the event occurred in the system organ class and the highest grade for each unique preferred term within that system organ class. Therefore, patients may only contribute once to each preferred term and once to each system organ class. The missing severity grade will be reported in a separate category.

4) Grade 3 or higher AEs, overall and by system organ class and preferred term

5) Study-treatment related AEs by grade (severity) , overall and by system organ class and preferred term

6) AEs leading to study treatment termination, overall and by system organ class and preferred term. Additional summary by system organ class, preferred term and grade (including Total and >= grade 3 categories) will also be generated.

7) AEs with outcome of deaths, overall and by system organ class and preferred term

The time to onset of some special AEs of interest in the study may be summarized if appropriate.

Severity of hyperphosphatemia will be graded based on serum phosphate levels as illustrated in Table 8 using identical derivation criteria as specified in the protocol (Protocol section 8.1.3.1.1,).

In addition, hyperphosphatemia toxicities grading based on CTCAE v5.0 will also be provided using the derivation criteria presented in Table 9.

Table 8. Hyperphosphatemia Toxicity Grading based on serum phosphate levels as specified in Protocol *

	Grade 1	Grade 2	Grade 3	Grade 4
Serum Phosphorus Result (mg/dL and mmol/L)	ULN < P < 5.5 (mg/dL) ULN < P < 1.78 (mmol/L)	5.5 ≤ P ≤ 7.0 (mg/dL) 1.78 ≤ P ≤ 2.26 mmol/L)	7.0 < P ≤ 10.0 (mg/dL) 2.26< P ≤ 3.23 (mmol/L)	P > 10.0 (mg/dL) P > 3.23 (mmol/L)

* Section 8.1.3.1.1, protocol amendment 9

Table 9. Hyperphosphatemia Toxicity Grading per CTCAE v5.0 and derivation criteria

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
CTCAE v5.0 criteria	Laboratory finding only and intervention no indicated	Noninvasive intervention indicated	Severe or medically significant but no immediately life threatening; hospitalization or prolongation of existing hospitalization indicated	Life-threatening consequences; urgent intervention indicated (e.g., dialysis)	Death
Derivation criteria	Serum phosphate > ULN	Serum phosphate > ULN **AND** concomitant therapy with phosphate binder	Serum phosphate > ULN **AND** Concomitant therapy with phosphate binder **AND** SAE of hyperphosphatemia/ related toxicity*	Serum phosphate > ULN **AND** Concomitant therapy with phosphate binder **AND** SAE of hyperphosphatemia/ related toxicity with immediately life threatening consequences*	Death due to hyperphosphatemia or related toxicity*

* as assessed by the sponsor

6.5.2.6. Adverse Events of Special Interest

Incidence:

Adverse event of special interest (AESI, for definition see Section 7.3), including hyperphosphatemia, will be summarized for each category/subcategory:

- Overall summary of AESI by worst CTC grade presented by category or subcategory / PT

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

Time to Onset:

Time-to-onset of selected AESI, including hyperphosphatemia, will be graphically displayed for each category/subcategory of AESI using the Kaplan-Meier technique:

- Time to AESI
- Time to AESI of Grade ≥3

Summary statistics for time to onset on the patients who had AESI will also be provided.

Time to Resolution:

Time-to-resolution of selected AESI, including hyperphosphatemia, will be summarized separately for each category / subcategory:

- Time to resolution of AESI
- Time to resolution of AESI of Grade ≥3

Time-to-resolution analyses are restricted to treated patients who experienced the specific events.

The following summary statistics will be reported: percentage of subjects who experienced the specific events, percentage of subjects with resolution of the longest AESI, median time-to resolution and to ≤ Grade 2 along with 95% CI (derived from Kaplan-Meier estimation, if estimable) and ranges.

6.5.2.7. Multiple Adverse Events

The following summary tables will be provided:

- Total number and rate (exposure adjusted) of occurrences for all AEs.
- For AESI: number of subjects experiencing an AESI once or multiple times

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

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

Y = 365.25 for years or Y = 30.4375 for months

Listing displaying the unique instances of all AEs (that is, after duplicates have been eliminated and overlapping and contiguous occurrences of the same event (same PT) have been collapsed) will be provided.

6.5.3. Clinical Laboratory Evaluations

Clinical laboratory results will be summarized using SI units. Laboratory measurements will be summarized for all protocol scheduled time points for all patients in the safety population. Descriptive (n, mean, STD, median, min and max) statistics will be presented for all clinical

chemistry, hematology and coagulation laboratory parameters at each scheduled visit. Change from baseline at each scheduled post-baseline visit will also be presented.

Patient counts and percentages of patient for each category of each urinalysis parameters will be summarized at each scheduled visit.

Shift tables will be presented for each laboratory parameter to display the shift from baseline to the maximum post-baseline CTCAE grade (v4.03), where applicable (see also Section 6.5.2.5). Summary tables will be provided presenting the count and percentage of patients for each laboratory test by the maximum post-baseline CTCAE grade reported. All post-baseline assessments (including unscheduled visits) will be used to determine the maximum (worst) post-baseline CTCAE grade. Time to maximum Grade 3/4 and time to resolution (return to grade <=2 or baseline grade or below) may be summarized as appropriate.

A baseline laboratory value will be defined as the last assessment performed on or prior to the date and time of first dose of study treatment. Laboratory test results will be categorized by CTCAE criteria V4.03.

Estimated creatinine clearance (CLcr) will be calculated using baseline creatinine value according to the following formula.

$$\text{CLcr(mL/min)} = \frac{[140 - \text{age(years)}] * \text{weight(kg)}}{72 * \text{serum creatinine(mg/dL)}} \{* 0.85 \text{ if female}\}$$

All clinical laboratory data will be presented in patient level listings.

The laboratory tests among Hematology, Serum chemistry, Coagulation, and Urinalysis are listed in Table 10.

Percentage change from baseline will be summarized for [CCI]. Summary for [CCI] levels at time points: screening, at the end of every 2 cycles up to cycle 4, every 3 cycles thereafter, and at the end of treatment will be presented. Subject level listing will also be generated.

Table 10. Laboratory Tests

Assessment	Test Items
Hematology and Coagulation	Red blood cell count, hemoglobin, hematocrit, platelets, white blood cell count with differential, neutrophils, lymphocytes, monocytes, eosinophils, basophils, International normalized ratio (INR), Activated partial thromboplastin time (APTT)
Serum chemistry	AST, ALT, ALP, total bilirubin, glucose, creatinine clearance, blood urea nitrogen (BUN) or urea, phosphorus, calcium, chloride, sodium, potassium, creatine kinase (CK), creatinine kinase MB (CK-MB), Troponin I, Troponin T
Urinalysis	Urine protein, glucose
Other	[CCI]

- Neutrophils includes both segmented and band neutrophils
- creatinine clearance includes calculated (Ccr) or measured creatinine clearance

Additional Analysis

In addition, further analyses on specific laboratory parameters will be performed:

Abnormal Hepatic Function Test

The number of subjects with the following laboratory abnormalities from on-treatment evaluations will be summarized by treatment group:

- ALT or AST > 3 x ULN, > 5 x ULN, > 10 x ULN and > 20 x ULN
- Total bilirubin > 2 x ULN
- Concurrent (within 1 day) ALT or AST > 3 x ULN and total bilirubin > 2 x ULN
- Concurrent (within 30 days) ALT or AST > 3 x ULN and total bilirubin > 2 x ULN

The following scatterplots will be produced for the following hepatic laboratory parameters:

- Total bilirubin peak vs. AST peak
- Total bilirubin peak vs. ALT peak

On-treatment peak total bilirubin and on-treatment peak AST/ALT may or may not happen on the same day of liver testing.

A by-subject listing of these specific abnormalities will be provided.

6.5.3.1.1. Ophthalmological Examination

Ophthalmological examination is performed at screening (within 28 days prior to study medication administration on Day 1 of Cycle 1), 4-6 weeks after starting treatment with TAS-120, End of treatment visit. Ophthalmological examination results will be summarized and listed.

6.5.3.1.2. Neurological Examination

The neurological examination is obtained at screening within 28 days prior to TAS-120 administration on Day 1 of cycle 1, other time due to local requirements or physician judgement, end of treatment visit, and 30-day safety follow-up visit. The examination results will be summarized and listed.

6.5.4. Vital Signs

Vital sign measurements including systolic blood pressure, diastolic blood pressure, pulse rate, respiration rate, and temperature at each scheduled and changes from baseline in vital sign measurements will be summarized with descriptive statistics at each scheduled time point.

Weight at each scheduled time and changes from baseline will be summarized with descriptive statistics at each scheduled time point for the safety population. Weight will be displayed in kilograms, height, collected only at baseline, will be displayed in centimeters, and temperature will be displayed in Celsius. The safety population will be used.

All vital signs data will be presented in a listing.

6.5.5. Electrocardiograms

Descriptive statistics for ECG parameters and changes from baseline will be presented by visit and treatment group (and/or dose).

Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to end of treatment (or end of phase or by visit).

In addition, the number (percentage) of patients with at least 1 post-baseline abnormal ECG result in QTc Fridericia during the on-treatment period will be summarized. Clinically abnormal ECG results based on QTc Fridericia correction will be categorized as follows:

Absolute QTcF interval prolongation:

- QTc interval <= 470 ms
- QTc interval >470 - 480 ms
- QTc interval > 480 - 500 ms
- QTc interval > 500 ms

Change from baseline in QTcF interval:

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

The number patient who experienced QTc abnormalities during the post baseline, but not presented in the baseline measurements will be summarized.

A subject level listing of ECG will be provided.

6.5.6. Physical Examination

All physical examination is performed 24 hours prior to TAS-120 administration on day 1 beginning with cycle 2. The baseline screening measurement of physical examination will be taken on screening within 28 days prior to TAS-120 administration on Day 1 of Cycle 1. The physical examination will also obtain at the End of Treatment Administration, and 30-day safety follow-up visit.

The physical examination data will be presented in a patient level listing.

6.5.7. ECOG Performance Status

The ECOG performance status score will be obtained at the following time points: screening, and 24 hours prior to TAS-120 on day 1 beginning with cycle 2, the End of Treatment Administration, and 30-day safety follow-up visit. The ECOG performance status scores and the grades from 0 to 5 are described in the following table:

Table 11. Grade Categories of Eastern Cooperative Oncology Group Score

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

The change from day 1 in cycle 1 in the ECOG performance status scores will be presented in a shift table. Time to Deterioration of ECOG performance status to 2 or greater will be summarized. A patient level listing will also be presented.

6.5.8. Pregnancy Test

For female patients with child bearing potential, pregnancy test result will be listed.

6.5.9. Tumor Tissue Sample Collection

The archived formalin fix paraffin embedded (FFPE) tumor tissue samples will be collected at any time while on the study from patients who signed the ICF if available. A patient level listing will be produced to display the FFPE output.

6.6. Patient Reported Outcomes (PRO)

Unless otherwise specified, the primary timepoint for the analysis of PRO endpoints is the last analysis visit before data is missing for more than 50% of the PRO population. This 'censoring' is done since when there is more than 50% missing data, reported PRO scores will be very sensitive to missing data assumptions. The primary assessment timepoint for the PRO analysis will be determined based on a data review prior to the database lock.

All EQ-5D and EORTC-QLQ-C30 questionnaires completed at baseline and on-study will be assigned to a time-point according to the windowing criteria in Table 12 and included in the analysis. In case a patient has two on-study assessments within the same window, the assessment closest to the time-point will be used. And, in the case of two assessments at a similar distance to the time-point, the latest one will be chosen. In the event where the patient has no assessment at all in a specific window, the observation will be treated as missing for that time-point.

Table 12. Time Windows for EQ-5D and EORTC-QLQ-C30 Assessment

Nominal Time-Point	Time Window
Screening	-28 to -1 days
Cycle 2, Cycle 4	Day 1 ± 3 days
>Cycle 4	Every 3 cycles on day 1 of the cycle ± 7 days
End of Treatment	Within 3 days of the decision to discontinuation

The Patient-Reported Outcomes (PRO) will be evaluated as close as possible to the tumor assessment schedules.

6.6.1. EQ-5D

PRO endpoints relating to the EQ-5D are as follows:

- Shift from screening in the EQ-5D 5 dimensions
- Change from screening in the EQ-5D-3L Index
- Change from screening in the EQ-5D-3L VAS score

There are 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression in EQ-5D questionnaire. Each dimension has 3 levels: no problems, some problems, severe problems (EQ-5D-3L). Once the data have been collected and a database created, a scoring function can be used to assign a value (i.e., EQ-5D index score: 5 dimensions digits combined in a 5-digit number) to self-reported health states from a set of population-based preference weights.

The EQ VAS records the patient's self-rated health state on a 100-point vertical, visual analogue scale (0 = worst imaginable health state; 100 = best imaginable health state).

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), EQ-5D Index and EQ-VAS will be provided.

6.6.2. EORTC QLQ-C30

Functional scales:

- Physical functioning: (1 - ((Q1+Q2+Q3+Q4+Q5)/5 -1)/3) * 100
- Role functioning: (1 - ((Q6+Q7)/2-1)/3) * 100
- Emotional functioning: (1 - ((Q21+Q22+Q23+Q24)/4-1)/3) * 100
- Cognitive functioning: (1 - ((Q20+Q25)/2-1)/3) * 100
- Social functioning: (1 - ((Q26+Q27)/2-1)/3) * 100

Global health status:

- Global health status/QoL: ((Q29+Q30)/2-1)/6 * 100

Symptom scales/items:

- Fatigue: ((Q10+Q12+Q18)/3-1)/3 * 100
- Nausea and vomiting: ((Q14+Q15)/2-1)/3 * 100
- Pain: ((Q9+Q19)/2-1)/3 * 100
- Dyspnea: ((Q8-1)/3 * 100
- Insomnia: (Q11-1)/3 * 100
- Appetite loss: (Q13-1)/3 * 100
- Constipation: (Q16-1)/3 * 100
- Diarrhea: (Q17-1)/3 * 100
- Financial difficulties: (Q28-1)/3 * 100

Missing values will be imputed for missing items by "assuming that the missing items have values equal to the average of those items which are present" for any scale in which at least half the items are completed. A scale in which less than half of the items are completed will be treated as missing. A questionnaire will be considered as received if at least one of the 15 scales is non-missing (after imputation).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.

PRO endpoints relating to the EORTC QLQ-C30 are as follows:

- Change from screening in each EORTC QLQ-C30 scale
- Time to first deterioration in the EORTC QLQ-C30 global health status and physical functioning scores
- Proportion of patients with deterioration based on the EORTC QLQ-C30 global health status and physical functioning scores

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.

The changes values from baseline to post-baseline and shift evaluation from baseline to post-baseline will be summarized.

Time to deterioration (TTD) of PRO scores is defined as the period between PRO at screening and the first deterioration (including death). Patient who did not have post-baseline deterioration will be censored on the last date of assessment.

CCI

[redacted]

6.7.1. PK Analysis

Blood samples of TAS-120 will be collected for patient on Day 1 of Cycle 2 pre-dose, post-dose 1 hour ±0.5 and 3 hours ±0.5 to assess the plasma exposure at 20 mg QD. In addition, blood samples will be collected on Day 1 of Cycle 3 and Day 1 of Cycle 4 pre-dose.

A summary table and subject level listing for plasma concentration will be provided.

Concentrations in pre-dose samples will be compared among Cycle 2, Cycle 3, and Cycle 4 by analysis of variance (ANOVA) with only patients who had neither dose modification nor dose interruption. Any samples that were collected after dosing will not be used in the comparison by ANOVA. Any patient who have only one pre-dose sample will be excluded from the comparison.

6.8. Interim Analyses

For interim review of safety, interim analyses of safety will be performed approximately every 3 months until the formal interim analysis cut-off. These interim safety review will be performed by a Safety Review Committee (SRC). 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. The tables, graphs, and listings to support the interim safety analyses will be provided in the safety review charter.

In addition, a formal interim analysis of safety and efficacy 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 both interim and primary efficacy analysis of primary efficacy endpoint.

To facilitate discussion with health authority, additional ad-hoc analysis may be performed as deemed appropriate by the sponsor.

7. DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

7.1. Baseline Period

Baseline evaluations or events are defined as evaluations or events that occur before the date and time of first dose during study treatment.

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

- Pre-treatment AEs will be defined as AEs with an onset date prior to but not including the day of the first dose during study treatment
- Baseline evaluations (laboratory tests, vital signs) will be defined as evaluations with a date on or prior to the day of first dose during study treatment

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

7.2. Post-Baseline Period

On-treatment AEs will be defined as AEs with an onset date and time on or after the date-time of the first dose of study drug (or with an onset date on or after the day of first dose of study treatment if time is not collected or is missing). An AE will be counted as on-treatment if the event occurred within 30 days of the last dose of study treatment.

On-treatment evaluations (laboratory tests, vital signs) will be defined as evaluations taken after the day (and time, if collected and not missing) of first dose of study treatment. An evaluation will be counted as on-treatment if it occurred within 30 days of the last dose of study treatment.

7.3. AESI Definition and Conventions

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

7.4. Time-to-Onset Definition

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

If the subject did not experience an AESI (of any grade) in the category, time-to-onset will be censored at the maximum follow-up time of each subject in their respective treatment group (that

is, for subjects without an event, follow-up time is defined from first dosing date up to last dosing date +30 days if subjects are off treatment and followed for at least 30 days, otherwise it is defined up to the last known alive date). The resulting Kaplan-Meier plot will represent the cumulative rate of the AESI (any grade) in the category over time.

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

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

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

7.5. Time-to-Resolution Definition

In order to derive the time-to-resolution, overlapping or contiguous AESI within a specific category will be collapsed into what will be termed "clustered" AESI. For example, if a subject (without pre-treatment AE) experienced an AE from 01 January to 05 January, another AE (with different PT but within same category) from 06 January to 11 January, and the same AE from 10 January to 12 January, these will be collapsed into one clustered AESI from 01 January to 12 January. Table 13 summarizes key derivation steps for each type of clustered select AEs. Algorithm for collapsing multiple records of adverse event is summarized in Section 7.6.

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

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

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

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

Table 13. Derivation of Clustered AESI

Type of clustered select AE	Derivation
Any grade	Collapse any on-treatment AESI from the same category
Study treatment-related of any grade	Collapse any on-treatment, study treatment-related AESI from the same category
Grade 3-5	Collapse any on-treatment AESI from the same category. Resolution will be based on the onset date of the earliest Grade 3-5 records (if no Grade 3-5 record, clustered AESI is excluded)
Study treatment-related of Grade 3-5	Collapse any on-treatment, study treatment-related AESI from the same category. Resolution will be based on the onset date of the earliest Grade 3-5 record (if no Grade 3-5 record, clustered AESI is excluded)

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

7.6. Multiple Adverse Events

The algorithm for collapsing multiple records of select adverse event is using the following conventions. For each patient and specified category, the corresponding adverse event records will be collapsed when:

Multiple adverse event records have the same onset date.

The onset date of an event record is either the same day or 1 day later than the resolution date of a preceding event record (contiguous events).

The onset date of an event record is after the onset date and prior to or on the resolution date of a preceding event record (overlapping events).

7.7. Other Data Handling Rules

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

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

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

Table 14. Partial Date Imputation Rule for TEAE or Medication

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

The rule above in Table 14 is also used for determining the cycles of adverse events and concomitant medications.

The derived date is only used for determining TEAEs, cycle of adverse events and concomitant medications. The collected partial dates will be reported in the listings.

For the medical history, prior surgery, prior radiotherapy, and prior systemic cancer therapies:

- Missing day and month - January 1 will be assigned to the missing fields.
- Missing month only - Treat day as missing and replace both month and day according to the above procedure.
- Missing day only - Assign first of the month to the missing day.

Partially missing stop dates for the types of data listed above will be imputed as:

- year is missing, no imputation. Date left missing.
- month is missing and year is prior to year of first dose of study medication- impute 'December'.
- month is missing and year the same as the year of the first dose of study medication – impute same month as in start date of study medication.
- day is missing, impute 'last date of that month'. If results in a date ≥ the date of the first dose of study medication impute day as the day prior to the first dose of study medication.

8. REFERENCES

1. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000 Jan 7;100:57-70.
2. Borad, M. J., Gores, G. J., & Roberts, L. R. (2015). Fibroblast growth factor receptor 2 fusions as a target for treating cholangiocarcinoma. Current Opinion in Gastroenterology, 31(3), 264–268. http://doi.org/10.1097/MOG.0000000000000171
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4. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.
5. Lamarca A, Hubner RA, Ryder WD, et al. Second-line chemotherapy in advanced biliary cancer: a systematic review. Annals of Oncology. 2014;25:2328-2338.

9. REVISION HISTORY

Table 15: List of changes from Version 1.0

Section	Changes from Version 1.0	Revision Rationale
5.4	Section 5.4 Timing of Analysis is added as a new section: The final analysis for primary objective will be performed when majority of treated patients responding to futibatinib had at least 6 months of follow-up from onset of response.	The timing for analysis is added per FDA's requirement for a complete package including efficacy data for all patients enrolled in this study and ensure that the majority of patients have sufficient follow up (i.e., a minimum of 6 months from onset of response) for the NDA submission
6.4.2	'Liver lesions only vs. lesions in and outside of liver' is removed from subgroup analysis	This information was not collected in the EDC per CRF design.
6.4.2	The following subgroup analysis is added: • Prior (neo) adjuvant treatment (Yes, No) • Baseline *FGFR* rearrangements status by local lab (commercial test provided to clinician as standard of care based on tumor tissue) and/or central lab (clinical trial assay performed on tumor tissue) • Patients with solid tissue sample and report	(neo) Adjuvant is a relevant subgroup of interest Biomarker test subgroup analysis are added per FDA CDx request
6.5.2.5	Add additional analysis of Hyperphosphatemia toxicities based on CTCAE v5.0 criteria (Table 9)	To have a comprehensive assessment of hyperphosphatemia, analysis based on both CTCAE v5.0 criteria and protocol specified criteria will be performed.
6.5.3	Liver toxicity analysis are added. The number of subjects with the following laboratory abnormalities from on-treatment evaluations will be summarized	Revised per the FDA's recommendation to include liver toxicity analysis.

	• ALT or AST > 3 x ULN, > 5 x ULN, > 10 x ULN and > 20 x ULN • Total bilirubin > 2 x ULN • Concurrent (within 1 day) ALT or AST > 3 x ULN and total bilirubin > 2 x ULN • Concurrent (within 30 days) ALT or AST > 3 x ULN and total bilirubin > 2 x ULN The following scatterplots will be produced for the following hepatic laboratory parameters: • Total bilirubin peak vs. AST peak • Total bilirubin peak vs. ALT peak On-treatment peak total bilirubin and on-treatment peak AST/ALT may or may not happen on the same day of liver testing. A by-subject listing of these specific abnormalities will be provided.	
6.5.3	Delete following paragraphs in section 6.5.3 "Any laboratory abnormality that has a clinical impact on the patient, eg, results in delay of study drug 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 < 1000/mm^3 with a single body temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than 1 hour. All laboratory data will be analyzed using CTCAE grade criteria (Version 4.03)." "Evaluation of any clinically significant laboratory test will be repeated, as clinically indicated, until the value returns to the baseline level or clinically stabilizes, or until another anticancer treatment is started."	Deleted paragraphs are described in protocol. They are guidance as what should have been reported as AE/clinical follow-up. It is not necessary to repeat them in SAP.

	"For all the patients, blood samples for measurement of [redacted] levels is collected during Screening within 28 days prior to TAS-120 administration on Day 1 of Cycle 1. Thereafter, samples will be collected in conjunction with tumor assessments/scans, i.e., at the end of every 2 cycles up to Cycle 4, and every 3 cycles thereafter, or as clinically indicated, and at the EOT Visit."	
Other	Editorial changes include: 1. Change "drug related" to "treatment related" throughout the document 2. change "anti-cancer therapy" to "systemic anti-cancer therapy" 3. Remove abbreviation and reference that were not used anywhere in this SAP	