1. PROTOCOL AND AMENDMENTS

The final global protocol for study TAS-114-201 (Amendment 1.0, dated 27 September 2016) is provided in this appendix. Other versions of the study protocol (including the original protocol dated 03 May 2016 and 2 amendments specific to sites in Japan) are available upon request.

A RANDOMIZED, OPEN-LABEL, MULTI-CENTER, INTERNATIONAL PHASE 2 STUDY OF TAS-114 IN COMBINATION WITH S-1 IN PATIENTS WITH ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER

TAS-114/S-1

Protocol No.: TO-TAS-114-201

IND No.: CCI

EudraCT No: 2016-001806-40

03 MAY 2016 Version 1.0

27 SEPTEMBER 2016 Version 2.0 Amendment 1.0 (except Japan)

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

SPONSOR CONTACT and MEDICAL MONITOR:

Western Region

PPD, MD, PhD

Taiho Oncology, Inc.

101 Carnegie Center, Suite 101

Princeton, NJ 08540

US

Tel: PPD

Cell: PPD

Fax: PPD

PPD

Japan

PPD, MD, PhD

Taiho Pharmaceutical Co., Ltd.

1-2-4, Uchikanda, Chiyoda-ku,

Tokyo, 101-0047

Japan

Tel: PPD

Cell: PPD

Fax: PPD

PPD

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

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2. SYNOPSIS

Title of Study: **A RANDOMIZED, OPEN-LABEL, MULTI-CENTER, INTERNATIONAL PHASE 2 STUDY OF TAS-114 IN COMBINATION WITH S-1 IN PATIENTS WITH ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER**	
Protocol Number:	TO-TAS-114-201
Phase:	2
Indication:	Advanced or metastatic non-small cell lung cancer

Background:

TAS-114 is a modulator of 5-fluorouracil (5-FU). TAS-114 potently inhibits the conversion of 2'-deoxyuridine-5'-triphosphate (dUTP; FdUTP) into 2'-deoxyuridine-5'-monophosphate (dUMP; FdUMP) by the reversible inhibition of deoxyuridine triphosphatase (dUTPase), which acts as a gatekeeper protein for uracil and 5-FU misincorporation into DNA.

S-1 is an oral fluoropyrimidine that combines tegafur (5-fluoro-1-(tetrahydro-2-furyl) uracil, FT), a prodrug of 5-FU, with two modulators, gimeracil (CDHP, 5-chloro-2,4-dihydroxypyridine), which inhibits 5-FU degradation by inhibition of dihydropyrimidine dehydrogenase (DPD), and oteracil potassium (Oxo, monopotassium 1,2,3,4-tetrahydro-2,4-dioxo-1,3,5-triazine- 6- carboxylate), which inhibits the phosphorylation of 5-FU in the digestive tract, in a molar ratio of 1:0.4:1. In studies conducted in Europe, Japan, and the United States (US), S-1 has demonstrated itself to be an effective fluoropyrimidine in the treatment of various advanced cancers, including lung tumors. In an S-1 Phase 2 study for 2nd line non-small cell lung cancer (NSCLC), a total of 57 patients with advanced NSCLC received S-1 30 mg/m^2. Median progression-free survival (PFS) (2.9 months) and overall survival (OS) (7.3 months) were comparable to those observed with pemetrexed and docetaxel.

Based on non-clinical pharmacology and toxicology models, the combination of TAS-114 with S-1 has demonstrated a potential to enhance the antitumor activity of S-1 with acceptable changes in its toxicity profile.

Wilson et al reported that uracil misincorporation is a potent determinant of cytotoxicity to thymidylate synthase (TS) inhibition in NSCLC and that inhibition of dUTPase is a mechanism-based therapeutic approach to significantly enhance the efficacy of TS-targeted chemotherapeutic agents.

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Study Objectives:

Primary

- To compare the PFS of patients with advanced or metastatic NSCLC, when treated with TAS-114/S-1 combination versus S-1.

Secondary

- To investigate the OS, overall response rate (ORR), disease control rate (DCR), and duration of response (DR).
- To investigate the safety and tolerability.

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Study Design:

This is a randomized, open-label, Phase 2 study of TAS-114 administered in combination with S-1, to investigate the efficacy, safety and tolerability of the TAS-114/S-1 regimen in patients with advanced or metastatic NSCLC.

The study will be conducted internationally in 2 regions: Asian [Japan] and Western [Europe and US]. Patients will be randomized into TAS-114/S-1 arm versus S-1 control arm in a 1:1 ratio.

Randomization will take place once the consented patient has completed all the necessary baseline procedures and is deemed eligible for study entry. Treatment assignment will be done centrally using a dynamic allocation method (biased coin) via an interactive voice/web response system (IXRS) stratified by:

- Geographical region (Region 1: Asian [Japan]; Region 2: Western [Europe and US])
- Histological subtypes (nonsquamous cell carcinoma [including mixed] and squamous cell carcinoma)

Study Duration:

Patients will receive the study drug according to the proposed treatment schedule until progressive disease (PD), occurrence of intolerable side effects, removal by the Investigator, or withdrawal of consent. A patient is considered discontinued from study treatment when either TAS-114/S-1 or S-1 alone is discontinued.

For the purpose of the final analyses, the study will be considered completed when all patients have discontinued from treatment or a minimum of 12 months from the date of the first day of treatment with TAS-114/S-1 or S-1 of the last patient enrolled or until the target number of events (deaths, n=80) is reached, whichever occurs first.

Inclusion Criteria:

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

1. Provision of written informed consent consistent with International Council for Harmonisation (ICH)-Good Clinical Practice (GCP) guidelines and respective local law;
2. Age ≥ 18 years old (≥ 20 years old in Japan);
3. Histologically diagnosed or cytologically proven advanced or metastatic NSCLC patients, either Stage IIIB/Stage IV disease (according to Version 7 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology), or recurrent disease following radiation therapy or surgical resection;
4. Patients who had received at least 2 prior therapies for advanced or metastatic disease condition, including platinum doublet and pemetrexed, docetaxel, or immunotherapy, and were refractory to or unable to tolerate their last prior therapy. For patients with known epidermal growth factor receptor (EGFR) activating mutations or anaplastic lymphoma kinase translocations, and/or ROS1 rearrangements, appropriate targeted treatment should have been used. The following histological tumor types are also eligible to be included:
   - Adenocarcinoma with bronchiolo-alveolar differentiation
   - Large cell carcinoma
5. Tumor is locally advanced or metastatic and not suitable for surgery and radiotherapy is not indicated;
6. Measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) criteria (Version 1.1, 2009);
7. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1;
8. Predicted life expectancy of at least 3 months;
9. Able to take medications orally;
10. Adequate organ function as defined by:
    - Adequate bone marrow function: absolute neutrophil count (ANC) ≥ 1500/mm^3, hemoglobin ≥ 10.0 g/dL, platelets ≥ 100,000/mm^3
    - Adequate liver function: Total bilirubin ≤ 1.5 × upper limit of normal (ULN), aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤ 3 × ULN (existent liver metastases ≤ 5 × ULN)
    - Adequate renal function: Calculated creatinine clearance ≥ 50 mL/min (Cockcroft-Gault

Equation)

11. Women of childbearing potential (WOCBP) must have a negative pregnancy test (urine or serum) within 7 days prior to starting the study drug. Both males and females must agree to use effective birth control during the study (prior to the first dose and for 6 months after the last dose) if conception is possible during this interval. Female patients are considered to not be of childbearing potential if they have a history of hysterectomy, or are post-menopausal defined as no menses for 12 months without an alternative medical cause. For both males and females, see Section 8.7.2 for definitions of contraceptive methods considered effective for this protocol;
12. Willing and able to comply with required scheduled visits and study procedures.

Exclusion Criteria:

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

1. Treatment with any of the following within the specified time frame prior to the study drug administration:
   - Major surgery within prior 4 weeks and minor surgery within 7 days;
   - Radiotherapy for extended field within prior 4 weeks or limited field within prior 2 weeks;
   - Any anticancer therapy or investigational agent within prior 3 weeks.
2. A serious illness or medical condition including but not limited to the following:
   - Patients with brain or subdural metastases are not eligible unless they have completed local therapy and have discontinued the use of therapeutic corticosteroids and are stable for at least 1 month before study drug administration;
   - Known leptomeningeal metastatic disease;
   - Known acute or chronic active systemic infection;
   - Any cardiac disease, such as myocardial infarction, unstable angina, symptomatic congestive heart failure (CHF) New York Heart Association (NYHA) class III or IV within the last 6 months. If > 6 months, cardiac function must be within normal limits and the patient must be free of cardiac-related symptoms;
   - Chronic nausea, vomiting, or diarrhea considered to be clinically significant by investigator's discretion;
   - Current or past severe lung disease (eg, interstitial pneumonia, pulmonary fibrosis, or severe emphysema);
   - Pleural, peritoneal, or pericardial effusion which will require surgical intervention in the near term;
   - Any history or presence of poorly controlled gastrointestinal (GI) disorders that could affect the absorption of the trial drug (eg, Crohn's disease, ulcerative colitis);
   - Known human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS)-related illness, or chronic or acute hepatitis B or C;
   - Any other clinically significant acute or chronic medical or psychiatric condition or any laboratory abnormality that may increase the risk associated with study drug administration, or may interfere with the interpretation of study results;
   - Poorly controlled (despite medication) or severe diabetes mellitus;
   - Continuous systemic steroid administration (oral or intravenous);
   - Other concurrent active cancer (synchronous double cancer or heterochronous double cancer with a disease-free interval of 3 years or shorter, excluding lesions consistent with intraepithelial cancer, ie, carcinoma in situ, or intramucosal cancer) that is assessed as cured

by local treatment.

3. Concomitant treatment with the following drugs that may interact with S-1:
   - Sorivudine, brivudine, uracil, eniluracil, folinate/folinic acid, (enhance S-1 activity);
   - Cimetidine, dipyridamole, and nitroimidazoles, including metronidazole and misonidazole (may enhance S-1 activity);
   - Methotrexate (may enhance S-1 activity);
   - Clozapine (may increase risk and severity of hematologic toxicity with S-1);
   - Allopurinol (may diminish S-1 activity);
   - Phenytoin (S-1 may enhance phenytoin activity);
   - Flucytosine, a fluorinated pyrimidine antifungal agent (may enhance S-1 activity);
   - Coumarin-derivative anticoagulant (S-1 may enhance activity of coumarin-derivative anticoagulant);
4. Known hypersensitivity to S-1 or its metabolites (eg, 5-FU);
5. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose/galactose malabasorption since S-1 contains lactose.
6. Previous use of TAS-114, S-1, and 5-FU drugs;
7. A pregnant or lactating female or possibly pregnant women, or men or women wishing to have children during the study period;
8. A judgment of the investigator that the patient is inappropriate for study participation.

Planned Sample Size:

Approximately 124 advanced or metastatic NSCLC patients.

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Treatment Regimen:

Treatment cycle of the experimental arm (TAS-114/S-1) and control arm (S-1 alone) will be 21 days: 14 days of treatment and 7 days recovery. TAS-114 and S-1 will be administered orally with a glass of water BID at least one hour before or after a meal.

Safety Criteria for Evaluation:

Standard safety monitoring will be performed and adverse events (AEs) will be graded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

Efficacy Criteria for Evaluation:

Central tumor imaging assessments will be performed throughout study treatment using RECIST guidelines (Version 1.1, 2009). Computed tomography (CT) scans will be performed every 6 weeks.

Statistical Methods:

Safety data (AEs, vital sign measurements, and clinical laboratory results) will be summarized

descriptively. Efficacy data for PFS, OS, ORR, DR, and DCR will be summarized descriptively.

3. STUDY SCHEDULES

Table 1: Study Schedule of TAS-114 and S-1 Arm

	Baseline		On-Treatment						End of Treatment/Study		
	Baseline Day		Cycle 1 (Day of Cycle)			Subsequent Cycles (Day of Cycle)			End of Treatment[1]	30-Day Safety Follow-up Visit[2]	Survival Follow-up
Visit ID/Procedure	**-28 to -1**	**-7 to 0[3]**	**1**	**8**	**15**	**1**	**15**	**End of Recovery**			
Visit Window	**0**	**0**	**-1 to 0**	**± 3**	**± 3**	**-1 to 0**	**± 3**	**± 7**	**± 3**	**-7**	
Sign ICF	X										
Inclusion/Exclusion	X		X								
Assign Patient Number	X[4]										
Medical History	X										
Baseline Signs and Symptoms	X	X	X								
Physical Exam[5]	X	X	X[5]	X	X	X[5]			X	X	
Height	X										
Vital Signs/Weight[5]	X	X		X		X[5]			X	X	
Performance Status[5]	X	X	X			X[5]			X	X	
ECG	X								X	X	
Hematology[5]	X	X		X	X	X[5]	X[5]		X	X	
Serum Chemistry[5]	X	X		X	X	X[5]	X[5]		X	X	
Coagulation[5]	X	X		X	X	X[5]	X[5]		X	X	
Urinalysis	X	X							X	X	
Pregnancy test[6]		X									
Concomitant Medications[7]	→	→	→	→	→	→	→	→	→	→	
AE/Toxicity Assessment[7]			→	→	→	→	→	→	→	→	
Tumor Assessment[8]	X							X[8]	X[8]		
TAS-114[9]			→	→	→	→	→				
S-1.[10]			→	→	→	→	→				

	Baseline		On-Treatment						End of Treatment/Study		
	Baseline Day		Cycle 1 (Day of Cycle)			Subsequent Cycles (Day of Cycle)			End of Treatment[1]	30-Day Safety Follow-up Visit[2]	Survival Follow-up
Visit ID/Procedure	-28 to -1	-7 to 0[3]	1	8	15	1	15	End of Recovery			
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Survival Status[12]	→										

Abbreviations: AE = adverse event; BID = twice daily; ECG = electrocardiogram; ICF = informed consent; CCI .

[1] End of Treatment: If the decision to discontinue TAS-114/S-1 is made within 2 weeks after the patient's last treatment visit, an End of Treatment visit is not required unless deemed clinically necessary by the investigator. If the decision to discontinue TAS-114 (because of disease progression or other reasons) is made more than 2 weeks after the last treatment visit, an End of Treatment visit is required. See Section 10.4.1.

[2] 30-Day Safety Follow-up Visit: If the patient starts new anticancer therapy within 30 days of the end of treatment, the 30-day Safety Follow-up visit should be performed before the start of new anticancer therapy within the 30-day window. See Section 11.13.

[3] Baseline Assessment (Day -7 to -1) will be obtained within 7 days before treatment on Day 1 of Cycle 1.

[4] Patient Number Assignment: A patient number will be assigned once a patient has entered study screening (ie, has signed the ICF).

[5] The physical exam, vital signs determination, weight, performance status, laboratory evaluations (hematology, serum chemistry, and coagulation) will be obtained within 1 day before study drug administration on Day 1 of each cycle. After Cycle 4, the Day 15 laboratory evaluations are not required unless clinically indicated by the investigator. After Cycle 6, the laboratory evaluations can be accepted within 2 days before study drug administration on Day 1 of each cycle, if there are no drug-related AEs greater than Grade 2 observed in the latest cycle.

[6] Pregnancy Test: Pregnancy test is required at Baseline (within 7 days prior to Day 1 of Cycle 1) and at End of Treatment and 30-day Safety Follow-up visit. More frequent pregnancy assessments may be performed as required by local law.

[7] Concomitant medications will be collected from the time of signing of the ICF through 30 days after administration of the last dose of study drug or until the start of new antitumor therapy, whichever is earlier.
AE/toxicity assessments will be collected from the time a patient starts receiving study treatment through 30 days after administration of the last dose of study drug or until the start of new antitumor therapy, whichever is earlier.

[8] Tumor assessments/scans will be performed at baseline, at the end of every 6 weeks (± 7 days) beginning at Cycle 2 throughout all the treatment cycles, and at the time of discontinuation. See Section 11.12, Tumor Assessments/Scans for details. Computerized tomography (CT) scans obtained before signing the ICF may be used as the baseline tumor scan if it is within 28 days of the first study drug administration. If the patient has discontinued treatment for reasons other than radiologic disease progression, a CT scan should be performed every 6 weeks (± 1 week) until the patient starts new anticancer therapy visit. Following Cycle 6, CT assessments may be adjusted to every 9 weeks.

[9] TAS-114 administration: orally BID together with S-1 on Days 1 through 14 of each cycle. See Section 9.1.2.1 for TAS-114 Dose Levels.

[10] S-1 administration: orally BID together with TAS-114 on Days 1 through 14 of each cycle.

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[12] Survival Follow-up: Obtain survival status (alive/dead) at scheduled 8-week intervals until death. Survival status should be collected for up to approximately 12 months after the first dose of treatment with TAS-114/S-1 of the last patient enrolled or until the target number of events is reached, whichever occurs first, even if consent for study participation has been withdrawn.

Table 2: Study Schedule of S-1 Arm

	Baseline		On-Treatment						End of Treatment/Study		
	Baseline Days		Cycle 1 (Day of Cycle)			Subsequent Cycles (Day of Cycle)			End of Treatment[1] for S-1	30-Day Safety Follow-up Visit[2]	Survival Follow-up
Visit ID/Procedure	**-28 to -1**	**-7 to 0[3]**	**1**	**8**	**15**	**1**	**15**	**End of Recovery**			
Visit Window	**0**	**0**	**-1 to 0**	**± 3**	**± 3**	**-1 to 0**	**± 3**	**± 3**	**± 3**	**-7**	
Sign ICF	X										
Inclusion/Exclusion	X		X								
Assign Patient Number	X[4]										
Medical History	X										
Baseline Signs and Symptoms	X	X	X								
Physical Exam[5]	X	X	X[5]	X	X	X[5]			X	X	
Height	X										
Vital Signs/Weight[5]	X	X		X		X[5]			X	X	
Performance Status[5]	X	X	X			X[5]			X	X	
ECG	X								X	X	
Hematology[5]	X	X		X	X	X[5]	X[5]		X	X	
Serum Chemistry[5]	X	X		X	X	X[5]	X[5]		X	X	
Coagulation[5]	X	X		X	X	X[5]	X[5]		X	X	
Urinalysis	X	X							X	X	
Pregnancy test[6]		X									
Concomitant Medications[7]	→	→	→	→	→	→	→	→	→	→	
AE/Toxicity Assessment[7]			→	→	→	→	→	→	→	→	
Tumor Assessment[8]	X							X[8]	X[8]		
S-1 Treatment[9]			→	→		→	→				
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Survival Status[11]	→	→	→	→	→	→	→	→	→	→	→

Abbreviations: AE = adverse event; BID = twice daily; ECG = electrocardiogram; ICF = informed consent; CCI .

[1] End of Treatment: If the decision to discontinue S-1 is made within 2 weeks after the patient's last treatment visit, an End of Treatment visit is not required unless deemed clinically necessary by the investigator. If the decision to discontinue S-1 (because of disease progression or other reasons) is made more than 2 weeks after the last treatment visit, an End of Treatment visit is required. See Section 10.4.1.

[2] 30-Day Safety Follow-up Visit: If the patient starts new anticancer therapy within 30 days of the end of treatment, the 30-day Safety Follow-up visit should be performed before the start of new anticancer therapy within the 30-day window. See Section 11.13.

[3] Baseline Assessment (Day -7 to -1) will be obtained within 7 days before treatment on Day 1 of Cycle 1.

[4] Patient Number Assignment: A patient number will be assigned once a patient has entered study screening (ie, has signed the ICF).

[5] The physical exam, vital signs determination, weight, performance status, laboratory evaluations (hematology, serum chemistry, and coagulation) will be obtained within 1 day before study drug administration on Day 1 of each cycle starting at Cycle 2. After Cycle 4, the Day 15 laboratory evaluations are not required unless clinically indicated by the investigator. After Cycle 6, the laboratory evaluations can be accepted within 2 days before study drug administration on Day 1 of each cycle, if there are no drug-related AEs greater than Grade 2 observed in the latest cycle.

[6] Pregnancy Test: Pregnancy test is required at Baseline (within 7 days prior to Day 1 of Cycle 1) and at End of Treatment and 30-day Safety Follow-up visit. More frequent pregnancy assessments may be performed as required by local law.

[7] Concomitant medications will be collected from the time of signing of the ICF through 30 days after administration of the last dose of study drug or until the start of new antitumor therapy, whichever is earlier.
AE/toxicity assessments will be collected from the time a patient starts receiving study treatment through 30 days after administration of the last dose of study drug or until the start of new antitumor therapy, whichever is earlier.

[8] Tumor assessments/scans will be performed at baseline, at the end of every 6 weeks (± 7 days) beginning at Cycle 1 Day 1 throughout all the treatment cycles, and at the time of discontinuation. See Section 11.12, Tumor Assessments/Scans for details. Computerized tomography (CT) scans obtained before signing the ICF may be used as the baseline tumor scan if it is within 28 days of the first study drug administration. If the patient has discontinued treatment for reasons other than radiologic disease progression, a CT scan should be performed within 2 weeks of the End of Treatment visit. Following Cycle 6, CT assessments may be adjusted to every 9 weeks.

[9] S-1 administration: orally BID on Days 1 through 14 of each cycle.

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[11] Survival Follow-up: Obtain survival status (alive/dead) at scheduled 8-week intervals until death. Survival status should be collected for up to approximately 12 months after the first dose of treatment with S-1 of the last patient enrolled or until the target number of events is reached, whichever occurs first, even if consent for study participation has been withdrawn.

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5. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 3: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
5-FU	5-fluorouracil
AE	Adverse event
AIDS	acquired immune deficiency syndrome
ALK	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the concentration time curve
BID	Twice daily
BRCA1	breast cancer 1, early onset
BRCA2	breast cancer 2, early onset
BSA	body surface area
CHF	Congestive heart failure
CI	Confidence interval
CK	Creatine kinase
CK-MB	Creatine kinase (isoform heart muscle)
CK-MM	Creatine kinase (isoform skeletal muscle)
CL/F	Oral clearance
C_{max}	Maximum observed plasma concentration
CPK	Creatine phosphokinase
CR	Complete response
CRO	Contract Research Organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DCR	Disease control rate
DLT	Dose-limiting toxicity
DPD	dihydropyrimidine dehydrogenase
DR	Duration of response
dUMP	2'-deoxyuridine-5'-monophosphate
dUTP	Deoxyuridine triphosphate
dUTPase	Deoxyuridine triphosphatase
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group

Abbreviation or Specialist Term	Explanation
eCRF	Electronic case report form
EGFR	epidermal growth factor receptor
FDA	Food and Drug Administration
FdUrd	2'-deoxy-5-fluorouridine
FdUTP	2'-deoxy-5-fluorouridine 5'-triphosphate
FFPE	Formalin fixed paraffin embedded
G-CSF	Granulocyte colony-stimulating factor
GCP	Good Clinical Practice
GI	gastrointestinal
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC50	50% inhibitory concentration
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IND	Investigational New Drug
IRB	Institutional Review Board
IU	International Units
IXRS	Interactive voice/web response system
J GCP	Japanese Good Clinical Practice
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	progression-free survival
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PK	Pharmacokinetic(s)
PR	Partial response
RBC	Red blood cell
RD	Recommended dose
RECIST	Response Evaluation Criteria in Solid Tumors
RT-PCR	reverse transcription polymerase chain reaction

Abbreviation or Specialist Term	Explanation
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SI	International System (of Units)
$t_{1/2}$	Elimination half-life
TKI	tyrosine kinase inhibitor
T_{max}	Time to maximum plasma concentration
TOI	Taiho Oncology, Incorporated
TS	Thymidylate synthase
ULN	Upper limit of normal
UNG	Uracil-DNA glycosylase
US	United States
WBC	White blood cell
WHO	World Health Organization
WOCBP	Women of childbearing potential

6. INTRODUCTION AND STUDY RATIONALE

6.1. Unmet Medical Need

5-fluorouracil (5-FU), an anti-malignant tumor antimetabolite, was discovered by Heidelberger et al. in 1957[1]. Chemotherapy regimens containing 5-FU drugs as the backbone are mainstays for the treatment of many cancers including breast, colorectal, and gastric cancer. Many combination chemotherapies employing 5-FU with chemical modulators such as leucovorin and other anti-malignant tumor agents have been investigated and have demonstrated efficacy against a variety of carcinomas to date[2]. Oral fluoropyrimidines such as S-1, a fixed dose combination of tegafur, a prodrug of 5-FU, gimeracil, a dihydropyrimidine dehydrogenase (DPD) inhibitor that prevents degradation of 5-FU by the body and maintains 5-FU exposure, and oteracil potassium, an orotate phosphoribosyltransferase (OPRT) inhibitor that decreases the activity of 5-FU in normal gastrointestinal (GI) mucosa have been developed [3]. However, chemotherapies using 5-FU or S-1 can cause intrinsic and acquired resistance to the 5-FU drugs. In non-clinical models, overexpression of deoxyuridine triphosphatase (dUTPase) reduced the sensitivity of cancer cells to 2′-deoxy-5-fluorouridine (FdUrd) by fourfold–fivefold[4] and transient suppression of dUTPase sensitized cancer cells to FdUrd with the intracellular accumulation of deoxyuridine triphosphate (dUTP).[5] In clinical studies in patients with colorectal cancer (CRC), dUTPase expression in the tumor tissue appeared to correlate with poor prognosis and overall survival (OS) outcomes as well as resistance to 5-FU-based chemotherapy[6]. These observations indicate that dUTPase may be one of the causal factors for resistance to 5-FU-based chemotherapies. Therefore, the development of new drugs that can be expected to achieve higher efficacy than the existing 5-FU drugs is urgently required.

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related mortality worldwide[7]. Despite treatment with immunotherapy, platinum- and taxane-based chemotherapy, patients with refractory metastatic NSCLC have a median survival of approximately 8 to 10 months. Despite the increased number of treatment options available for patients with NSCLC, there has been little OS improvement from several new agents, including pemetrexed, erlotinib and bevacizumab beyond very small subpopulations. Overall, this group of patients only has an OS of about 8 months after progression from platinum agents. Once resistance to tyrosine kinase inhibitors (TKIs) occurs, the patients who have epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase or ROS translocations will have a rapid disease progression.[8] Therefore, the majority of NSCLC cases remain a disease with high burden and unmet medical need.

6.2. TAS-114

TAS-114 is a modulator of 5-FU. TAS-114 potently inhibits the conversion of 2'-deoxyuridine-5'-triphosphate (dUTP; FdUTP) into 2'-deoxyuridine-5'-monophosphate (dUMP; FdUMP) by the reversible inhibition of dUTPase which acts as a gatekeeper protein for uracil and 5-FU misincorporation into DNA.

TAS-114 itself does not have an antitumor effect. TAS-114 can enhance antitumor activity of 5-FU. Section 6.4.1 describes the mechanism of action when TAS-114 is used in combination with 5-FU.

6.2.1. ADME and Toxicological Profiles of TAS-114

The pharmacokinetics (PK) of TAS-114 were evaluated in the Japanese healthy volunteers, and the plasma protein binding and metabolism of TAS-114 have been studied in non-clinical studies.

6.2.1.1. Absorption

The absorption of TAS-114 was increased dose-proportionality in healthy human volunteers under the fasting condition at dose ranges from 6 mg to 300 mg. The average of time to maximum plasma concentration (t_{max}) and elimination half-life ($t_{1/2}$) were 1.00 hour to 2.00 hours and 1.49 hour to 3.38 hours, respectively, and multiple administration of TAS-114 at 60 mg and 150 mg did not give any effects on the PK of TAS-114. Although the mean plasma concentrations of TAS-114 were increased by food at a dose of 60 mg, there was no significant food effect on TAS-114 absorption.

6.2.1.2. Distribution

The plasma protein binding ratios of TAS-114 were 78.1 to 81.5% in humans.[9]

Metabolism

Cytochrome P-450 (CYP) isozymes involved in the metabolism of TAS-114 were investigated using human hepatic microsomes in which various CYP isozymes were expressed.[10] The results have shown that M-1, a primary metabolite of TAS-114, is produced specifically by CYP3A4.

6.2.1.3. Excretion

In humans, the urinary excretion of TAS-114 was only 1.28% to 5.56% of dose, suggesting that the urinary excretion of TAS-114 was a minor pathway of TAS-114 elimination. Based on the mass balance study of animals,[11] the major elimination pathway of TAS-114 was considered to be metabolism and subsequent biliary excretion of TAS-114 metabolites.

6.2.1.4. Drug Interactions

In 2 drug interaction studies, the inhibitory effect of TAS-114 on various CYP isozymes was examined using human hepatic microsomes. The results showed that TAS-114 exhibited the most potent inhibitory effect on CYP2C9 (50% inhibitory concentration [IC50 value] = 57.7 μmol/L), and the IC50 values for TAS-114 on the CYP isozymes other than CYP2C9 were 100 μmol/L or higher.

Enzyme induction for CYP isozymes by TAS-114 (including CYP3A4) was investigated using cryopreserved human hepatocytes during which enzyme induction (auto induction) for CYP3A4 by TAS-114 was observed. However, in a Phase 1 clinical study in healthy volunteers, the plasma concentration of TAS-114 and the urinary excretion of cortisol and 6β-hydroxycortisol suggested that although enzyme induction of CYP3A4 occurred after multiple administration of TAS-114 at 150 mg/body/dose twice daily (BID), the extent of auto induction was minimal. TAS-114 did not induce other CYP isozymes, such as CYP1A2. An in vitro study using human liver S9 fraction showed that TAS-114 has the potential to inhibit DPD, an enzyme responsible for 5-FU degradation.

6.2.1.5. Toxicology

No effect of TAS-114 on the central nervous system or respiratory system was observed after single-dose oral administration at doses up to 1000 mg/kg in rats. In studies of the cardiovascular system, TAS-114 suppressed the human ether-a-go-go related gene current at doses of 10 μmol/L or higher in vitro (a concentration about 6 times higher than the mean maximum observed plasma concentration (C_{max}) value in human subjects administered 300 mg/body TAS-114); however, in conscious dogs, no effect was observed after single-dose oral administration at doses up to 500 mg/kg.

Multiple dose toxicity was examined in rats and dogs including 4-week oral toxicity studies.[12,13,14] The observed significant toxicities included: a prolongation of prothrombin time or activated partial thromboplastin time, slight vacuolation in the hepatocytes, decreased body weights, decreases in white blood cell (WBC) and erythrocyte counts, and atrophic changes in the lymphatic and hematopoietic tissues. No observed adverse effect levels were determined to be 200 mg/kg/day in rats and 10 mg/kg/day in dogs based on the 4-week repeated oral dose toxicity studies.

6.3. S-1

In an S-1 Phase 2 study for 2nd line NSCLC, a total of 57 patients with advanced NSCLC received S-1 30 mg/m^2 of S-1 every 12 hours for 14 days followed by a 7-day recovery period repeated every 3 weeks until death, progression of disease, occurrence of intolerable side effects, withdrawal of consent, or removal by Investigator. The following conclusions can be drawn:

- Although the study did not meet the criteria for progressing to Stage 3, S-1 showed antitumor activity in NSCLC, achieving a best overall confirmed response rate of 7.1%.
- Median progression-free survival (PFS) (2.9 months) and OS were comparable to those observed with pemetrexed and docetaxel when used as 2nd-line treatment for patients with NSCLC.

- S-1 30 mg/m^2, administered orally BID from Days 1 through 14, with a recovery period on Days 15 through 21, demonstrated a safety profile consistent with previous reports of S-1.[16]

S-1 is approved in Japan for the treatment of NSCLC. However, whilst S-1 is approved in the European Union and a number of other Asian countries for the treatment of a number of other advanced cancers, it is not approved for the treatment of NSCLC elsewhere in the world. In addition, S-1 is not approved in the United States (US). As of January 24, 2016, over 1.7 million patients have been treated with S-1 in the post-authorization setting since first approval in 1999.

6.4. TAS-114/S-1

CCI

[redacted]

CCI

[redacted]

CCI

CCI

6.5. Study Rationale

CCI

CCI

The summary of PK parameters is presented in Table 4 (European study) and Table 5 (Japanese study). CCI

CCI

[redacted]

6.6. Rationale for Selection of TAS-114 and S-1 Doses and Schedules

CCI [redacted]

CCI [redacted]

6.6.2. Rationale for S-1 Dose Selection

Two previous Phase 1 studies with S-1 monotherapy have been conducted. In the first study, conducted in the US[17], the MTD for S-1 was established as 30 mg/m^2 administered orally BID in a fasting condition. In the second study, conducted by the European Organisation for Research and Treatment of Cancer[18] the MTD for S-1 was established as 40 mg/m^2 administered orally BID in a fasting condition although the MTD was found out to be intolerable because of GI toxicities in the Phase 2 trial.

CCI [redacted]

CCI

6.6.3. TAS-114/S-1 Dose Selection for Phase 2 Study

In conclusion, the dose of TAS-114/S-1 to be used in this Phase 2 (TO-TAS-114-201), to be conducted in Europe, Japan, and US, was determined to be 400 mg/30 mg/m^2 BID.

7. STUDY OBJECTIVES

7.1. Primary

- To compare PFS of patients with advanced or metastatic NSCLC, when treated with TAS-114/S-1 combination versus S-1.

7.2. Secondary

- To investigate the OS, overall response rate (ORR), disease control rate (DCR), and duration of response (DR)
- To investigate the safety and tolerability.

CCI

8. INVESTIGATIONAL PLAN

8.1. Study Design

This is a randomized, open-label, Phase 2 study of TAS-114 administered in combination with S-1, to investigate the efficacy, safety, and tolerability of the TAS-114/S-1 regimen in patients with advanced or metastatic NSCLC.

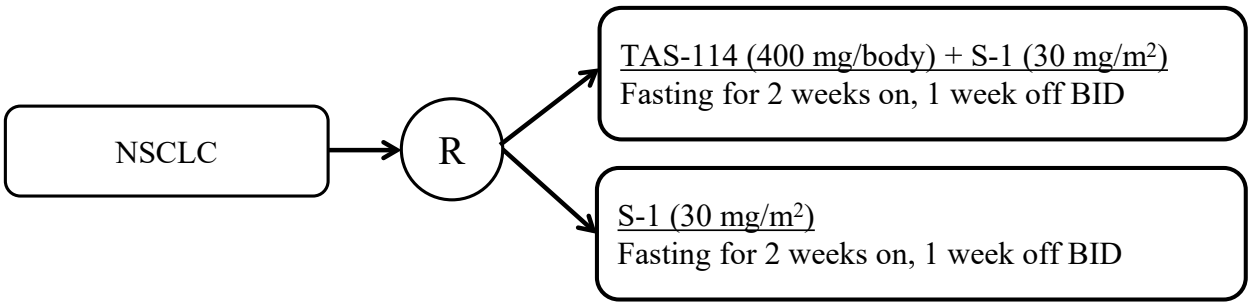
The study will be conducted internationally in 2 regions: Asian (Japan) and Western (Europe and US). Patients will be randomized to TAS-114/S-1 arm versus S-1 control arm in a 1:1 ratio.

Randomization will take place once the consented patient has completed all the necessary baseline procedures and is deemed eligible for study entry. Treatment assignment will be done centrally using a dynamic allocation method (biased coin) via an interactive voice/web response system (IXRS) stratified by:

- Geographical region (Region 1: Asian [Japan]; Region 2: Western [Europe and US])
- Histological subtypes (nonsquamous cell carcinoma [including mixed] and squamous cell carcinoma)

The overall study design is described in Figure 3.

Figure 3: Study Schema



Stratification factors:

1. Geographical: Region 1: Asian (Japan); Region 2: Western (Europe and US)
2. Histological subtypes: non-squamous (including mixed); squamous

R = Randomization

8.1.1. Study Duration

Patients will receive the study drug according to the proposed treatment schedule until progressive disease (PD), occurrence of intolerable side effects, removal by the Investigator, or withdrawal of consent. A patient is considered discontinued from study treatment when either TAS-114/S-1 or S-1 alone is discontinued.

For the purpose of the final analyses, the study will be considered completed when all patients have discontinued from treatment or a minimum of 12 months from the date of the first day of treatment with TAS-114/S-1 or S-1 of the last patient enrolled or until the target number of

events (deaths, n=80) is reached, whichever occurs last. This analysis may still be done even if there are patients still on treatment.

8.2. Study Population

The study population will include male and female patients age 18 years or older (20 and older in Japan) with histologically or cytologically confirmed advanced or metastatic NSCLC for whom standard therapy no longer exists, based on local guidelines and practices, and according to the following inclusion and exclusion criteria.

8.2.1. Inclusion Criteria

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

1. Provision of written informed consent consistent with International Council for Harmonisation (ICH)-Good Clinical Practice (GCP) guidelines, and respective local law;
2. Age ≥ 18 years old (≥ 20 years old in Japan);
3. Histologically diagnosed or cytologically proven advanced or metastatic NSCLC patients, either Stage IIIB/Stage IV disease (according to Version 7 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology[20]), or recurrent disease following radiation therapy or surgical resection;
4. Patients who had received at least 2 prior therapies for advanced or metastatic disease condition, including platinum doublet and pemetrexed, docetaxel, or immunotherapy and were refractory to or unable to tolerate their last prior therapy. For patients with known EGFR activating mutations or anaplastic lymphoma kinase translocations and/or ROS1 rearrangements, appropriate targeted treatment should have been used. The following histological tumor types are also eligible to be included:
    - Adenocarcinoma with bronchiolo-alveolar differentiation
    - Large cell carcinoma
5. Tumor is locally advanced or metastatic and not suitable for surgery and radiotherapy is not indicated;
6. Measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) criteria (Version 1.1, 2009)[20];
7. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 (see Appendix A);
8. Predicted life expectancy of at least 3 months;
9. Able to take medications orally;
10. Adequate organ function as defined by:
    a. Adequate bone marrow function: absolute neutrophil count (ANC) ≥ 1500/mm^3, hemoglobin ≥ 10.0 g/dL, platelets ≥ 100,000/mm^3
    b. Adequate liver function: Total bilirubin ≤ 1.5 × upper limit of normal (ULN), ALT/AST ≤ 3 × ULN (existent liver metastases ≤ 5 × ULN)

c. Adequate renal function: Calculated creatinine clearance ≥ 50 mL/min (Cockcroft-Gault Equation)

11. Women of childbearing potential (WOCBP) must have a negative pregnancy test (urine or serum) within 7 days prior to starting the study drug. Both males and females must agree to use effective birth control during the study (prior to the first dose and for 6 months after the last dose) if conception is possible during this interval. Female patients are considered to not be of childbearing potential if they have a history of hysterectomy, or are postmenopausal defined as no menses for 12 months without an alternative medical cause. For both males and females, see Section 8.7.2 for definitions of contraceptive methods considered effective for this protocol;
12. Willing and able to comply with required scheduled visits and study procedures.

8.2.2. Exclusion Criteria

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

1. Treatment with any of the following within the specified time frame prior to study drug administration:
    - Major surgery within prior 4 weeks and minor surgery within 7 days;
    - Radiotherapy for extended field within prior 4 weeks or limited field within prior 2 weeks;
    - Any anticancer therapy or investigational agent within prior 3 weeks.
2. A serious illness or medical condition including but not limited to the following:
    - Patients with brain or subdural metastases are not eligible unless they have completed local therapy and have discontinued the use of therapeutic corticosteroids and are stable for at least 1 month before study drug administration;
    - Known leptomeningeal metastatic disease;
    - Known acute or chronic active systemic infection;
    - Any cardiac disease, such as myocardial infarction, unstable angina, symptomatic congestive heart failure (CHF) New York Heart Association (NYHA) class III or IV (see Appendix B) within the last 6 months. If > 6 months, cardiac function must be within normal limits and the patient must be free of cardiac-related symptoms;
    - Chronic nausea, vomiting, or diarrhea considered to be clinically significant by investigator's discretion;
    - Current or past severe lung disease (eg, interstitial pneumonia, pulmonary fibrosis, or severe emphysema);
    - Pleural, peritoneal, or pericardial effusion which will require surgical intervention in the near term;
    - Any history or presence of poorly controlled GI disorders that could affect the absorption of the trial drug (eg, Crohn's disease, ulcerative colitis);

- Known human immunodeficiency virus (HIV) or acquired immune deficiency syndrome-related illness (AIDS), or chronic or acute hepatitis B or C;
- Any other clinically significant acute or chronic medical or psychiatric condition or any laboratory abnormality that may increase the risk associated with study drug administration, or may interfere with the interpretation of study results;
- Poorly controlled (despite medication) or severe diabetes mellitus;
- Continuous systemic steroid administration (oral or intravenous);
- Other concurrent active cancer (synchronous double cancer or heterochronous double cancer with a disease-free interval of 3 years or shorter, excluding lesions consistent with intraepithelial cancer, ie, carcinoma in situ, or intramucosal cancer) that is assessed as cured by local treatment.

3. Concomitant treatment with the following drugs that may interact with S-1:
    - Sorivudine, brivudine, uracil, eniluracil, folinate/folinic acid, (enhance S-1 activity);
    - Cimetidine, dipyridamole, and nitroimidazoles, including metronidazole and misonidazole (may enhance S-1 activity);
    - Methotrexate (may enhance S-1 activity);
    - Clozapine (may increase risk and severity of hematologic toxicity with S-1);
    - Allopurinol (may diminish S-1 activity);
    - Phenytoin (S-1 may enhance phenytoin activity);
    - Flucytosine, a fluorinated pyrimidine antifungal agent (may enhance S-1 activity);
    - Coumarin-derivative anticoagulant (S-1 may enhance activity of coumarin-derivative anticoagulant).
4. Known hypersensitivity to S-1 or its metabolites (eg, 5-FU);
5. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose/galactose malabasorption since S-1 contains lactose.
6. Previous use of TAS-114, S-1, and 5-FU drugs;
7. A pregnant or lactating female or possibly pregnant women, or men or women wishing to have children during the study period.
8. A judgment of the investigator that the patient is inappropriate for study participation.

8.3. Discontinuation Criteria

A patient is considered discontinued from study treatment when the decision to permanently stop TAS-114 or S-1 for the TAS-114/S-1 arm and S-1 for the S-1 control arm is made, including those decisions made during TAS-114 or S-1 interruptions and recovery periods.

Study drug should be continued whenever possible. In the event study drug is stopped, it should be determined if the stop can be made temporarily; permanent study drug discontinuation should be a last resort. If the decision to discontinue TAS-114 or S-1 is made within 2 weeks after the

patient's last treatment visit, an End of Treatment visit is not required unless deemed clinically necessary by the investigator. If the decision to discontinue TAS-114 or S-1 (because of disease progression or other reasons) is made more than 2 weeks after the last treatment visit, the End of Treatment visit is required.

Any TAS-114 or S-1 discontinuation should be fully documented.

8.3.1. End of Treatment Discontinuation Criteria

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

Patients can be withdrawn from treatment for the following reasons:

- At their own request at any time irrespective of the reason.
- RECIST-defined disease progression of solid tumors.
- Clinical progression.
- Unacceptable adverse events (AEs), or change in underlying condition such that the patient can no longer tolerate therapy, as evidenced by:
  - A maximum dose delay >14 days from the scheduled start date of the next cycle.
  - Need for more than 2 dose reductions of study drug (maximum of 2 dose reductions allowed as described in Section 9.1.2.1.)
- Investigator's decision including need for other anticancer therapy not specified in the protocol, or surgery or radiotherapy to the only site(s) of disease being evaluated in this protocol.
- Pregnancy.

If there is strong evidence of clinical benefit and reasons to justify continuation of TAS-114 or S-1 dosing even though treatment discontinuation criteria have been met, this decision must be reviewed with the sponsor on a case-by-case basis, and continuation of therapy may be allowed assuming all other treatment resumption criteria have been met.

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

- The clinical research associate must be notified immediately; and
- The Study Treatment Discontinuation form in the electronic case report form (eCRF) must be completed, specifying the primary reason for the patient's withdrawal from treatment.

8.4. Patient Numbering and Treatment Allocation

All patients will sign an informed consent form (ICF) and be assigned a unique patient number. The patient numbering process is defined in the Case Report Form Completion Manual.

Investigative sites must complete all relevant eCRFs for all enrolled patients, even if the patient is not treated with study drug.

Randomization will take place once the consented patient has completed all the necessary baseline procedures and is deemed eligible for study entry. Treatment assignment will be done centrally using a dynamic allocation method (biased coin) via an IXRS stratified by:

- Geographical region (Region 1: Asian [Japan]; Region 2: Western [Europe and US])
- Histological subtype (nonsquamous cell carcinoma [including mix] and squamous cell carcinoma).

8.5. Replacement Criteria

No patients will be replaced at any time during this study.

8.6. Prohibited Medications and Therapies

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

Palliative radiotherapy is not permitted while the patient is receiving study treatment.

Other fluoropyrimidine-group antineoplastic agents such as 5-FU, tegafur, or flucytosine are not permitted within 7 days after withdrawal of TAS-114/S-1 or S-1.

The following drugs are prohibited:

Medication	**Reason for Exclusion**
Sorivudine	Enhances S-1/5-FU activity
Brivudine	Enhances S-1/5-FU activity
Uracil	Enhances S-1/5-FU activity
Eniluracil	Enhances S-1/5-FU activity
Folinate/Folinic acid	Enhances S-1/5-FU activity
Cimetidine	May enhance S-1/5-FU activity
Dipyridamole	May enhance S-1/5-FU activity
Nitroimidazoles including metronidazole & misonidazole	May enhance S-1/5FU activity
Methotrexate	May enhance S-1/5FU activity
Clozapine	May increase risk and severity of hematologic toxicity with S-1
Allopurinol	May diminish S-1/5-FU activity
Phenytoin	S-1 may enhance phenytoin activity
Flucytosine (a fluorinated pyrimidine antifungal agent)	May enhance S-1/5-FU activity
Coumarin-derivative anticoagulant including warfarin	S-1 may enhance activity of coumarin-derivative anticoagulant

8.7. Concomitant Medications and Therapies

8.7.1. Concomitant Medications and Therapies

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

Hematologic Support

Administer hematologic support as medically indicated (eg, blood transfusions, granulocyte colony-stimulating factor [G-CSF]) according to the institutional site standards. If there are no standard procedures for the use of growth factors, follow the American Society of Clinical Oncology (ASCO) Guidelines for Use of Hematopoietic Colony-Stimulating Factors available at www.asco.org.

Management of Diarrhea

Educate both patients and patients' families and/or caregivers regarding the potential seriousness of chemotherapy-induced diarrhea. Instruct patients to immediately contact the clinical site staff at the first sign of a loose stool.

If there are no institutional standards, refer to the guidelines published by Benson AB et al in *Journal of Clinical Oncology*.[22]

In addition, patients should be instructed to report to the investigator or his or her designee the relevant information concerning their use of antidiarrheal medication and any episodes of diarrhea they experience.

Management of Nausea/Vomiting

Administer antiemetics as clinically indicated. If there are no institutional standards refer to the ASCO Guidelines for Antiemetics in Oncology.[23]

Drug interactions with TAS-114

Drug interaction studies have not been conducted. The following information is based on results from in vitro studies and clinical phase 1 study. Caution is advised if these drugs are given concomitantly (see Appendix E, Classification of Substrates, Inhibitors, and Inducers of Cytochrome P450 Isoenzymes and Transporters).

CYP3A4/5 inhibitors

CYP3A4/5 inhibitors may increase the concentration and activity of TAS-114. Care should be exercised when TAS-114 is co-administered with CYP3A4/5 inhibitors.

CYP3A4 inducers

CYP3A4 inducers may decrease the concentration and activity of TAS-114. Care should be exercised when TAS-114 is co-administered with CYP3A4 inducers.

CYP3A4/5 substrates

TAS-114 may decrease the concentration and activity of CYP3A4/5 substrates. Care should be exercised when TAS-114 is co-administered with CYP3A4/5 substrates.

Drug interactions with S-1

Other fluoropyrimidines

Co-administration of other fluoropyrimidines such as capecitabine, 5-FU, tegafur, or flucytosine can lead to additive toxicities, and is contraindicated. A minimum washout period of 7 days is recommended between administration of S-1 and other fluoropyrimidines.

Sorivudine and brivudine

Sorivudine or its chemically-related analogues such as brivudine irreversibly inhibit DPD, resulting in a significant increase in 5-FU exposure. This may lead to increased clinically significant fluoropyrimidine-related toxicities with potentially fatal outcomes. S-1 must not be used with sorivudine or brivudine or within 4 weeks of the last dose of sorivudine or brivudine.

CYP2A6 inhibitors

As CYP2A6 is the major enzyme responsible for the conversion of tegafur to 5-FU, co-administration of a known CYP2A6 inhibitor and S-1 should be avoided as effectiveness of S-1 could be decreased.

Folinate/folinic acid

Metabolites of folinate/folinic acid will form a ternary structure with thymidylate synthase (TS) and FdUMP, potentially increasing the cytotoxicity of 5-FU. Caution is advised as folinic acid is known to enhance the activity of 5-FU.

Nitroimidazoles, including metronidazole and misonidazole

No data are available on the concomitant use of nitromidazoles with S-1. However, nitromidazoles may reduce clearance of 5-FU and thus increase plasma levels of 5-FU. Caution is advised as co-administration may increase the toxicity of S-1.

Methotrexate

No data are available on the concomitant use of methotrexate with S-1. However, polyglutamated methotrexate inhibits thymidylate synthase and dihydrofolate reductase, potentially increasing cytotoxicity of 5-FU. Caution is advised as co-administration may increase the toxicity of S-1.

Clozapine

No data are available on the concomitant use of clozapine with S-1. However, due to possible additive pharmacodynamic effects (myelotoxicity), caution is advised as co-administration may increase the risk and severity of haematologic toxicity of S-1.

Cimetidine

No data are available on the concomitant use of cimetidine with S-1. However, co-administration may decrease clearance and, thus increase plasma levels of 5-FU. Caution is advised as co-administration may increase the toxicity of S-1.

Coumarin-derivative anticoagulant

The activity of a coumarin-derivative anticoagulant was enhanced by S-1. Caution is advised as co-administration of S-1 and coumarin anticoagulation therapy may increase the risk of bleeding.

Phenytoin

Fluoropyrimidines may increase phenytoin plasma concentration when administered concomitantly with phenytoin causing phenytoin toxicity. Frequent monitoring of phenytoin blood/plasma levels is advised when S-1 and phenytoin are administered concomitantly. If indicated, the dose of phenytoin should be adjusted according to the phenytoin Summary of Product Characteristics (SmPC). If phenytoin toxicity develops, appropriate measures should be taken.

Other

Based on non-clinical data, allopurinol may decrease antitumor activity due to suppression of phosphorylation of 5-FU. Therefore, concurrent administration with S-1 should be avoided.

8.7.2. Effective Contraception During Study

Female patients who are considered not to be of childbearing potential must have a history of being postmenopausal (no menses for 12 months without an alternative medical cause), or hysterectomy that is clearly documented in the patient's source documents (see Section 8.2.1).

For WOCBP, including female study participants and partners of male participants, effective contraception is defined as follows:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- intrauterine device
- intrauterine hormone-releasing system
- bilateral tubal occlusion
- vasectomized partner with documentation of the success of the vasectomy
- complete abstinence from heterosexual intercourse (periodic abstinence is not a safe method)

Male patients with partners who are WOCBP should use a combination of male condom with either cap, diaphragm or sponge with spermicide during the trial and for 6 months after the last dose of study drug.

8.8. Dietary Restrictions

TAS-114 and S-1 should be taken orally BID with a glass of water at least 1 hour before or after a meal.

9. STUDY DRUG

Compliance to all study drug regimens should be documented in the patient's source documents.

9.1. Study Drug Administration and Dose Modification Procedures

9.1.1. Treatment Regimen

Each TAS-114/S-1 and S-1 treatment cycle will be 21 days: 14 days of treatment and 7 days of recovery. TAS-114 and S-1 will be administered orally BID with a glass of water at least 1 hour before or after a meal.

Study sites will call/login to the IXRS at the beginning of each patient treatment cycle to record the current cycle number, record the patient's current weight and obtain the patient's BSA, and obtain the recommended study medication dosage of S-1.

The BSA will be calculated by the IXRS using the following DuBois formula (all BSA calculations are rounded to 2 decimal places).

BSA (m^2) = ([Body Weight (kg)] $^{0.425}$ x [Height (cm)] $^{0.725}$) x 0.007184

If at the beginning of the next treatment cycle, a patient's body weight decreases by ≥10% from baseline, the IXRS will recalculate the patient's BSA and provide the site with the adjusted study medication dosage.

9.1.1.1. TAS-114/S-1 Arm Drug administration

Days 1 through 14: TAS-114 and S-1 orally BID (with a glass of water at least 1 hour before or 1 hour after completion of morning and evening meals) with the first dose administered in the morning of Day 1 of each cycle and the last dose administered in the evening of Day 14.

Days 15 through 21: Recovery. See required number of study drugs for TAS-114 (Table 6) and S-1 (Table 7).

Table 6: Number of TAS-114 Tablets per Dose

Tablets per dose (2x daily every 12 h)	
TAS-114 Dose (2x daily)	**100 mg tablets/dose (pale-yellow)**
400 mg	4
300 mg	3
200 mg	2

Extension of TAS-114/S-1 treatment into the recovery period is not permitted.

Any missed doses reported by the patient should be recorded in the patient's source documents.

Table 7: Number of S-1 Capsules per Dose

S-1 Dose (2x daily)	BSA (m^2)	Dosage in mg (2x daily)	Total daily dose (mg)	Capsules per dose (2x daily every 12 h)	
				15 mg (brown/white)	20 mg (white)
30 mg/m^2/dose	≥2.25m^2	70	140	2	2
	2.09-2.24m^2	65	130	3	1
	1.92-2.08m^2	60	120	0	3
	1.75-1.91m^2	55	110	1	2
	1.59-1.74m^2	50	100	2	1
	1.42-1.58m^2	45	90	3	0
	1.25-1.41m^2	40	80	0	2
	≤1.24m^2	35	70	1	1
25 mg/m^2/dose	≥2.25m^2	60	120	0	3
	2.09-2.24m^2	55	110	1	2
	1.92-2.08m^2	50	100	2	1
	1.75-1.91m^2	45	90	3	0
	1.59-1.74m^2	40	80	0	2
	1.42-1.58m^2	40	80	0	2
	1.25-1.41m^2	35	70	1	1
	≤1.24m^2	30	60	2	0
20 mg/m^2/dose	≥2.25m^2	50	100	2	1
	2.09-2.24m^2	45	90	3	0
	1.92-2.08m^2	40	80	0	2
	1.75-1.91m^2	35	70	1	1
	1.59-1.74m^2	35	70	1	1
	1.42-1.58m^2	30	60	2	0
	1.25-1.41m^2	30	60	2	0
	≤1.24m^2	20	40	0	1

9.1.1.2. S-1 Arm Drug Administration

S-1 should only be given on Days 1 through 14 of each cycle even if doses are missed or held for any reason during Days 1 through 14. See required number of study drugs in Table 7 (S-1).

Extension of S-1 treatment into the recovery period is not permitted.

Any missed doses reported by the patient should be recorded in the patient's source documents.

9.1.2. Dose Reduction/Modification Procedures

Section 9.1.2.1 provides the amount that each treatment should be reduced. Section 9.1.2.2 describes dose reductions for treatment-related toxicities. Section 9.1.2.3 provides the timing of dose resumption for both nonhematologic and hematologic toxicities and Section 9.1.2.4 provides the guidance for starting subsequent cycles. Dose escalations are not permitted at any time for either study drug. At the discretion of the investigator, patients may continue on study drug at the same dose without reduction or interruption for AEs (irrespective of grade) considered unlikely to become serious or life threatening (including but not limited to fatigue and dry skin). In addition, at the discretion of the investigator, patients' doses may be interrupted or reduced as medically needed.

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

9.1.2.1. Dose Reduction for TAS-114 and S-1

If dose reductions are required because of AEs, both TAS-114 and S-1 should be reduced concurrently in the TAS-114/S-1 arm. As shown in Table 8, the dose of TAS-114 will be reduced from 400 mg BID to 300 mg BID, and the dose of S-1 will be reduced from 30 mg/m^2 BID to 25 mg/m^2 BID. If a second dose reduction of TAS-114 is necessary, the dose of TAS-114 will be reduced from 300 mg to 200 mg BID, and the dose of S-1 will be reduced from 25 mg/m^2 BID to 20 mg/m^2 BID. No additional dose reductions for TAS-114 and S-1 will be allowed.

Table 8: Dose Reduction for TAS-114 and S-1

Dose Level	TAS-114 (mg)	S-1 (mg/m^2)
Starting dose	400	30
First dose reduction	300	25
Second dose reduction	200	20

9.1.2.2. TAS-114 and S-1 Dose Reductions for Treatment-related Toxicities

TAS-114 dose reductions are to be applied in case of a toxicity according to the criteria described below. The TAS-114 dose will be reduced by a dose level, for a maximum of 2 dose levels (see Section 9.1.2.1). Should the toxicities that require further dose reduction recur after the second dose reduction, the affected patient should be discontinued from treatment.

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

S-1 dose reductions are to be applied concurrently for all TAS-114 dose reductions (see Section 9.1.2.1).

9.1.2.2.1. Dose Modification in Response to Nonhematologic Drug-related Toxicities

Rules for dosing modifications for treatment-related non-hematologic toxicities are provided in Table 9. Hold both TAS-114 and S-1 when the dose hold criteria are met.

Table 9: Dosing Modification Criteria for Non-Hematologic Drug-Related Toxicities

Grade[1]	Dose Hold/Resumption within a 21-day Treatment Cycle	Dose Adjustment for Next Cycle
Grade 1 or 2	Maintain treatment at the same dose level	None
Grade 3[2] or higher	Suspend treatment until Grade 0 or 1	Reduce both TAS-114 and S-1 by 1 dose level[3] from the previous level not to exceed 2 dose levels

[1] At the discretion of the investigator, patients may continue on study drug at the same dose without reduction or interruption for AEs (irrespective of grade) considered unlikely to become serious or life threatening (including but not limited to fatigue and dry skin).
[2] Except for Grade 3 nausea and/or vomiting controlled by aggressive antiemetic therapy or diarrhea responsive to antidiarrheal medication.
[3] See Section 9.1.2.2 for the recommended dose level modifications.

There will be no dose reductions after the second dose reduction. If there is any uncertainty about continuing therapy or resuming therapy in a patient with Grade ≥ 3 non-hematologic AEs, the case must be discussed with the designated Medical Monitor before continuing therapy.

9.1.2.2.2. Dose Reduction in Response to Hematologic Toxicities

Criteria for dose hold and resumption in response to hematologic toxicities related to myelosuppression are described in Table 10. Note that for all patients with decreases in neutrophils and/or platelets, the next cycle of study treatment should not be started until the resumption criteria in Table 11 are met even if the decreases did not meet the hold criteria.

Uncomplicated neutropenia or thrombocytopenia ≤ Grade 3 does not require a reduction in dose of study drug. Patients who experience 1 or more of the following should start their next cycle at 1 reduced dose level as described in Section 9.1.2.1.

- Grade 3 or 4 neutropenia associated with fever and/or infection
- Grade 3 or 4 thrombocytopenia associated with significant bleeding
- Uncomplicated Grade 4 neutropenia or thrombocytopenia that results in a > 1 week delay of the start of the next cycle (if the delay is ≤ 1 week, the patient should start the next cycle at the same dose level).

Table 10: Dose Hold and Resumption Criteria for Hematologic Toxicities Related to Myelosuppression

Parameter	Hold Criteria		Resumption Criteria[1]
	Conventional Units	SI Units	
Neutrophils	$< 500/mm^3$	$< 0.5 \times 10^9$ /L	$\geq 1500/mm^3$ (IU: $\geq 1.5 \times 10^9$ /L)
Platelets	$25{,}000/mm^3$	$< 25 \times 10^9$ /L	$\geq 100{,}000/mm^3$ (IU: $\geq 100 \times 10^9$ /L)

[1] These resumption criteria apply to the start of the next cycle for all patients regardless of whether or not the hold criteria were met.

Note: Both conventional and standard international (International System) units (IU) are presented in the Common Terminology Criteria for Adverse Events Version 4.03.

9.1.2.3. Dose Resumption Timing for Nonhematologic and Hematologic Toxicities

If the patient recovers from the toxicities to the resumption criteria defined in Section 9.1.2.2.2 during the 2-week treatment period (treatment Days 1 through 14), and no dose reduction is required, study drug therapy may be resumed during the treatment period. If a dose reduction is required, study drug therapy should be resumed at the start of the next cycle at the appropriate dose level according to instructions provided in Section 9.1.2.2. If the TAS-114 and S-1 dose is reduced, the dose must not be increased for subsequent cycles.

If the toxicities that are defined above recover during the recovery period (Days 15 through 21), start the next cycle on schedule at the appropriate dose level according to instructions provided in Section 9.1.2.2. If the toxicities that are defined above do not recover during the treatment or rest period, the start of the next cycle can be delayed for a maximum of 14 days. If resumption criteria are met by this maximum 14-day delay, start the next cycle at the appropriate dose level according to instructions provided in Section 9.1.2.2.

Patients who require more than a 14-day delay in the scheduled start date of the next cycle will be discontinued from the study.

9.1.2.4. Criteria for Starting Subsequent Cycle

The minimal criteria to start a subsequent cycle are described in Table 11. If any of the criteria specified in this table are not met on the planned Day 1 of a subsequent treatment cycle, study treatment should be held. The subsequent cycle should be started when the patient meets the criteria. Please note calculated creatinine clearance criteria should be followed regardless of whether study drug-related or not.

Table 11: Minimum Criteria to Start Subsequent Cycle

Non-Hematologic	Hematologic
Baseline or ≤ Grade 1 (exceptions noted Section 9.1.2.2.1) .	Neutrophils ≥ 1500/mm^3 (IU: ≥ 1.5 × 10^9/L)
	Platelet ≥ 100,000/mm^3 (IU: ≥ 100 × 10^9/L) .
Calculated Creatinine Clearance[1]	
≥ 50 mL/min.	Start the cycle with no dose reduction
30 to 49 mL/min .	Start the cycle at one reduced dose level for TAS-114 and S-1
< 30 mL/min .	Suspend the cycle until ≥ 30 mL/min is met and then start treatment at one reduced dose level for TAS-114 and S-1

Abbreviations: IU = international unit; min = minute.
[1] Calculated creatinine clearance must be calculated on Day 1 of every cycle before the start of study drug treatment.

9.2. Description and Labeling

9.2.1. TAS-114

A description of the study drug and the recommended storage conditions are provided in Section 9.2.1.1 and Section 9.2.1.2 , respectively.

TAS-114 100 mg tablets will be packaged in kits containing 20 tablets for Europe and US and 120 tablets for Japan. TAS-114 is formulated as an immediate-release pale yellow oval tablet.

Patients will be dispensed study drug at the beginning of each cycle. Each kit will be labeled with information including the following:

a. Protocol number
b. Sponsor name
c. Storage conditions
d. Directions for use
e. Investigational caution statement
f. Unique kit number

Additional statements will be printed on the label(s) as required by local regulation. Study drug will be shipped from a regional Distribution Center directly to clinical sites.

9.2.1.1. Description

TAS-114 100-mg tablet is an oval pale-yellow uncoated tablet.

9.2.1.2. Storage

TAS-114 must be stored as labeled at room temperature (according to the country's regulatory definition* for room temperature).

All study drugs must be kept in a locked area with access restricted to specific study personnel.

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9.2.2. S-1

A description of the study drug and the recommended storage conditions are provided in Section 9.2.2.1 and Section 9.2.2.2, respectively.

S-1 is an immediate release dosage form contained in hard gelatin capsules in which tegafur (FT), gimeracil (CDHP), and oteracil as monopotassium salt (Oxo) are combined at a molar ratio of 1:0.4:1. Study drug will be packaged in kits containing 28 capsules for all regions.

Each kit will be labeled with information including the following:

a. Protocol number
b. Sponsor name
c. Storage conditions
d. Directions for use
e. Investigational caution statement
f. Unique kit number

Additional statements will be printed on the label(s) as required by local regulation. Study drug will be shipped from a regional Distribution Center directly to clinical sites.

9.2.2.1. Description

All S-1 capsule dose strengths are expressed as the amount of tegafur per capsule.

S-1 is supplied as 15 or 20 mg capsules.

The 15 mg brown and white capsules imprinted “TC448” in grey contain 15 mg tegafur, 4.35 mg gimeracil, and 14.7 mg oteracil as monopotassium salt as active ingredients.

The 20 mg white capsules imprinted “TC442” in grey contain 20 mg tegafur, 5.8 mg gimeracil, and 19.6 mg oteracil as monopotassium salt as active ingredients.

9.2.2.2. Storage

S-1 must be stored at room temperature according to the country’s regulatory definition* for room temperature).

All study drugs must be kept in a locked area with access restricted to specific study personnel.

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9.2.3. Patient Instructions for Handling All Study Drug

The patient must be instructed in the handling of study drug as follows:

- Store the study drug at room temperature;
- Only remove the amount of TAS-114 and S-1 needed at the time of dosing;
- Not to remove doses in advance of the next scheduled dosing;
- Bring all used and unused blister packs to the site at each visit;

- Study drug should be kept in a safe place and out of sight and reach of children;
- TAS-114/S-1 should be taken at least 1 hour before or after completing a meal (morning and evening meal) with a glass of water;
- Doses are not to be replaced if the patient misses a dose or vomits a dose;
- Make every effort to take doses on schedule;
- Report any missed doses.

9.3. Accountability

In accordance with ICH and local regulatory requirements, the investigator and/or the person responsible for dispensing investigational drug must be able at all times to account for all investigational product provided to the site. The institutional designee is required to call the IXRS each time TAS-114 and S-1 study drug is received at the site.

Dose reductions, interruptions, and reason for these actions must be recorded in the patient's source documents and IXRS. Prior to each treatment cycle, the person responsible for dispensing the drug must call/log in to the IXRS to provide the information required and to request additional study product. Accountability logs with the required information (eg, lot number and expiration date, patient ID number, unique id number of each treatment kit [IXRS], and dispensing date) will be maintained for the study.

At the conclusion of the study, all used and unused TAS-114 and S-1 study drug shipped to the investigator must be returned to the sponsor or designated contract research organization (CRO). If on-site destruction is required by site policy, such requirements must be documented in the institution's Standard Operating Procedures and provided to the sponsor or its representative for review.

No TAS-114 or S-1 is to be used outside of this study.

9.4. Blinding

This is an open-label, randomized study.

10. STUDY VISITS AND BY-VISIT ASSESSMENTS

This section provides the by-visit list of assessments and procedures to be performed on each study day.

Please note that the Screening/Baseline assessments (Section 10.1), End of Therapy/Early Termination assessments (Section 10.4.1), and Follow-Up assessments (Section 10.4.2) apply to all patients in the study.

All information required by the protocol must be recorded. The study schedule must be followed; however, under special conditions (eg, holidays, weekends, etc.), a window of ± 3 days is allowable for study procedures, as long as the proper order of procedures and assessments is maintained. A window of ± 7 days is allowable for computed tomography (CT) scans. These windows are not applicable during the screening period.

10.1. Screening/Baseline Visit and Assessments

Screening Visit assessments may be completed up to 28 days prior to the planned Day 1 date (Section 10.1.1); Baseline assessments and procedures should be completed within 3 days of Day 1 (Section 10.1.2).

10.1.1. Screening (Days -28 to -1)

The following assessments and procedures should be completed within 28 days of Day 1:

- Obtain signed, written, informed consent prior to performing any study procedures.
- Record inclusion and exclusion criteria.
- Obtain patient study number from the electronic data capture (EDC) system.
- Obtain medical history.
- Record Baseline signs and symptoms.
- Record current and concomitant medications.
- Record ECOG performance status (see Section 11.5).
- Obtain blood and urine samples for clinical laboratory assessments (hematology, serum chemistry, and urinalysis).
- Obtain a 12-lead electrocardiogram (ECG).
- CT scan and bone scan as described in Section 11.12. Tumor images obtained prior to the signed informed consent may be used as the Screening scan if they were obtained within 28 days of the 1st dose of study drug.

10.1.2. Baseline (Days -7 to 0)

The following assessments and procedures should be completed:

- Record Baseline signs and symptoms.

- Record current and concomitant medications.
- Perform a full physical examination.
- Record vital sign, height, and weight measurements.
- Record ECOG performance status (see Section 11.5).
- Obtain blood and urine samples for clinical laboratory assessments (hematology, serum chemistry, and urinalysis).
- Obtain blood samples for coagulation parameters.
- Pregnancy test

10.2. Treatment Period Visits and Assessments

By-visit assessments are shown in this section.

10.2.1. By-Visit Assessments for Cycle 1

Assessments for Cycle 1 are indicated in Table 1 for the TAS-114/S-1 treatment group and Table 2 for the S-1 treatment group and are listed below.

10.2.1.1. Cycle 1, Day 1 Predose

The following assessments and procedures should be completed:

- Review Inclusion and Exclusion Criteria to ensure continued eligibility for the trial.
- Record Baseline signs and symptoms.
- Physical exam
- Record ECOG Performance status (see Section 11.5)
- Record current and concomitant medications.
- Dispense TAS-114/S-1 or S-1 alone for Cycle 1.

10.2.1.2. Cycle 1, Day 1 Postdose

The following assessments and procedures should be performed:

- Record AE/Toxicity assessments as needed.

10.2.1.3. Cycle 1, Day 8 (Week 2) Predose

The following assessments and procedures should be completed:

- Update current and concomitant medications.
- Perform a full physical examination.
- Record vital sign measurements.
- Obtain blood samples for clinical laboratory assessments (hematology and serum chemistry).

- Obtain blood samples for coagulation parameters.

10.2.1.4. Cycle 1, Day 8 (Week 2) Postdose

The following assessments and procedures should be performed:

- Record AE/Toxicity assessments as needed.

10.2.1.5. Cycle 1, Day 15 (Week 3) Predose

The following assessments and procedures should be completed:

- Record current and concomitant medications.
- Perform a full physical examination.
- Obtain blood samples for clinical laboratory assessments (hematology, serum chemistry).
- Obtain blood samples for coagulation parameters.
- Record drug accountability. The return of all unused study drug should be confirmed, and all TAS-114/S-1 that was dispensed should be accounted for.
- Record AE/Toxicity assessments as needed.

10.2.2. By-Visit Assessments for Subsequent Cycles

Assessments for subsequent cycles are listed below.

10.2.2.1. Subsequent Cycles, Day 1 (Week 1) Predose

The following assessments and procedures should be completed:

- Record health changes since last visit.
- Record current and concomitant medications.
- Perform a full physical examination.
- Record vital sign and weight measurements.
- Record ECOG performance status (Section 11.5).
- Obtain blood and urine samples for clinical laboratory assessments (hematology, serum chemistry).
- Obtain blood samples for coagulation parameters.
- Dispense TAS-114/S-1 for cycle.

10.2.2.2. Subsequent Cycles, Day 1 (Week 1) Postdose

The following assessments and procedures should be performed:

- Record AE/Toxicity assessments as needed.

10.2.2.3. Subsequent Cycles, Day 15 (Week 3) Predose

The following assessments and procedures should be completed:

- Update current and concomitant medications.
- Obtain blood samples for clinical laboratory assessments (hematology and serum chemistry).
- Obtain blood samples for coagulation parameters.
- Record drug accountability. The return of all unused study drug should be confirmed, and all TAS-114/S-1 that was dispensed should be accounted for.
- Record AE/Toxicity assessments as needed.

10.3. End of Recovery

Tumor assessment is done at the End of Recovery Visit.

10.4. End of Treatment/Follow-Up

The End of Therapy and the Follow-Up Visit assessments and procedures are described below.

10.4.1. End of Treatment Visit

These assessments and procedures should be performed as much as possible for any patient discontinuing from the study prior to completing a cycle of treatment, or if completing a cycle of treatment and deciding not to continue to the next cycle.

- Record vital sign measurements.
- Perform a full physical examination.
- Record ECOG performance status.
- Record concomitant medications.
- Obtain a 12-lead ECG.
- Obtain blood and urine samples for clinical laboratory assessments (hematology, serum chemistry, and urinalysis).
- Obtain blood samples for coagulation parameters.
- Record AE/Toxicity assessments.
- Record the reason for discontinuation on the Discontinuation Record CRF page.
- Record drug accountability. The return of all unused study drug should be confirmed, and all TAS-114/S-1 that was dispensed should be accounted for.
- Schedule a clinic Follow-Up Visit in 30 days (± 14 days of the End of Therapy Visit).
- Tumor assessment/CT and bone scans described in Section 11.12.

10.4.2. 30-Day Follow-Up Visit

For any patient discontinuing from the study for any reason, the following assessments and procedures should be performed at the 30-Day Follow-Up Visit and should be performed prior to start of a new therapy; this visit should be omitted if it is within 14 days of the End of Therapy Visit:

- Record vital sign and weight measurements.
- Perform a full physical examination.
- Record ECOG performance status.
- Record concomitant medications.
- Obtain a 12-lead ECG.
- Obtain blood and urine samples for clinical laboratory assessments (hematology, serum chemistry, and urinalysis).
- Obtain blood samples for coagulation parameters.
- Record AE/Toxicity assessments.

10.4.3. Survival Follow-up

All patients will be followed for survival status (alive/dead) from the time of randomization and investigator will record time of disease progression. Obtain survival status (alive/dead) at scheduled 8-week intervals until death. Survival status should be collected for up to approximately 12 months after the first dose of treatment with TAS 114/S 1 of the last patient enrolled or until the target number of events is reached, whichever occurs first, even if consent for study participation has been withdrawn. The investigator should make every effort to contact the patient or primary caregiver to determine his/her survival status. Times and dates of contact must be documented in the patient's records.

All patients will be followed for survival status (alive/dead) even if consent for other study procedures is withdrawn.

11. STUDY PROCEDURES

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

The study schedule must be followed; however, in unavoidable circumstances (eg, holidays, weekends) a window of ± 3 days is allowable for study procedures as long as the proper order of procedures and assessments is maintained. A window of ± 7 days is allowable for CT scans and follow-up visits. These windows are not applicable during the Baseline Period. If any baseline assessments are repeated on Day 1 of Cycle 1, the site must ensure the patient meets the eligibility criteria listed in Section 8.2.1 and Section 8.2.2 before administration of the first dose of TAS-114.

11.1. Informed Consent

A signed and dated ICF will be obtained from the patient as required by the protocol before any baseline procedures are conducted. A signed copy of the ICF will be given to the patient.

Patient number will be assigned once the patient has entered the Baseline Period, ie, has signed the ICF, during baseline within 28 days before first TAS-114/S-1 or S-1 control administration on Day 1 of Cycle 1.

11.2. Medical History

A complete medical history will be obtained during baseline within 28 days before first TAS-114/S-1 or S-1 control administration on Day 1 of Cycle 1.

Existing signs and symptoms will be obtained within 7 days before TAS-114/S-1 or S-1 control administration on Day 1 of Cycle 1. Those pre-existing signs and symptoms and conditions are appropriately recorded in a respective medical history page.

11.3. Physical Examination

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

- Baseline within 7 days before TAS-114/S-1 or S-1 control administration on Day 1 and before administration of study drug on Days 1, 8, and 14 of Cycle 1.
- Beginning with Cycle 2, obtain within 1 day before TAS-114/S-1 or S-1 control administration on Day 1.
- End of treatment visit.
- 30-day safety follow-up visit.

11.4. Height, Vital Signs, and Weight

The patient's height will be obtained only during Baseline within 7 days before TAS-114/S-1 or S-1 control administration on Day 1 of Cycle 1.

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

- Baseline within 7 days before TAS-114/S-1 or S-1 control administration on Day 1 of Cycle 1.
- Within 1 day before TAS-114/S-1 or S-1 control administration on Day 1 of Cycle 2 and thereafter throughout all the treatment cycles.
- End of treatment visit.
- 30-day safety follow-up visit.

11.5. Performance Status

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

- Baseline within 28 days before the first TAS-114/S-1 or S-1 control administration on Day 1 of Cycle 1.
- On Day 1 of Cycle 1 before the first dose.
- Beginning with Cycle 2, obtain within 1 day before TAS-114/S-1 or S-1 control administration on Day 1.
- End of treatment visit.
- 30-day safety follow-up visit.

11.6. Electrocardiogram

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

- Baseline within 28 days before TAS-114/S-1 or S-1 control administration on Day 1 of Cycle 1.
- End of treatment visit.
- 30-day safety follow-up visit.

11.7. Clinical Laboratory Evaluations

Blood samples for hematology, coagulation, and serum chemistry assessments will be collected and measured as described in Section 11.7.1, Hematology and Coagulation, and Section 11.7.2, Serum Chemistry, respectively.

Laboratory assessments obtained before the signing of the ICF may be used as screening laboratory values if they were obtained within 28 days before TAS-114/S-1 (Table 1) or S-1 control (Table 2) administration on Day 1 of Cycle 1.

All laboratory results must be reviewed for clinically significant events. Any clinically significant event must be followed and reported as required by the protocol (see Section 13.1, Adverse Events/Serious Adverse Events and Section 13.2, Laboratory Evaluations).

11.7.1. Hematology and Coagulation

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

- Baseline within 7 days before the first TAS-114/S-1 or S-1 control administration on Day 1 of Cycle 1.
- On Days 8 and 15 of Cycle 1.
- Beginning with Cycle 2, obtain within 1 day before TAS-114/S-1 or S-1 control administration on Day 1 and Day 15.
- After Cycle 4, the Day 15 laboratory evaluations are not required unless clinically indicated by the Investigator.
- After Cycle 6, the laboratory evaluations can be accepted within 2 days before study drug administration on Day 1 of each cycle, if there are no drug-related AEs greater than Grade 2 observed in the latest cycle.
- End of treatment visit.
- 30-day safety follow-up visit.

In addition, the criteria for repeat testing listed in Section 13.2.2, will be followed as needed.

The following hematology and coagulation parameters will be measured:

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

[a] Includes both segmented and band neutrophils.

11.7.2. Serum Chemistry

Blood will be collected at the following time points for serum chemistry assessments:

- Baseline within 7 days before the first TAS-114/S-1 or S-1 control administration on Day 1 of Cycle 1 (must include creatine kinase [CK], which has to be repeated on Day 1 of Cycle 2 [± 3 days]).
- On Days 8 and 15 of Cycle 1.
- Beginning with Cycle 2, obtain within 1 day before TAS-114/S-1 or S-1 control administration on Day 1 and Day 15.
- After Cycle 4, the Day 15 laboratory evaluations are not required unless clinically indicated by the Investigator.

- After Cycle 6, the laboratory evaluations can be accepted within 2 days before study drug administration on Day 1 of each cycle, if there are no drug-related AEs greater than Grade 2 observed in the latest cycle.
- End of treatment visit.
- 30-day safety follow-up visit.

In addition, the criteria for repeat testing listed in Section 13.2.2, Repeat Testing, will be followed as needed.

Table 12 lists the serum chemistry parameters that will be measured:

Table 12: Laboratory Assessments for TAS-114/S-1 or S-1 control

Alanine aminotransferase (ALT)	Creatinine	Sodium
Aspartate aminotransferase (AST)	Blood urea nitrogen (BUN) or urea	Potassium
Alkaline phosphatase (ALK)	Phosphorus	Bicarbonate
Total bilirubin[a]	Calcium	Glucose
Albumin	Chloride	Creatine kinase (CK) creatine phosphokinase (CPK) [b]

[a] Fractionation of bilirubin (= direct/indirect bilirubin or conjugated/unconjugated) must be performed in case of an elevation of total bilirubin.

[b] 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 Baseline (Day -7 to -1), the results of the fractionation must be available prior to starting TAS-114 treatment for that patient but do not have to be within normal reference range.

11.7.3. Urinalysis

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

- Baseline within 7 days before the first TAS-114/S-1 or S-1 control administration on Day 1 of Cycle 1.
- End of treatment visit
- 30-day safety follow-up visit.

In addition, the criteria for repeat testing listed in Section 13.2.2 will be followed as needed.

The following parameters will be measured:

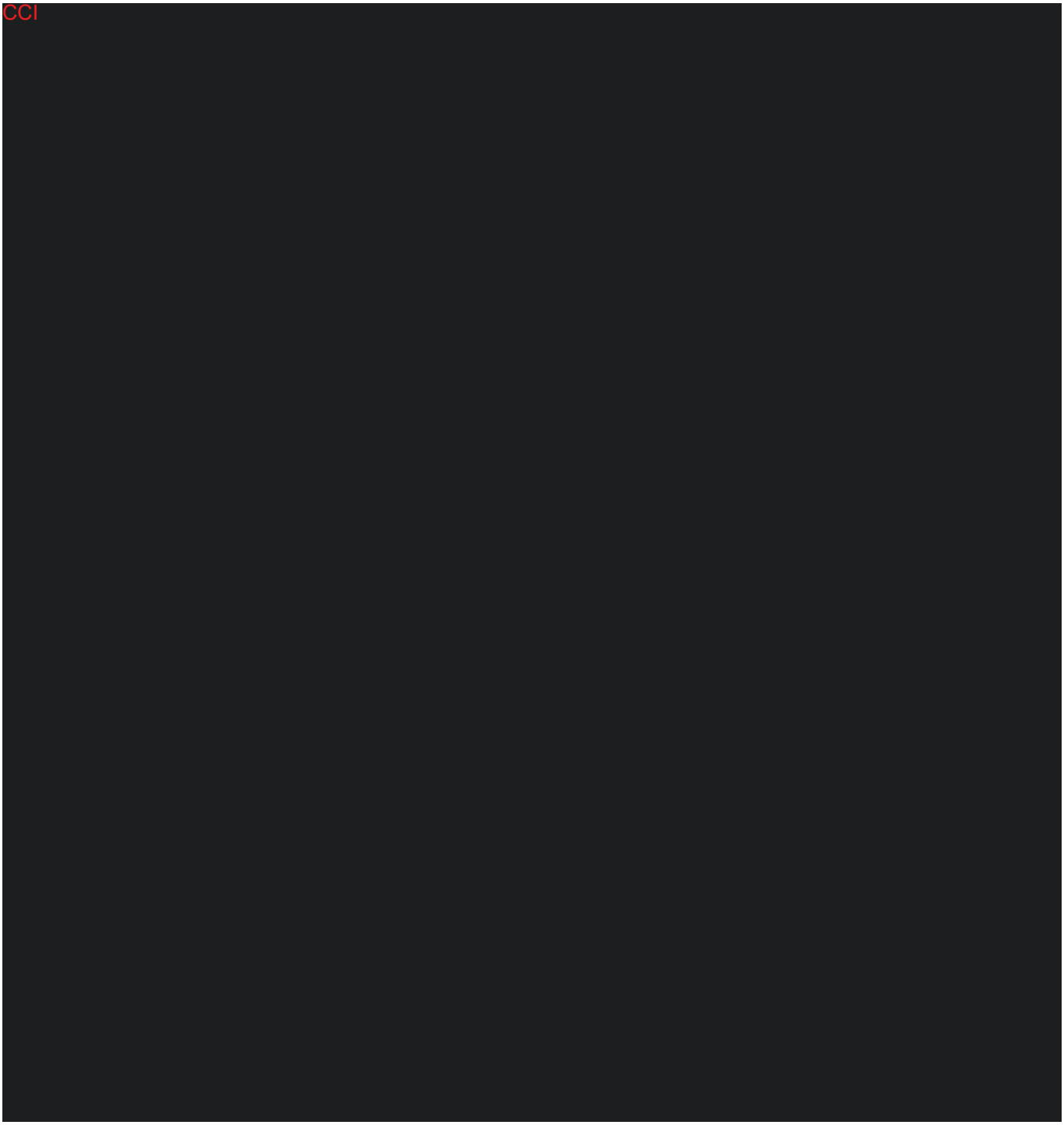
Protein	Glucose	Urine density

11.8. Pregnancy Test

If the patient is female and of childbearing potential, pregnancy testing by assessment of serum or urine beta-human chorionic gonadotropin will be conducted 7 days before the first

administration of TAS-114/S-1 or S-1 control on Day 1 of Cycle 1 or additionally according to local requirements. The date, time, and test results will be recorded in the patient's source documents.

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



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11.10. Prior and Concomitant Medications (Therapies)

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

11.11. Adverse Event Assessment

Patients will be monitored for any untoward medical events (AEs or SAEs) from the time of the initiation of study treatment through the period of safety follow-up (30 days after last dose of the study drug or until the start of new antitumor therapy, whichever is earlier).

Serious AEs (SAEs) should be reported to Taiho Pharmacovigilance or its designee. If serious medical occurrences or deaths **outside** the 30 day follow-up period are reported to or observed by the investigator that he/she believes are related to the administration of the study drug, it is the investigator's responsibility to record this occurrence in the eCRF and report to Taiho Pharmacovigilance or its designee.

See Sections 13.1.1, Adverse Events, and 13.1.2, Serious Adverse Events, for definitions and detailed reporting of AEs and SAEs.

11.12. Tumor Assessments/Scans

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

- Baseline within 28 days before Day 1 of Cycle 1. CT scans obtained before the ICF is signed, may be used as the baseline tumor scan if they were obtained within 28 days of the first dose of TAS-114/S-1 or S-1 control.
- At the end of every 6 weeks (± 7 days) beginning at Cycle 2 and thereafter throughout all the treatment cycles, and at the time of discontinuation. At the discretion of the investigator, patients may continue on study drug at the same dose without reduction or interruption for AEs (irrespective of grade) considered unlikely to become serious or life threatening (including but not limited to fatigue and dry skin). Following Cycle 6, CT assessments may be adjusted to every 9 weeks.
- A CT scan should be performed within 2 weeks after discontinuation of the End of Treatment visit if the patient discontinued for reasons other than radiologic disease progression.

On-site tumor assessments by the investigator/local radiologist according to RECIST guidelines (Version 1.1, 2009) as well as central imaging assessment for efficacy evaluation will be performed. 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-114/S-1 or S-1 control. Response definitions are provided in Section 12, Efficacy Assessment Criteria.

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

The same method of assessment and the same technique must be used to characterize each identified and reported lesion at Screening, throughout the study, and during the follow-up period.

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

11.13. 30-Day Safety Follow-up

A safety follow-up visit will be conducted 30 days after the last dose of TAS-114/S-1 or S-1 control. If the patient starts new anticancer therapy within 30 days of the last dose of TAS-114/S-1 or S-1 control, the 30-day safety follow-up visit should be performed before the start of new anticancer therapy within the 30-day window. If the patient is unable to return to the site before the initiation of new treatment, a follow-up phone call can be conducted by the site to collect any new safety information that occurred between discontinuation of study treatment and the initiation of the new anticancer treatment.

12. EFFICACY ASSESSMENT CRITERIA

12.1. Efficacy Assessment for Solid Tumors

The determination of antitumor efficacy will be based on objective tumor assessments made by the investigator according to the revised RECIST guidelines (Version 1.1, 2009) of unidimensional evaluation. Calculated creatinine clearance treatment decisions by the investigator will also be based on these criteria.

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

12.1.1. Method of Imaging

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

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

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

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

For additional guidance refer to the revised RECIST guidelines (Version 1.1, 2009)[20] specifications for standard anatomical radiological imaging, which are included in the Imaging Manual.

12.1.2. Tumor Definitions

Measurable Lesions:

- Measurable visceral lesions: Lesions that can be accurately measured in at least 1 dimension with the longest diameter (to be recorded) ≥ 10 mm by CT scan if using slice thickness of 5 mm or less, or at least double the slice thickness of the CT or MRI scan if the slice thickness is > 5 mm.

- Measurable pathological lymph nodes: A malignant lymph node must be considered pathologically enlarged with high suspicion of metastasis and measure ≥ 15 mm in the short axis when assessed by CT scan. The short axis is defined as the longest linear dimension perpendicular to the node's longest diameter as assessed within the same plane that the scan was acquired.

Only measurable lesions can be selected as target lesions.

Non-measurable lesions include:

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

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

Target Lesions:

- All measurable lesions up to a maximum of 2 lesions/organ and 5 lesions in total, representative of all involved organs/tissues should be identified as target lesions.
- Target lesions should be selected on the basis of their size (visceral lesion with the longest diameter and lymph node with the measurement of short axis), be representative of all involved organs/tissues, but in addition should be those that lend themselves to reproducible repeated measurements.
- When recording tumor measurements, the longest diameter will be measured for each non-nodal target lesion. For measurable pathological lymph nodes that may be identified as target lesions, the short axis measurement will be combined with the measurements of non-nodal (ie, visceral lesion) target lesions. Therefore, in cases of complete response (CR) when abnormal nodes have been used as target lesions, the sum of diameters will not reduce to a null value.
- Target lesions will be followed up and measured at each subsequent time point.

The sum of the diameters for all target lesions will be calculated and recorded. The baseline sum will be used as a reference to further characterize any objective tumor assessment in the measurable dimension of the disease.

- Assign a measurement to all target lesions regardless of size. An option of "too small to measure" will be provided if a measurement cannot be assigned. A value of zero should only be assigned in the case of a CR.
- An option of "not assessable" for a lesion will only apply to lesions that that cannot be read due to technical reasons, for example:
  - CT artifact.
  - Patient positioning where the lesions are obstructed or cannot be seen.
  - Lesions that may not be seen in their entirety due to CT slice thickness.

- In cases where a lesion divides into 2 lesions, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum.
- In cases where 2 lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion."

Non-target Lesions:

Non-target lesions include all non-measurable lesions and measurable lesions that have not been selected as target lesions.

The primary lesion should always be classified as a non-target lesion irrespective of its size and whether or not it can be accurately measured.

Lymph nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded.

Any equivocal lesion without clear diagnosis (eg, uncharacteristic solitary lung nodule without biopsy, uncharacteristic thyroid mass lesion without fine needle aspiration) may be considered a non-target lesion if it cannot be differentiated from a benign lesion.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at Baseline. Measurements are not required, but their presence, absence, or unequivocal progression should be followed throughout the study.

It is possible to record multiple non-target lesions involving the same organ as a single item on the eCRF (eg, multiple enlarged pelvic lymph nodes or multiple liver metastases).

12.1.3. Response Criteria

On-site assessments will include the assessment of:

- Target and non-target tumor responses
- Overall response

The above assessments will be made as per the time points identified in Section 11.12, Tumor Assessments/Scans.

12.1.3.1. Target and Non-Target Response Assessments

Assessments will be based on the definitions below.

TARGET LESIONS	
Lesions Response:	**Definition:**
Complete Response (CR)	The disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of the target lesions, taking as a reference the baseline sum diameters.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of the target lesions, taking as a reference the smallest sum on study, including the baseline sum. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Definitive new lesion presence also indicates progression.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as a reference the smallest sum diameters while on study.

NON-TARGET LESIONS	
Lesions Response:	**Definition:**
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10-mm short axis)
Non-CR/Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions (see definition below).

<u>Progression in Non-target Disease:</u>

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

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

12.1.3.2. Additional Criteria to Consider When Making Tumor Response Assessments

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

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

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

12.1.3.3. Overall Response Assessment

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

Table 13: Time Point Response for Patients with Target (+/- Non-Target) Disease

Target Lesions	Non-Target Lesions	New Lesions	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

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

Table 14: Time Point Response for Patients with Only Non-target Disease

Non-Target Lesions	New Lesions	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

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

12.1.4. Best Overall Response Assessment for Solid Tumors

The best overall response for solid tumors will be assessed as defined in the Statistical Analysis Plan (SAP) per RECIST guidelines (Version 1.1, 2009).

13. REPORTING SAFETY INFORMATION

13.1. Adverse Events/Serious Adverse Events

13.1.1. Adverse Events

An AE is any untoward medical condition that occurs in a patient after treatment initiation and does not necessarily have a causal relationship with the use of the product.

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

For definitions and reporting of pregnancy, overdoses, and medication errors, refer to Section 13.1.5, Pregnancy, Section 13.1.6, Overdose, and Section 13.1.7, Medication Errors, respectively.

Any untoward medical event that occurs outside the period of patient follow-up (30 days after the last dose of study drug or until the start of new antitumor therapy, whichever is earlier) is not required to be reported as an AE/SAE, unless it is assessed to be related to study drug by the investigator.

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

All AEs will be reported from the time a patient starts receiving study treatment through the period of patient follow-up (30 days after the last dose of study drug or until the start of new antitumor therapy, whichever is earlier). All AEs will be documented in the eCRF. Documentation should include onset and resolution/stabilization dates, severity/grade, relationship to study drug, and outcome of the event. All AEs should be entered in the eCRF within 10 business days from the time the investigator first becomes aware of the AE.

Causal relationship is assessed based on the following:

1. Select "Related" if the event follows a reasonable temporal sequence from administration of study drug and at least **one** of the following conditions is true:
    - A positive dechallenge: This means that the event improves or resolves after the drug is stopped (temporarily or permanently).
    - A positive rechallenge: This means that the event reappears after the drug is restarted.
    - The event cannot be reasonably explained by the patient's clinical state and/or other therapies administered.

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

2. Select "Not related" if there is no **reasonable** possibility that the study drug caused the event, or if the event does not follow a reasonable temporal sequence from administration of study drug and could have been produced by a documented pre-existing condition, concomitant medication, or patient's clinical state. For the purposes of safety reporting, "no reasonable possibility" means there is no evidence to suggest a causal relationship between the drug and the AE.

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

- AE has resolved.
- 30-Day Follow-up Visit.
- The start of new antitumor therapy.
- The patient withdrew consent.
- The patient dies.

13.1.2. Serious Adverse Events

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

a. Results in death.
b. Is life threatening (eg, an event that, in the view of the investigator, places the patient at immediate risk of death from the event as it occurred [it does not include an event, which hypothetically might have caused death if it were more severe]).
c. Requires inpatient hospitalization or prolongation of existing hospitalization. The following are not considered hospitalizations for the purposes of assessing seriousness:
    - Emergency room visits < 24 hours.
    - Hospitalizations for preplanned procedures.
    - Hospitalization for study-related treatment and procedures.
d. Results in persistent or significant disability or incapacity, where disability is defined as a substantial disruption of a person's ability to conduct normal life functions, either reported or defined as per clinical judgment.
e. Is a congenital anomaly/birth defect (if exposure to product just before conception or during pregnancy resulted in an adverse outcome in the child).
f. Is any other important medical event (eg, may not result in death, be life-threatening, or require hospitalization), but based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the points above. Examples of such events include allergic

bronchospasm requiring intensive treatment in an emergency room or at home, and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

Serious AEs must be reported to Taiho Pharmacovigilance or designee **within 24 hours** from the time the investigator first becomes aware of the SAE. Comprehensive information available at the time of initial reporting (including narrative description, medical history, and concomitant medications) needs to be provided with careful consideration regarding causality and serious criterion. The SAE reporting process and contact information for reporting the SAE are provided in the eCRF Completion Guidelines.

After the initial SAE notification to Taiho Pharmacovigilance or designee, follow-up SAE information will be submitted each time that important follow-up information (eg, diagnosis, outcome, causality assessment, results of specific investigations) becomes available.

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

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

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

- SAE has resolved.
- SAE has stabilized. An SAE can only be considered "stabilized" if the physical or laboratory AE being followed/assessed has remained constant (is not worsening) based on the investigator's assessment for a minimum of 30 days post study drug discontinuation.
- The start of new antitumor therapy.
- The patient dies.

13.1.3. Reporting of Deaths

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

- Death is not an acceptable SAE term. Death is an outcome of an SAE. The primary cause of death should be reported as the SAE term.

When reporting a death in the eCRF, site personnel will be required to identify which of the following best describes the category of death:

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

13.1.4. Disease Progression

How to report events related to nonfatal disease progression:

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

How to report events related to fatal disease progression:

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

13.1.5. Pregnancy

If a patient becomes pregnant while in the study, the study treatment must be immediately discontinued. Pregnancy information in a female patient should be reported **within 24 hours** from the time the investigator first becomes aware of a pregnancy or its outcome. This should be performed by completing a Pregnancy Form and faxing it to Taiho Pharmacovigilance or designee.

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

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

13.1.6. Overdose

An overdose with TAS-114 and S-1 for this clinical trial is defined as:

Taking a dose beyond the recommended dose in 1 day or beyond the recommended total dose in each cycle.

An overdose of TAS-114 and/or S-1 must be recorded on the AE and SAE Forms and reported to Taiho Pharmacovigilance, or designee, within 24 hours from the time the investigator first becomes aware of the overdose whether or not it was accidental or intentional, and whether or not the patient developed an AE (even if not fulfilling a seriousness criteria).

There is no known antidote available in case of TAS-114 and/or S-1 overdose. Overdose should be managed aggressively with close monitoring and administration of prophylactic and symptomatic therapies to prevent or correct potential side effects.

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

13.1.7. Medication Errors

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

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

The following types of medication errors, whether or not they meet the serious criteria, should be reported to Taiho Pharmacovigilance **within 24 hours of first awareness**, utilizing the AE and SAE forms in the eCRF:

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

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

13.1.8. Breaking the Study Blind

This is an open-label study.

13.2. Laboratory Evaluations

13.2.1. Reporting and Evaluation of Laboratory Test Results

Laboratory tests are to be performed as required per the protocol. All laboratory values that are out of the normal range are to be evaluated for their clinical significance before exposing the patient to the next dose of TAS-114/S-1 or S-1 control.

The laboratory must provide normal reference ranges.

Any laboratory abnormality that has a clinical impact on the patient (eg, results in delay of TAS-114/S-1 or S-1 control dosing, study discontinuation) must be reported as an AE, unless it is considered a supporting laboratory 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 NCI CTCAE grade criteria (Version 4.03).

13.2.2. Repeat Testing

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

13.3. Physical Examination and ECOG Performance Status

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

13.4. Vital Signs and Body Weight

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

14. STATISTICS

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

Study Populations

The study populations include safety and efficacy populations.

Safety and Efficacy Populations

All safety and efficacy analyses will be based on patients who received at least 1 dose of TAS-114/S-1 or S-1 control.

14.1. Statistical Analysis

14.1.1. Patient Disposition, Baseline and Treatment Characteristics

14.1.1.1. Patient Disposition

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

14.1.1.2. Patient Baseline Characteristics

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

14.1.1.3. Study Treatment

The TAS-114/S-1 or S-1 control administration profile will be summarized with respect to number of cycles taken, the dose intensity, dose modifications, reasons for deviations from the planned regimen, and the reason for discontinuing the study treatment.

14.1.2. Efficacy Analysis

Tumor assessments will be performed as described in Section 11.12, Tumor Assessments/Scans, for patients with solid tumors. The primary endpoint of PFS and secondary endpoints of ORR, DCR, and DR will be investigated based on the independent review of the images by the Core Imaging Laboratory. The investigators or local radiologists will evaluate the imaging studies for tumor response and/or progression. Response assessments will be made based on RECIST guidelines (Version 1.1, 2009) for solid tumors (see Section 12.1, Efficacy Assessment for Solid Tumors).

14.1.2.1. Primary Efficacy Analysis

14.1.2.1.1. Progression Free Survival

PFS is defined as the time from the day of randomization to the start of disease progression or death (any cause), whichever occurs first, based on the blinded radiological review assessment of response. Patients who do not have disease progression or have not died will be censored at the last known time that the patient was progression free.

PFS in the efficacy population will be compared between the 2 treatment groups using the stratified log-rank test with significance level of one-sided 5%. PD events assessed by the central independent review will be used for primary efficacy analysis. The estimate of the hazard ratio and corresponding 90% and 95% confidence interval (CI) will be provided using a Cox proportional hazards (CPH) model including treatment and the 2 stratifications factors in the model. The survival curves will be estimated using the Kaplan-Meier method. The primary analysis for PFS will be conducted after 60 events have been observed based on independent assessment or after all patients have been followed for at least 3 months, whichever is later.

14.1.2.2. Secondary Efficacy Analysis

14.1.2.2.1. Overall Survival

OS is defined as the time from the day of randomization to any cause of death. The estimate of the hazard ratio and corresponding 95% CI will be provided using a univariate CPH model (only treatment effect in the model). The survival curves will be estimated using the Kaplan-Meier method. The unstratified log-rank test will be done for the comparison of treatment effect.

14.1.2.2.2. Overall Response Rate and Disease Control Rate

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

- Local CT image assessment and collect CT scans for central independent review

At the analysis stage, the best overall response will be assigned for each patient as the best response recorded after initiation of study treatment. If applicable, responses recorded after disease progression or initiation of new anticancer treatment will be excluded.

The assessment of DCR will parallel that of ORR, with DCR defined as the proportion of patients with objective evidence of CR, PR, or SD.

ORR and DCR in the efficacy population will be compared between the 2 treatment groups using Fisher's exact test. The estimates and differences will be presented along with the associated 95% CIs.

14.1.2.2.3. Duration of Response

DR is derived for those patients with objective evidence of PR or CR. DR is defined as the time from the first documentation of response (CR or PR) to the first documentation of objective tumor progression or death due to any cause. Patients who are alive and progression free as of

the analysis cut-off date will be censored at their last evaluable tumor response assessment before initiation of any new anticancer cancer treatment.

Duration of response will be analyzed in the same manner as OS.

14.1.3. Safety

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

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

All AEs will be summarized (incidence) and listed by the system organ class, preferred term, toxicity/severity grade, and causal relationship to TAS-114/S-1 or S-1 control. In addition, separate summaries of SAEs and grade 3 or 4 AEs will be presented.

Hematological and chemistry laboratory parameters will be graded according to the NCI CTCAE (Version 4.03) where applicable. The worst severity grade, time to maximum grade 3 or 4 value, and time to resolution (return to baseline grade or below) will be summarized.

CCI [redacted]

[redacted]

14.2. Determination of Sample Size

The study is designed to differentiate 4.2 months median PFS of treatment with TAS-114/S-1 from 2.2 months median PFS of treatment with S-1 (hazard ratio of 0.524) with 80% statistical power and a 1-sided type 1 error of 0.05. Using a treatment allocation of 1:1 (TAS-114/S-1: S-1), a target of 60 events (PD or deaths) will be required for the primary analysis, which corresponds to 71 events based on investigator review under the assumption that the discrepancy in PD events between the independent central review and investigator review is 15%. A total sample size of 124 patients is planned from the assumption that accrual period is 10 months, the percentage of PFS events is 65%, and the percentage of patients lost to tumor follow-up caused by study discontinuation is 10%.

14.3. Interim Analyses

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

15. ETHICS

15.1. Ethical Considerations

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

15.2. Informed Consent and Patient Information

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

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

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

15.3. Institutional Review Board/Independent Ethics Committee Approval

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

The IRB/IEC must provide written approval of the study. The written approval/favorable opinion should include protocol (title, number and version number), list of documents reviewed (eg, protocol, ICF, Investigator's Brochure [IB], curriculum vitae), and the date of the review.

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

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

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

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

16. ADMINISTRATIVE CONSIDERATIONS

16.1. Protocol Amendments

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

16.2. Curriculum Vitae

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

16.3. Administrative Structure

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

In addition to ongoing safety monitoring during the study, a more comprehensive evaluation of the ongoing study safety profile will take place when key study milestones are met.

16.4. Monitoring Procedures

16.4.1. Investigator's Responsibilities

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

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

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

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

16.4.2. Sponsor's Responsibilities

The sponsor is responsible to health authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial protocol with regard to ethics, protocol compliance, and integrity and validity of the data recorded in the eCRFs. Thus the main duty of the monitor is to help the investigator and the sponsor maintain a high level of ethical, scientific, technical, regulatory, and quality in all aspects of the trial.

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

16.4.3. Source Documents

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

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

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

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

16.4.4. Case Report Form

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

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

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

16.4.5. Sponsor's Audits and Regulatory Inspections

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

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

The investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data and documents pertaining to the clinical trial. As soon as the investigator is notified of a planned inspection by the regulatory authorities or IRB/IEC, the investigator will inform the sponsor. Any results arising from such inspections will be immediately communicated by the investigator to the sponsor. The investigator shall take appropriate measures required by the sponsor to take corrective actions for all problems found during audits and or inspections.

16.5. Archiving of Records

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

The investigator agrees to inform sponsor in writing of the intention to remove or destroy any study-related records. Prior to contacting sponsor, the investigator must ensure that institutional and local requirements (for example, ICH Guidelines and Japanese Good Clinical Practice [J-GCP]) have been satisfied. The sponsor will evaluate the investigator's request and will provide authorization for destruction of such records to the investigator in writing.

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

16.6. Final Report

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

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

16.7. Use and Publication of Study Results

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

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

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

16.8. Financial Disclosure

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

16.9. Termination of the Study

In the event that the investigator is unable to continue the study and another suitable person is designated as the investigator, the sponsor must be notified in advance (30 days prior to notice). The new investigator must accept the responsibility in writing and be approved by the sponsor and the IRB/IEC.

If the sponsor and/or the investigator should discover conditions arising during the study that indicate it should be terminated, an appropriate schedule for termination will be instituted. The sponsor also reserves the right to discontinue this study for administrative reasons at any time. The investigator will be reimbursed for reasonable expenses incurred, if it is necessary to terminate the study or an individual patient's participation. The sponsor will not reimburse the investigator for the evaluation of patients if the evaluations are not conducted in compliance with the final protocol.

17. CONFIDENTIALITY AND DATA PROTECTION

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

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

The patient's personal data and investigator's personal data which may be included in the sponsor's database shall be treated in compliance with all applicable laws and regulations.

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

18. SIGNATURES OF SPONSOR AND INVESTIGATOR

18.1. Declaration of the Sponsor

A RANDOMIZED, OPEN-LABEL, MULTI-CENTER, INTERNATIONAL PHASE 2 STUDY OF TAS-114 IN COMBINATION WITH S-1 IN PATIENTS WITH ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER

Declaration of Sponsor

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

- The current risk-benefit evaluation of TAS-114.
- The moral, ethical, and scientific principles governing clinical research as set out in the protocol, GCP, ICH Guidelines, the ethical principles that have their origin in the Declaration of Helsinki, and all applicable regulatory requirements.

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

PPD

Dat[redacted] Signatur[redacted]

PPD

PPD MD, PhD

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

PPD

18.2. Declaration of the Investigator

A RANDOMIZED, OPEN-LABEL, MULTI-CENTER, INTERNATIONAL PHASE 2 STUDY OF TAS-114 IN COMBINATION WITH S-1 IN PATIENTS WITH ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER

Declaration of Investigator:

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

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

Investigator

Date: _____Signature: _____
Name (block letters): _____

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