TAS-102

PROTOCOL TO-TAS-102-302

RANDOMIZED, DOUBLE-BLIND, PHASE 3 STUDY EVALUATING TAS-102 PLUS BEST SUPPORTIVE CARE (BSC) VERSUS PLACEBO PLUS BSC IN PATIENTS WITH METASTATIC GASTRIC CANCER REFRACTORY TO STANDARD TREATMENTS

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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:

[redacted]

Sponsor Contact:

[redacted]

SPONSOR'S MEDICAL MONITORS:

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Japan:

[redacted]

PRINCIPAL INVESTIGATORS:

[redacted]

STEERING COMMITTEE:

PRINCIPAL INVESTIGATORS [redacted]

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

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2. SYNOPSIS

Name of Sponsor/Company:	Taiho Oncology, Inc.; Taiho Pharmaceutical Co., Ltd.
Name of Investigational Product:	TAS-102
Name of Active Ingredients:	trifluridine (FTD) and tipiracil hydrochloride (TPI)
Title of Study: **RANDOMIZED, DOUBLE-BLIND, PHASE 3 STUDY EVALUATING TAS-102 PLUS BEST SUPPORTIVE CARE (BSC) VERSUS PLACEBO PLUS BSC IN PATIENTS WITH METASTATIC GASTRIC CANCER REFRACTORY TO STANDARD TREATMENTS**	
Protocol Number:	TO-TAS-102-302
Phase of Development:	3
Indication:	Refractory metastatic gastric cancer
Background/Rationale:	• TAS-102 is an oral combination of 1M trifluridine (FTD) and 0.5M tipiracil hydrochloride (TPI). • The primary mechanism of action of FTD, an antineoplastic thymidine-based nucleoside analog, is incorporation into DNA via phosphorylation, resulting in a different cytotoxic mechanism from 5-fluorouracil (5-FU) and 2'-deoxy-5-fluorouridine (FdUrd) (uracil-based thymidylate synthase inhibitors). • FTD, when orally administered, is rapidly degraded to an inactive form by thymidine phosphorylase (TP). Co-administration of an inhibitor of TP (TPI) with FTD prevents the rapid degradation of FTD, resulting in a significant increase in systemic exposure to FTD. • In a previous Phase 3 global trial (RECOURSE; TPU-TAS-102-301), TAS-102 was shown to significantly improve overall survival (OS) in patients with metastatic colorectal cancer (mCRC) who have been previously treated with, or are not candidates for fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-vascular endothelial growth factor (VEGF) biological therapy, and an anti-epidermal growth factor receptor (EGFR) therapy (Mayer et al, 2015). • In a Phase 2 study conducted in Japan (EPOC1201), the efficacy and safety of TAS-102 was evaluated in patients with metastatic gastric cancer who had failed standard chemotherapies including fluoropyrimidines, platinum and any of the taxanes or irinotecan. The results demonstrated that TAS-102 was well tolerated; and TAS-102 treatment (35 mg/m^2 twice daily [BID]) led to an OS of 8.7 months with a disease control rate (DCR) of 65.5% (Muro et al, 2013). • This Phase 3 study will compare the efficacy, including OS, and safety of TAS-102 combined with best supportive care (BSC) to placebo plus BSC in patients with metastatic gastric cancer who have previously received at least 2 prior regimens for advanced disease and were refractory to or unable to tolerate their last prior therapy.

Study Objective/ Endpoints:	To evaluate the following endpoints in patients with refractory metastatic gastric cancer receiving TAS-102 plus BSC (experimental arm) or placebo plus BSC (control arm): **Primary** • Overall survival (OS) **Key Secondary** • Progression-free survival (PFS) based on Investigator assessment of radiologic images • Safety and tolerability **Other Secondary** • Overall response rate (ORR) • Disease control rate (DCR) • Time to deterioration of Eastern Cooperative Oncology Group (ECOG) performance status to score of 2 or higher • Quality of life (QoL) (EORTC QLQ-C30 and QLQ-STO22)
Study Design:	This is a multinational, double-blind, two-arm, parallel, randomized, Phase 3 study evaluating the efficacy and safety of TAS-102 plus BSC versus placebo plus BSC in patients with metastatic gastric cancer who have previously received at least 2 prior regimens for advanced disease. Eligible patients will be centrally randomized (2:1) to TAS-102 + BSC (experimental arm) or placebo + BSC (control arm) and stratified by: • Region (rest of world [ROW] vs. Japan) • ECOG performance status (0 vs. 1) • Prior treatment with ramucirumab (yes vs. no)
No. of Patients Planned:	Approximately 500 patients will be randomized using a treatment allocation of 2:1 (TAS-102 plus BSC: placebo plus BSC). A target of 384 events (deaths) will be required for the primary analysis.
Diagnosis/Main Criteria for Inclusion:	Male and female patients age 18 years or older (20 years or older for patients enrolled in Japan) with histologically confirmed, non-resectable, metastatic gastric adenocarcinoma including adenocarcinoma of the gastroesophageal (GE) junction, and an ECOG performance status of 0 or 1, who have received at least 2 prior regimens (at least 1 cycle per regimen) for advanced disease, and were refractory to or unable to tolerate their last prior therapy. • Prior regimen(s) must have included a fluoropyrimidine, platinum, and either a taxane- and/or irinotecan-containing regimen; patients whose tumors are known to be HER2-neu-positive (HER2+) must have received prior anti-HER2+ therapy if available. • Patients have progressed based on imaging during or within 3 months of the last administration of their last prior regimen. • Patients who have withdrawn from their last prior regimen due to unacceptable toxicity warranting discontinuation of treatment and precluding retreatment with the same agent prior to progression of disease will also be eligible to enter the study. • Patients who have received postoperative adjuvant chemotherapy or chemo-radiotherapy, and had recurrence during or within 6 months of completion of the adjuvant chemotherapy are allowed to count the adjuvant therapy as one prior regimen for advanced disease. Patients who have received pre- and post-operative adjuvant chemotherapy, and had recurrence during or within 6 months of completion of the adjuvant chemotherapy are allowed to count the adjuvant therapy as one prior

	regimen only if the same regimen was administered both pre- and post-operatively.
Treatment Regimens:	TAS-102 (starting dose of 35 mg/m^2/dose) or placebo will be administered orally BID, within 1 hour after completion of morning and evening meals, for 5 days a week with 2 days rest for 2 weeks, followed by a 14-day rest, repeated every 4 weeks. Patients will receive blinded study medication until a discontinuation criterion is met or until completion of the primary endpoint analysis, whichever is sooner.
Study Duration:	After the end of treatment, all patients will be followed for survival every 4 weeks until death or until the target number of events (deaths) is met. If the primary endpoint of the study is met and efficacy as well as safety support a favorable benefit/risk ratio for TAS-102, patients currently or previously treated with placebo who continue to meet study eligibility criteria will be offered the option to crossover to open-label TAS-102. Patients receiving TAS-102 will also be switched to open-label TAS-102 at that time. Patients who receive open-label TAS-102 treatment after conclusion of survival follow-up will be followed for safety and tumor response according to the site standard of care.
Efficacy Criteria for Evaluation:	Computed tomography (CT) scans will be performed every 8 weeks. On-site tumor assessments will be performed by the Investigator/local radiologist. Tumor assessments will be analyzed using Response Evaluation Criteria in Solid Tumors (RECIST) criteria (Version 1.1, 2009). Progression-free survival will be determined for all patients. Quality of Life assessments will be performed prior to start of dose administration in each cycle.
Safety Criteria for Evaluation:	Standard safety monitoring will be performed and adverse events (AEs) will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.
Statistical Methods:	**Study Populations** The study populations for all analyses are defined as follows. • Intent-to-Treat (ITT) population: This population includes all randomized patients and is the primary population for all efficacy parameters. All analyses using this population will be based on the treatment assigned by Interactive Voice/Web Response System (IXRS). • As-Treated (AT) population: This population includes all patients who took part of any dose of study treatment. This population is for safety analyses. All analyses using this population will be based on the treatment actually received. • Tumor Response (TR) Population: All patients in the ITT population with measurable disease (at least one target lesion) at baseline and with at least one tumor evaluation while on treatment. (Patients who have disease progression or a cancer-related death prior to their first on treatment tumor evaluation will also be considered evaluable.) All analyses using this population will be based on the treatment assigned by IXRS. **Primary Efficacy Endpoint (OS)** OS is defined as the time from the date of randomization to the date of death. If death is not observed during the study, the time will be censored at the last date patient is known to be alive or the cut-off date, whichever is earlier. For the primary analysis of OS, the two treatment arms will be compared using the stratified log-rank test using the 3 stratification factors in the randomization as per IXRS assignment. The hazard ratio (HR) will be estimated, along with the associated 2-

	sided 95% confidence intervals (CI), using a stratified Cox's proportional hazard (CPH) model. Survival for each arm will be summarized using Kaplan Meier curves and further characterized in terms of the median and survival probability at 3, 6, 9 and 12 months, along with the corresponding 2-sided 95% CI for the estimates.
Statistical Methods (continued):	**Key Secondary Efficacy Endpoint (PFS)** PFS will be evaluated from date of randomization to the first occurrence of radiologic progression or death. Treatment comparisons for PFS will use similar analytical methods as the OS endpoint. **Other Secondary Efficacy Endpoints** ORR and DCR will be compared between treatment arms using Fisher's exact test and associated 95% CIs will also be derived. Time to deterioration of ECOG performance status to a score of 2 or higher will be analyzed as described for PFS. Change in QoL scores prior to cycles 2, 3 and 4 will be determined for the summary, all domains and single items by subtracting each patient's score from their corresponding baseline score. For each domain, the proportion of patients with deteriorating, stable or improving scores prior to cycles 2, 3 and 4 will be compared using Fisher's exact test. Time to QoL deterioration will be evaluated for each arm using Kaplan-Meier estimates and compared using the log-rank test. **Safety Analyses** Simple descriptive statistics will be provided for safety endpoints and demographic/baseline characteristics.
Sample Size Justification:	The study is designed to detect with 90% power a HR for death of 0.70 (30% risk reduction) in the TAS-102 arm compared with the placebo arm with an overall 1-sided type 1 error of 0.025. A variable accrual period of 18 months and a 5%/year loss to survival follow-up rate has been assumed. Using a treatment allocation of 2:1 (TAS-102:placebo) of 500 patients, 384 deaths will be targeted for the final OS analysis.
Interim Analyses:	One interim analysis for efficacy and futility is planned to be performed after approximately one-half of the total target events are observed.
Independent Data Monitoring Committee:	An independent Data Monitoring Committee (DMC) will periodically assess the cumulative safety data and results of the interim analysis and recommend study continuation, discontinuation, or study modification. A description of the roles and responsibilities of the DMC and details of the review processes and monitoring guidelines are provided in a separate DMC charter.

3. STUDY SCHEDULES

Figure 1: Study Design Schema

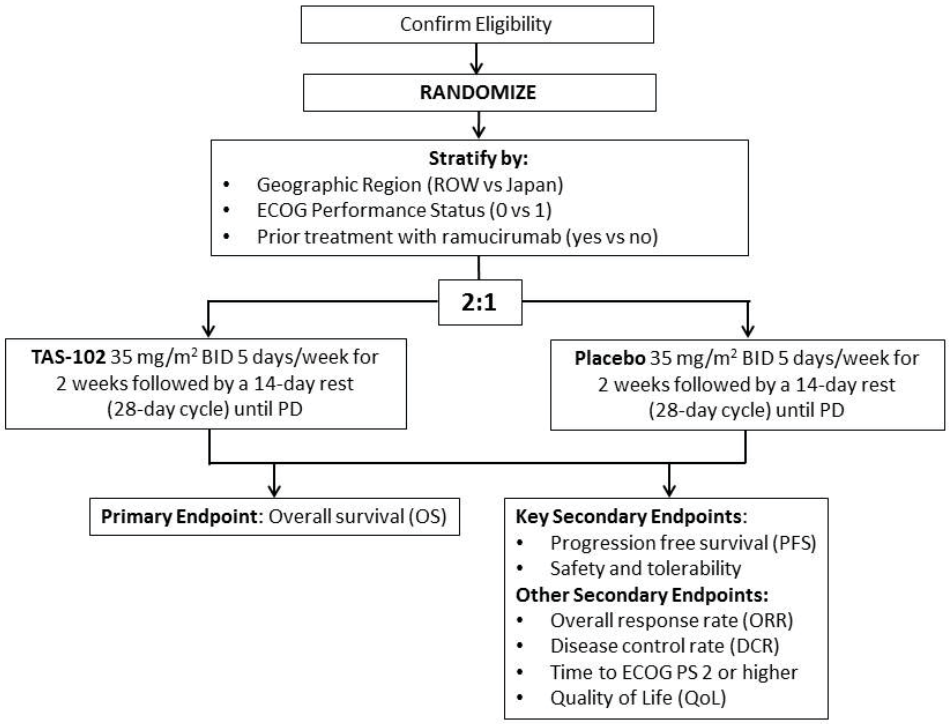

Table 1: Study Schedule

Visit ID / Procedure	Baseline Period		On-Treatment Period								End of Treatment/ End of Study Period		
	Baseline Day		CYCLE 1 Day of Cycle[14]				SUBSEQUENT CYCLES Day of Cycle[14]				End of Treat-ment[16]	30-Day Safety Follow-up Visit	Survival Follow-up
	-28 to -1	-7 to -1	1	12	15	End of Recovery	1	12	15	End of Recovery			
Sign ICF	X[1]												
Enrollment	X[2]												
Randomization			X[3]										
Medical History	X												
Histological Confirmation	X												
HER2 status (if available)	X												
Physical Examination[4]		X					X[15]				X	X	
Baseline Signs & Symptoms		X											
Height		X											
Vital Signs[5] & Weight		X					X[15]				X	X	
ECOG Performance Status	X		X[6]				X[15]				X	X	
Hematology[7]		X			X		X[15]				X	X	
Serum Chemistry[7]		X			X		X[15]				X	X	
Urinalysis[7]		X											
Pregnancy Test[8]		X									X	X	
Tumor Measurements[9]	X									X[9]	X[9]		X[9]
Quality of Life Assessment[18]		X[18]					X[18]					X[18]	
Concomitant Medications[10]	X	→	→	→	→	→	→	→	→	→	→	→[10]	X[11]
AE/SAE Assessment[12]			X	→	→	→	→	→	→	→	→	X	
TAS-102 or Placebo Treatment[13]			X (D 1-5)	X (D 8-12)			X (D 1-5)	X (D 8-12)					
Survival Status			→	→	→	→	→	→	→	→	→	→	X[17]

1 Sign ICF: Written informed consent should be obtained prior to the performance of any study procedure.
2 Enrollment: Enroll patient by entering baseline data into the electronic case report form (eCRF) in order to receive a unique 6-digit patient number.
3 Randomization: Central randomization via IXRS following confirmation of baseline eligibility criteria. The maximum screening period is 28 days; eligible patients must be randomized by Day 29 of screening. The patients should receive the first dose of study medication within 3 calendar days of randomization.
4 Physical Exam: Beginning with Cycle 2, and for all subsequent cycles, perform within 24 hours prior to Day 1 study drug administration.
5 Vital Signs: Heart rate, blood pressure, body temperature, respiratory rate; beginning with Cycle 2, and for all subsequent cycles; collect within 24 hours prior to Day 1 study drug administration.
6 ECOG Performance Status: Collect at time of randomization (within 3 calendar days prior to start of study treatment on Day 1 of Cycle 1) and within 24 hours prior to start of study treatment in every cycle thereafter.

(Footnotes continue on next page)

7 Hematology, Serum Chemistry, Urinalysis: Hematology and serum chemistry assessments will be performed at Baseline (within 7 days prior to Day 1 of Cycle 1; on Day 15 of Cycle 1; and within 24 hours prior to Day 1 study drug administration of Cycles ≥2. Urinalysis is required at Baseline and thereafter as clinically indicated. Laboratory results obtained prior to signing ICF may be used if the results were obtained within 7 days prior to Day 1 of Cycle 1.

8 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.

9 Tumor Measurements: Obtain a contrast-enhanced computed tomography (CT) scan of the chest and abdomen (and pelvis, if clinically indicated) within 28 days prior to Day 1 of Cycle 1 and every 8 weeks thereafter during study treatment. If a patient discontinues treatment due to radiologic disease progression, additional tumor assessment is not required at the End of Treatment visit. For patients who discontinue treatment for reasons other than radiologic disease progression, every effort should be made to perform an end of treatment tumor assessment prior to the start of new anticancer therapy. Patients that discontinued treatment for reasons other than disease progression should continue to be followed for tumor response every 8 weeks until the patient develops radiologic disease progression (or death) or initiation of new anticancer therapy (whichever occurs first). Tumor assessments should be performed according to RECIST criteria (v. 1.1, 2009). CT scans obtained prior to signing ICF may be used if the date of the scan is within 28 days prior to Day 1 of Cycle 1.

10 Concomitant Medications: Collect from time of signed Informed Consent Form (ICF) through the end of therapy, including any medications used to treat AEs or SAEs; at the 30-day safety follow-up period, collect date of initiation of any new anticancer therapy.

11 Concomitant Medications: Collect anticancer therapies only during survival follow-up.

12 AE/SAE Assessment: Monitor patients for any untoward medical events from the first dose of study drug through the 30-day safety follow-up period or until initiation of new anticancer treatment, whichever comes first. Adverse events reported from time of signed ICF to first dose of study drug should be recorded as Medical History.

13 Study Drug Treatment: TAS-102 or placebo will be administered twice daily (BID) on Days 1 through 5 and 8 through 12 of each cycle.

14 Assessment Windows: A window of +/-3 days is allowable for study procedures (+/-7 days allowable for CT scans), as long as the proper order is maintained.

15 Subsequent Cycles ≥2: Obtain within 24 hours prior to Day 1 study drug administration. Prior to starting subsequent cycles, verify that patients with toxicities have met resumption criteria prior to administering study drug.

16 End of Treatment: Assessments will be performed at time of withdrawal of study medication (TAS-102 or Placebo). If the decision to discontinue study medication 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 study medication (due to proven radiologic disease progression or other reasons) is made more than 2 weeks after the last treatment visit, an End of Treatment Visit is required. If this visit occurs within 2 weeks of the 30-day Safety Follow-up Visit, the 2 visits can be combined.

17 Survival Status: Obtain survival status (alive/dead) at scheduled 4-week time intervals until death. Survival status should be collected until the target number of events (deaths) is met.

18 Quality of Life: Patients should complete the EORTC – QLQ-C30 and QLQ-STO22 questionnaires within 7 days prior to randomization, prior to dose administration on Day 1 of Cycles ≥2, and at the 30-day safety follow-up if not performed within the prior 4 weeks.

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5. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
5-FU	5-fluorouracil
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase (SGPT)
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase (SGOT)
AT	As treated (population)
β-HCG	Beta-human chorionic gonadotrophin
BID	Twice daily
BSA	Body surface area
BSC	Best supportive care
BUN	Blood urea nitrogen
°C	Degrees Celsius
CFR	Code of Federal Regulations
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
cm	Centimeter
CPH	Cox proportional hazards
CR	Complete response
CRA	Clinical Research Associate
CRC	Colorectal cancer
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
dL	Deciliter
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid

Abbreviation	Definition
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQ-C30	EORTC Quality of Life Questionnaire - Core Questionnaire
EORTC QLQ-STO22	EORTC Quality of Life Questionnaire - Gastric-specific module
EU	European Union
°F	Degrees Fahrenheit
FDG-PET	Fluorodeoxyglucose positron emission tomography
FdUrd	2'-deoxy-5-fluorouridine
FTD	Trifluridine. α,α,α-trifluorothymidine
g	Gram
G-CSF	Granulocyte colony-stimulating factor
GCP	Good Clinical Practice
GE	Gastroesophageal
HER2	Human epidermal growth factor receptor 2
HER2+	HER2-neu-positive
HIV	Human immunodeficiency virus
HR	Hazard ratio
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-treat (population)
IU	International Units
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IXRS	Interactive Voice/Web Response System
Kg	Kilogram

Abbreviation	Definition
KRAS	GTPase KRas; V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
L	Liter
m^2	Meters squared
mCRC	Metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mm	Millimeter
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression free survival
PR	Partial response
PS	Performance status
PT	Preferred term (MedDRA)
QoL	Quality of Life
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RECOURSE	**Re**fractory **Co**lo**re**ctal Cancer **S**tudy (TPU-TAS-102-301 Phase 3 study; NCT01607957)
ROW	Rest of world
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious Adverse Reaction
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SI	International System (of Units)
SOC	System Organ Class (MedDRA)
SOP	Standard Operating Procedure

Abbreviation	Definition
SUSAR	Suspected Unexpected Serious Adverse Reaction
TOI	Taiho Oncology, Inc.
TP	TPase; Thymidine phosphorylase
TPC	Taiho Pharmaceutical Co., Ltd.
TPI	Tipiracil hydrochloride. 5-chloro-6-[(2-iminopyrrolidin-1-yl)methyl]pyrimidine-2,4-(1H,3H)-dione monohydrochloride
TR	Tumor response (evaluable population)
TS	Thymidylate synthase
ULN	Upper limit of normal
USA	United States of America
VEGF	Vascular endothelial growth factor
VEGFR-2	Vascular endothelial growth factor-2
WBC	White blood cell
WHODD	World Health Organization Drug Dictionary

6. INTRODUCTION

6.1. TAS-102

Detailed information on the nonclinical and clinical experience with TAS-102 is provided in the Investigator's Brochure (IB).

6.1.1. Mechanism of Action

TAS-102 is an oral combination of an antineoplastic thymidine-based nucleoside analogue (trifluridine [FTD]) and a thymidine phosphorylase inhibitor (tipiracil hydrochloride [TPI]). Following uptake into cancer cells, FTD is phosphorylated by thymidine kinase, further metabolized in cells to a deoxyribonucleic acid (DNA) substrate, and incorporated directly into DNA, thereby interfering with DNA function to prevent cell proliferation. When orally administered, FTD is rapidly degraded to an inactive form by thymidine phosphorylase (TP). Co-administration of TPI, an inhibitor of TP, with FTD prevents the rapid degradation of FTD, resulting in a significant increase in systemic exposure to FTD.

FTD incorporation into DNA is markedly higher than that of other nucleoside analogues. The degree of incorporation of FTD into DNA ranges from approximately 10-fold up to 700-fold greater in comparison with that of 2'-deoxy-5-fluorouridine (FdUrd). FTD also exhibits thymidylate synthase (TS) inhibition. However, results of *in vivo* studies show FTD incorporation into DNA to be the primary mechanism of antitumor activity with oral administration.

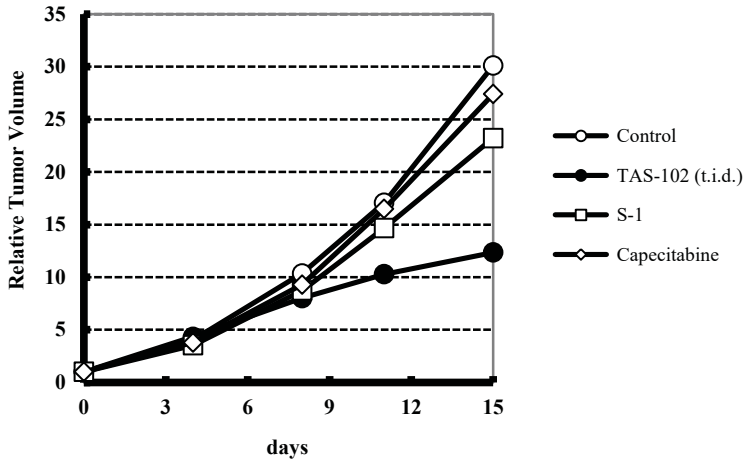
This mechanism of action of TAS-102 differentiates it from conventional fluoropyrimidines, which are uracil-based, and for which the primary mode of action is TS inhibition. In nonclinical studies, TAS-102 demonstrated antitumor activity against both 5-fluorouracil (5-FU) sensitive and resistant colorectal and gastric cancer cell lines.

6.1.2. TAS-102 in Gastric Cancer

6.1.2.1. Preclinical Findings

The efficacy of TAS-102 against tumors insensitive to 5-FU was demonstrated *in vivo* in a human gastric carcinoma xenograft model (Study No. 03-04-005). Mice with AZ-521 human gastric carcinoma xenografts were treated for 14 days with TAS-102 (150 mg/kg/day), capecitabine (539 mg/kg/day), or S-1 (8.3 mg/kg/day). S-1 is an oral, fixed-dose combination drug comprised of tegafur (a fluoropyrimidine prodrug of 5-FU) and 2 modulators of 5-FU metabolism (gimeracil and oteracil). Only the TAS-102 treatment group showed significant antitumor activity without any body weight loss (Figure 2).

Figure 2: Antitumor Efficacies of TAS-102, S-1 and Capecitabine in an AZ-521 Human Gastric Carcinoma Xenograft Model



6.1.2.2. Clinical Experience

In a Phase 2 study conducted in Japan (EPOC1201), the efficacy and safety of TAS-102 (35 mg/m^2 twice daily [BID]) was evaluated in 29 patients with metastatic gastric cancer who had failed standard chemotherapies including fluoropyrimidines, platinum and any of the taxanes or irinotecan.[1] The disease control rate (DCR) was 65.5% (95% confidence interval [CI]: 45.7, 82.1). Median progression free survival (PFS) was 2.9 months and median overall survival (OS) was 8.7 months.

In this population of heavily treated patients, TAS-102 was well tolerated. Common Grade 3 or 4 adverse events (AEs) included neutropenia (69.0%), leukopenia (41.4%), anemia (20.7%) and anorexia (10.3%). Only 2 (6.9%) patients discontinued treatment due to AEs. No treatment-related deaths were observed.

6.2. Rationale for Study and Selection of Dose

6.2.1. Unmet Medical Need

Gastric cancer is the fifth most common cancer worldwide and the third most common cause of cancer-related death (after lung and liver cancer), with an estimate of 723,073 deaths annually.[2] Currently, patients with gastric cancer can be cured only when diagnosed with early stage disease in which a complete resection of the tumor can be achieved (gastrectomy with lymphadenectomy, with or without chemotherapy or radiation therapy). Approximately 50% of patients with gastric cancer have advanced disease at the time of diagnosis.[3] Standard chemotherapy regimens for advanced gastric cancer include fluoropyrimidines, platinum derivatives, and taxanes, or irinotecan. Based on the results of the ToGA study,[4] the addition of trastuzumab to chemotherapy has become standard of care, where available, for first-line treatment of patients with HER2-neu-positive (HER2+) advanced or metastatic gastric adenocarcinoma. Among patients with advanced metastatic gastric cancer who have received standard first-line therapies, the 5-year survival rate remains less than 5% and the median OS is less than 12 months. Ramucirumab, a vascular endothelial growth factor-2 (VEGFR-2)

antibody, has been shown to increase OS when administered alone[5] or in combination with paclitaxel[6] in patients who have progressed following first-line therapy; and was recently approved in select countries for second-line therapy of gastric cancer. However, after failure of first- and second-line therapies, there are no approved or standard 3rd line treatments.

6.2.2. Rationale for Study Design

This present study is designed as a randomized, double-blind, Phase 3 study comparing TAS-102 plus best supportive care (BSC) to placebo plus BSC in patients with metastatic gastric cancer who have received at least 2 prior regimens for advanced disease and were refractory or unable to tolerate their last prior therapy.

A placebo-controlled design was considered appropriate as there are currently no standard therapies for patients with metastatic gastric cancer who have failed first- and second-line therapies.

Approximately 500 patients will be randomized 2:1 to TAS-102 plus BSC or placebo plus BSC. In order to ensure comparability of groups, patients will be stratified by geographic region (rest of world [ROW] vs Japan); Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1); and prior ramucirumab treatment (yes vs. no).

Overall survival was chosen as the primary endpoint because it is the gold standard endpoint for cancer indications in which there are no other therapy options with demonstrated survival benefit. Measurement of this endpoint is not questionable and patients with either measurable or non-measurable disease can be evaluated without the possibility of discrepancies in interpretations.

Standard safety assessments, including assessment of the type, incidence, severity (graded by National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE], Version 4.03), timing, seriousness, and relatedness of AEs and laboratory assessments will be used.

6.2.3. Selection of TAS-102 Dose

TAS-102 (35 mg/m^2/dose) will be administered orally BID, within 1 hour after completion of morning and evening meals, for 5 days a week with 2 days rest for 2 weeks, followed by a 14-day rest. This treatment cycle will be repeated every 4 weeks.

The safety and tolerability of this TAS-102 regimen was demonstrated in a Phase 3, multinational, randomized, double-blind study (RECOURSE; TPU-TAS-102-301), in which TAS-102 was shown to significantly improve OS compared to placebo in patients with metastatic colorectal cancer (mCRC), who had been previously treated with, or were not candidates for fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-vascular endothelial growth factor (VEGF) biological therapy, and an anti-epidermal growth factor receptor (EGFR) therapy.[7]

In addition, a statistically significant 34% risk reduction in worsening ECOG performance status (time to ECOG performance status ≥2) was observed for TAS-102 compared to placebo, suggesting that quality of life was maintained while on TAS-102 treatment.

In the RECOURSE study, the most common AEs associated with TAS-102 treatment were myelosuppressive and gastrointestinal toxicities. Up to 20% of patients receiving TAS-102 experienced Grade 3 or 4 hematologic events related to anemia and neutropenia/leukopenia; however, the incidence of febrile neutropenia was low (3.8%). These events were generally manageable with reductions in dose, delays in cycle initiation and occasional use of granulocyte colony-stimulating factor (G-CSF). Only 3 patients discontinued treatment due to hematologic AEs, and there was only one treatment-related death due to neutropenia-related infection. Events of nausea, decreased appetite, diarrhea and vomiting related to treatment were common in the TAS-102 group (20.1% to 39.4%); however, these AEs were rarely Grade 3 or 4. The incidence of stomatitis among patients receiving TAS-102 was 7.9%; Grade 3/4 events of stomatitis were rare (0.4%). In addition, hand-foot syndrome was reported in only 2.3% of patients receiving TAS-102 (all Grade 1 or 2), which was the same percentage reported in the placebo arm.

In a Phase 2 study conducted in Japan, this TAS-102 regimen was also well-tolerated in patients (N=29) with metastatic gastric cancer who had failed prior therapies. Common Grade 3 or 4 AEs included neutropenia, leukopenia, anemia, and anorexia. Only one case of febrile neutropenia was observed, and there were no treatment-related deaths as described in Section 6.1.2.2 above.

7. STUDY OBJECTIVES

The objectives of this study are to evaluate the following endpoints in patients with refractory metastatic gastric cancer receiving TAS-102 plus BSC or placebo plus BSC:

Primary

- Overall survival (OS)

Key Secondary

- Progression-free survival (PFS) based on Investigator assessment of radiologic images
- Safety and tolerability

Other Secondary

- Overall response rate (ORR)
- Disease control rate (DCR)
- Time to deterioration of Eastern Cooperative Oncology Group (ECOG) performance status to score of 2 or higher
- Quality of Life (QoL) (EORTC QLQ-C30, QLQ-STO22)[8]

8. INVESTIGATIONAL PLAN

8.1. Overall Study Design

This is a multinational, double-blind, two-arm, parallel, randomized, Phase 3 study evaluating the efficacy and safety of TAS-102 plus BSC versus placebo plus BSC in patients with metastatic gastric cancer who have received at least 2 prior regimens for advanced disease. The 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 (ROW).

Eligible patients will be centrally randomized (2:1) to TAS-102 + BSC (experimental arm) or placebo + BSC (control arm) using a dynamic allocation method (biased coin) via an Interactive Voice/Web Response System (IXRS), stratified by:

- Region (ROW vs. Japan)
- ECOG performance status (0 vs. 1)
- Prior treatment with ramucirumab (yes vs. no)

Study medication should be started within 3 calendar days after the date of randomization and continue until a discontinuation criterion is met or until completion of the primary endpoint analysis, whichever is sooner.

TAS-102 (35 mg/m^2/dose) or placebo will be administered orally BID, within 1 hour after completion of morning and evening meals, for 5 days a week with 2 days rest for 2 weeks, followed by a 14-day rest, repeated every 4 weeks.

Computed tomography (CT) scans will be performed at baseline and every 8 weeks thereafter until disease progression. On-site tumor assessments will be performed by the Investigator/local radiologist. Tumor assessments will be analyzed using Response Evaluation Criteria in Solid Tumors (RECIST) criteria (Version 1.1, 2009). If patient discontinuation is for reasons other than radiologic disease progression (ie, with intolerable side effects), patients will be followed every 8 weeks for tumor response until radiologic disease progression or initiation of new anticancer therapy (whichever occurs first).

Quality of life assessments (EORTC QLQ-C30 and QLQ-STO22) will be performed prior to start of dose administration in each cycle.

Standard safety monitoring will be performed and AEs will be graded using the NCI CTCAE Version 4.03.

8.2. Study Duration

After discontinuation of study treatment, all patients will be followed for survival every 4 weeks until death or until the target number of events (deaths) is met, unless the patient has withdrawn consent from the trial. Patients may request discontinuation of study treatment but agree to survival follow-up (this is not considered withdrawal of consent from the trial).

The final analysis will be performed once 384 events (deaths) are reached. If the primary endpoint of the study is met and efficacy as well as safety support a favorable benefit/risk ratio

for TAS-102, patients currently or previously treated with placebo who continue to meet study eligibility criteria will be offered the option to crossover to open-label TAS-102. Patients who are currently receiving TAS-102 will also be switched to open-label TAS-102 at that time.

Patients who receive open-label TAS-102 treatment after conclusion of survival follow-up will be followed for safety and tumor response according to the site standard of care (see Section 9.3). The end of study is defined as completion of safety follow-up for the last patient who discontinues study treatment, including patients who receive open-label TAS-102.

8.3. Study Population

Approximately 500 male and female patients with metastatic gastric cancer will be randomized.

8.3.1. Inclusion Criteria

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

1. Has provided written informed consent.
2. Has histologically confirmed non-resectable, metastatic gastric adenocarcinoma including adenocarcinoma of the gastroesophageal (GE) junction as defined by the American Joint Committee on Cancer (AJCC) staging classification (7th ed., 2010). Documentation of histology of the tumor (primary or metastasis) will be required prior to enrollment. Gastroesophageal junction involvement must be documented by endoscopic, radiologic, surgical or pathology report.
3. Has previously received at least 2 prior regimens (at least 1 cycle per regimen) for advanced disease and were refractory to or unable to tolerate their last prior therapy:
    a. Prior regimen(s) must have included a fluoropyrimidine, platinum, and either a taxane- and/or irinotecan-containing regimen; patients whose tumors are HER2-neu-positive (HER2+) must have received prior anti-HER2+ therapy if available.
    b. Patients have progressed based on imaging during or within 3 months of the last administration of their last prior regimen.
    c. Patients who have withdrawn from their last prior regimen due to unacceptable toxicity warranting discontinuation of treatment and precluding retreatment with the same agent prior to progression of disease will also be eligible to enter the study.
    d. Patients who have received postoperative adjuvant chemotherapy or chemo-radiotherapy, and had recurrence during or within 6 months of completion of the adjuvant chemotherapy are allowed to count the adjuvant therapy as one prior regimen for advanced disease. Patients who have received pre- and post-operative adjuvant chemotherapy, and had recurrence during or within 6 months of completion of the adjuvant chemotherapy are allowed to count the adjuvant therapy as one prior regimen only if the same regimen was administered both pre- and post-operatively.
4. Has measureable or nonmeasurable disease as defined by RECIST 1.1 criteria.
5. Is able to take medications orally (ie, study drug must not be administered via a feeding tube).
6. Is ≥18 years of age (≥20 years for patients in Japan).

7. Has an ECOG performance status of 0 or 1 (see Appendix A) at time of randomization.
8. Has adequate organ function as defined by the following criteria:
    a. Absolute neutrophil count (ANC) of ≥1,500/mm^3 (ie, ≥1.5 × 10^9/L by International Units [IU]).
    b. Platelet count ≥100,000/mm^3 (IU: ≥100 × 10^9/L).
    c. Hemoglobin value of ≥9.0 g/dL prior to randomization based on measurements obtained 2 weeks or more after last transfusion received.
    d. Aspartate aminotransferase (AST; SGOT) and alanine aminotransferase (ALT; SGPT) ≤3.0 × upper limit of normal (ULN); if liver function abnormalities are due to underlying liver metastasis, AST (SGOT) and ALT (SGPT) ≤5 × ULN.
    e. Total serum bilirubin of ≤1.5 × ULN (except for Grade 1 hyperbilirubinemia due solely to a medical diagnosis of Gilbert's syndrome).
    f. Serum creatinine ≤1.5 mg/dL.
9. Is willing and able to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures.
10. Women of childbearing potential 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 8.8.3 for definitions of contraceptive methods considered effective for this protocol.

8.3.2. Exclusion Criteria

Exclude a patient from this study if any of the following conditions are observed:

1. Has a serious illness or medical condition(s) including, but not limited to the following:
    a. Other concurrently active malignancies excluding malignancies that are disease free for more than 5 years or carcinoma-in-situ deemed cured by adequate treatment.
    b. Known brain metastasis or leptomeningeal metastasis.
    c. Active infection (ie, body temperature ≥38°C due to infection) including active or unresolved pneumonia/pneumonitis.
    d. Intestinal obstruction, pulmonary fibrosis, renal failure, liver failure, or cerebrovascular disorder.
    e. Uncontrolled diabetes.
    f. Myocardial infarction within 12 months prior to randomization, severe/unstable angina, symptomatic congestive heart failure New York Heart Association (NYHA) class III or IV (see Appendix B).
    g. Gastrointestinal hemorrhage (Grade ≥3) within 2 weeks prior to randomization.
    h. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or chronic or acute hepatitis B or hepatitis C.
    i. Patients with autoimmune disorders or history of organ transplantation who require immunosuppressive therapy.

j. Psychiatric disease that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results.

2. Has had treatment with any of the following within the specified time frame prior to randomization:
   a. Major surgery within prior 4 weeks (the surgical incision should be fully healed prior to study drug administration).
   b. Any anticancer therapy within prior 3 weeks.
   c. Extended field radiation within prior 4 weeks or limited field radiation within prior 2 weeks.
   d. Any investigational drug/device received within prior 4 weeks.
3. Has previously received TAS-102.
4. Has unresolved toxicity of greater than or equal to CTCAE Grade 2 attributed to any prior therapies (excluding anemia, alopecia, skin pigmentation, and platinum-induced neurotoxicity).
5. Is a pregnant or lactating female.
6. Is inappropriate for entry into this study in the judgment of the Investigator.
7. Known or assumed hypersensitivity to TAS-102 or any of its ingredients.

8.4. Treatment Assignment

8.4.1. Patient Numbering

Study sites will enter patient demographic and baseline data into the electronic Case Report Form (eCRF) in order to receive a patient number.

The eCRF will assign each patient a unique patient number. All patient numbers will be 6 digits; the first 3 digits will be the site number and the last 3 digits will be the patient's number. This patient number will be maintained throughout the study and will not be reassigned. Patients who withdraw consent or discontinue from the study after being assigned a patient number will retain their initial number.

8.4.2. Randomization

Once patient confirmation of eligibility and the criteria for randomization have been met, patients will be centrally randomized in a 2:1 ratio to TAS-102 plus BSC or placebo plus BSC via an IXRS based on a dynamic allocation method (biased coin).

The institutional designee will login to the IXRS and will enter the patient number, patient initials, stratification criteria, and other patient data as outlined in the IXRS manual.

Patients will be stratified by the following factors:

- Region (ROW vs. Japan)
- ECOG performance status (0 vs. 1)
- Prior treatment with ramucirumab (yes vs. no)

The IXRS will assign kit numbers for study medication (TAS-102 or placebo) corresponding to the patient's treatment assignment, inform the study site user of the kit number that has been assigned to the patient, and provide instructions for the dispensing of study drug. Please refer to the IXRS manual for detailed information.

If a patient is mistakenly given a study treatment that is not the treatment assigned by the IXRS, the IXRS help desk must be notified immediately. The reason for the misallocation of the study treatment must be documented by the study site.

If the misallocation of the study treatment results in the patient being initiated in the alternate arm from which they were assigned at randomization, the patient will continue to receive this treatment for the rest of the study.

Study medication administration should begin within 3 calendar days after randomization as described in Section 9.

For patients who sign an informed consent form (ICF) but are not randomized and patients who are randomized but never dosed, see the eCRF Completion Guidelines for instruction on which eCRF pages to complete.

After the final analysis is performed and the study has been unblinded, if the primary endpoint of the study is met and efficacy as well as safety support a favorable benefit/risk ratio for TAS-102, patients currently or previously treated with placebo who continue to meet study eligibility criteria will be offered the option to crossover to open-label TAS-102. Patients who are currently receiving TAS-102 will also be switched to open-label TAS-102 at that time. Patients who receive open-label TAS-102 will continue to have study medication kits (open-label) assigned through the IXRS system (see Section 9.3).

8.4.3. Blinding

This is a double-blind study. TAS-102 tablets of each strength, 15-mg or 20-mg, and the corresponding placebo tablets, 15-mg placebo and 20-mg placebo, respectively, will be identical in appearance and will be packaged in identical containers (see Section 9.1). During the conduct of the study, the treatment assignment will be unknown to all patients, investigators, and ancillary study personnel at each study site, and to employees of Taiho Oncology, Inc. and Taiho Pharmaceutical Co., Ltd.

See Section 12.1.8 for procedures related to breaking of the study blind.

8.4.4. Replacement of Patients

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

8.5. Discontinuation of Study Treatment

Patients will receive study medication until a discontinuation criterion (see Section 8.5.1) is met or until completion of the primary endpoint analysis, whichever is sooner.

A patient is considered discontinued from study treatment when the decision to permanently stop study medication is made, including those decisions made during study medication interruptions and recovery periods.

Study medication should be continued whenever possible. In case study medication is stopped, it should be determined if the stop can be made temporarily; permanent study medication discontinuation should be a last resort. Any study medication discontinuation should be fully documented.

8.5.1. Treatment Discontinuation Criteria

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

Patients can be withdrawn from treatment for the following reasons:

- Patient request at any time irrespective of the reason.
- RECIST-defined disease progression.
- Clinical progression.
- Patient experiences an irreversible, treatment-related, Grade 4, clinically relevant, non-hematologic event.
- Unacceptable AEs, or change in underlying condition such that the patient can no longer tolerate therapy, including:
  - A maximum dose delay >28 days from the scheduled start date of the next cycle of TAS-102.
  - Need for more than 3 dose reductions of TAS-102 (maximum of 3 dose reductions allowed as described in Section 9.2.4).
- Physician's decision including need for other anticancer therapy not specified in the protocol or surgery or radiotherapy to the only site(s) of disease being evaluated in this protocol.
- Pregnancy.

8.5.2. End of Treatment Procedures

Upon discontinuation of treatment the Investigator must:

- Notify the Clinical Research Associate (CRA) immediately;
- Register End of Treatment for the patient in the IXRS;
- Complete the Study Treatment Discontinuation Form in the eCRF, specifying the reason for the patient's withdrawal from treatment.
- If a patient is discontinued due to clinical progression, associated nonserious AEs should be reported on the treatment discontinuation page of the eCRF.

8.6. Discontinuation from Study Follow-up

As described in Section 10.1.13, patients who discontinue study treatment for reasons other than radiologic disease progression (eg, intolerable side effects) should continue to be followed for tumor response every 8 weeks until the patient develops radiologic disease progression (or death) or initiation of new anticancer therapy (whichever occurs first).

All treated patients will be followed for survival every 4 weeks until death, or until the target number of events is reached (whichever is sooner), unless the patient has withdrawn consent from the trial. Patients may request discontinuation of study treatment but agree to survival follow-up (this is not considered withdrawal of consent from the trial). 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.

A patient will be considered "Discontinued from Study Follow-up" when one of the following occurs:

- Patient dies
- Target number of events (384 events) is reached and final analysis performed
- Study is stopped based on Data Monitoring Committee (DMC) recommendation
- Study is terminated by the Sponsor or Regulatory Agencies

8.7. Patients Continuing Treatment after Completion of Final Analysis

Procedures to be followed if patients who are continuing to receive study medication at the conclusion of survival follow-up for the study (target number of events reached and final analysis performed) are described in Section 9.3.

The end of study is defined as completion of safety follow-up for the last patient who discontinues study treatment, including patients who are switched to open-label TAS-102 after completion of final analysis.

8.8. Other Medications and Therapies

8.8.1. Prohibited Medications and Therapies

Patients are not permitted to receive any other investigational or any other anticancer therapy, including chemotherapy, immunotherapy, biological response modifiers (BRMs), or endocrine therapy (except for megestrol acetate and steroids at doses less than or equal to 20 mg of prednisone equivalent per day for ≤2 weeks) during the study treatment period.

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

8.8.2. Concomitant Medications and Therapies

Caution is required when using drugs that are human thymidine kinase substrates, eg, zidovudine. Such drugs, if used concomitantly with TAS-102, may compete with the effector, trifluridine, for activation via thymidine kinases. Therefore, when using antiviral drugs that are human thymidine kinase substrates, monitor for possible decreased efficacy of the antiviral

agent, and consider switching to an alternative antiviral agent that is not a human thymidine kinase substrate, such as lamivudine, zalcitabine, didanosine and abacavir.

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

Hematologic Support

Administer hematologic support as medically indicated (eg, blood transfusions, G-CSF, erythropoietin, etc) according to the institutional site standards. If there are no standard procedures for the use of growth factors, follow American Society of Clinical Oncology (ASCO) 2006 Guidelines for Use of Hematopoietic Colony-Stimulating Factors, available at http://www.instituteforquality.org/practice-guidelines; or the European Organization for Research and Treatment of Cancer (EORTC) update to 2010 guidelines for the use of G-CSF,[9] available at http://www.eortc.org/investigators-area/eortc-guidelines.

Management of Diarrhea

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

Provide patients with loperamide or other standard antidiarrheal therapy and instruct the patient on how to use it at the first sign of diarrhea.

Monitor the patient's fluid and electrolyte balance, with appropriate intervention as clinically indicated with fluids and electrolyte replacement, antibiotics, and antiemetics.

Infection prophylaxis with oral antibiotics must be considered for patients with persistent diarrhea beyond 24 hours, or coincident with Grade ≥3 neutropenia.

Administer prophylactic treatment for diarrhea as clinically indicated.

If there are no institutional standards, refer to the guidelines published by Benson AB et al in Journal of Clinical Oncology.[10]

Management of Nausea/Vomiting

Administer antiemetics as clinically indicated. If there are no institutional standards refer to the ASCO Guidelines for Antiemetics in Oncology.[11]

8.8.3. Effective Contraception During Study

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

For women of childbearing potential, 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 (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomized partner with documentation of the success of the vasectomy
- complete abstinence from heterosexual intercourse (periodic abstinence is not a safe method)

Male patients with partners who are women of childbearing potential 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 medication.

8.9. Dietary Restrictions

TAS-102 should be taken with a glass of water within 1 hour after completion of the morning and evening meals.

9. STUDY TREATMENT

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 body surface area (BSA), and obtain the recommended study medication dosage.

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. No increase in dose due to increase in BSA is permitted.

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

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

Study sites are required to use the BSA calculation provided by the IXRS when determining patient doses unless their institutional policies do not permit it.

Please note the following:

- Dose escalations (on a mg/m^2 basis) of study medication are not permitted at any time.
- Only 3 dose reductions of study medication are permitted.
- Only a 28-day delay in the start of the next treatment cycle is permitted (see Section 9.2.4.4).

Study treatment should be started within 3 calendar days after randomization and should be administered as outlined in the following sections of the protocol. The Investigator always has the right to deviate from the established rules for dose modification at her/his discretion if he believes a more conservative approach is needed in the management of related or unrelated AEs. However, doses must be modified at least to the extent specified in Section 9.2.4. All deviations from protocol-specified dose modifications must be documented.

Patients will receive blinded study medication until one of the discontinuation criteria listed in Section 8.5.1 is met.

9.1. Description and Labeling

9.1.1. TAS-102

TAS-102 contains trifluridine (FTD) and tipiracil hydrochloride (TPI) as active ingredients with a molar ratio of 1:0.5.

TAS-102 is formulated as an immediate-release film-coated tablet, which is supplied in 2 strengths (expressed as FTD content):

- The 15 mg white, round tablet contains 15 mg FTD and 7.065 mg TPI as active ingredients.
- The 20 mg pale-red, round tablet contains 20 mg FTD and 9.42 mg TPI as active ingredients.

- Both tablet strengths contain the following inactive ingredients: lactose monohydrate, pregelatinized starch, stearic acid, hypromellose, titanium dioxide, polyethylene glycol, and magnesium stearate.
- The 20-mg tablet contains the following additional inactive ingredient: red ferric oxide.

9.1.2. TAS-102 Placebo

Placebo tablets identical in appearance to the TAS-102 15-mg (white, round) and 20-mg (pale-red, round) tablets will be used. The placebo tablets have a similar composition to the TAS-102 tablets, except for the active ingredients.

9.1.3. Packaging and Storage

TAS-102 and placebo tablets will be packaged in kits containing 20 tablets. Each kit will be enclosed in a foil pouch with desiccant.

Patients will be dispensed study medication 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 medication will be shipped from a regional Distribution Center directly to clinical sites.

All study medication must be stored at room temperature between 59°F and 86°F (15°C–30°C). All study medication must be kept in an area with restricted access.

Any country-specific requirements regarding packaging and storage of investigational drugs should be followed.

9.2. Study Medication Administration

9.2.1. Treatment Regimen

Each treatment cycle will be 28 days in duration. TAS-102 dosage is calculated according to body surface area.

One treatment cycle consists of the following:

Days 1-5:	TAS-102 (35 mg/m^2/dose) or placebo orally BID
Days 6-7:	Rest
Days 8-12:	TAS-102 (35 mg/m^2/dose) or placebo orally BID
Days 13-28:	Rest

Study medication should be taken only on Days 1-5 and 8-12 of each cycle. If doses are missed or held on those days, the patient should not make up for missed doses.

TAS-102 should be taken with a glass of water within 1 hour after completion of morning and evening meals.

9.2.2. Number of Tablets per Dose

The study drug tablet calculation is presented in Table 2, which shows the number of tablets that are needed per calculated BSA.

- Study medication should only be given on Days 1 through 5 and Days 8 through 12 of each cycle even if doses are missed or held for any reason during Days 1 through 12.
- Extension of study treatment into Days 6 and 7 or into the rest period (Days 13 through 28) is not permitted.

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

Table 2: Number of Tablets per Dose

TAS-102 Dose (2x daily)	BSA (m^2)	Dosage in mg (2x daily)	Total daily dose (mg)	Tablets per dose	
				15 mg	20 mg
35 mg/m^2	< 1.07	35	70	1	1
	1.07 - 1.22	40	80	0	2
	1.23 - 1.37	45	90	3	0
	1.38 - 1.52	50	100	2	1
	1.53 - 1.68	55	110	1	2
	1.69 - 1.83	60	120	0	3
	1.84 - 1.98	65	130	3	1
	1.99 - 2.14	70	140	2	2
	2.15 - 2.29	75	150	1	3
	≥2.30	80	160	0	4

BSA=body surface area (calculate to 2 decimal places)

9.2.3. Instruction to Patients for Handling Study Medication

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

- To store the study medication at room temperature
- To only remove from the study medication kit the amount of tablets needed at the time of dosing
- To wash their hands after handling study medication
- Not to remove doses in advance of the next scheduled dosing
- To make every effort to take doses on schedule
- To report any missed doses

- To take study medication within 1 hour after completing a meal (morning and evening meal) with a glass of water
- If the patient vomits after taking study medication, the patient should not take another dose
- To keep study medication in a safe place and out of reach of children
- To bring all used and unused study medication kits to the site at each visit

9.2.4. Dose Modifications

9.2.4.1. Dose Reduction Levels

Study medication dose reductions to be applied in case of toxicity and the number of tablets for each calculated BSA are described in Table 3. Patients are permitted dose reduction(s) to a minimum dose of 20 mg/m^2 (40 mg/m^2/day) in 5 mg/m^2 steps.

Table 3: TAS-102 Dose Reduction Levels and Number of Tables per Dose

TAS-102 Dose (2x daily)	BSA (m^2)	Dosage in mg (2x daily)	Total daily dose (mg)	Tablets per dose	
				15 mg	20 mg
Level 1 Dose Reduction: From 35 mg/m^2 to 30 mg/m^2					
30 mg/m^2	< 1.09	30	60	2	0
	1.09 - 1.24	35	70	1	1
	1.25 - 1.39	40	80	0	2
	1.40 - 1.54	45	90	3	0
	1.55 - 1.69	50	100	2	1
	1.70 - 1.94	55	110	1	2
	1.95 - 2.09	60	120	0	3
	2.10 - 2.28	65	130	3	1
	≥ 2.29	70	140	2	2
Level 2 Dose Reduction: From 30 mg/m^2 to 25 mg/m^2					
25 mg/m^2	< 1.10	25[a]	50[a]	2 (PM)[a]	1 (AM)[a]
	1.10 - 1.29	30	60	2	0
	1.30 - 1.49	35	70	1	1
	1.50 - 1.69	40	80	0	2
	1.70 - 1.89	45	90	3	0
	1.90 - 2.09	50	100	2	1
	2.10 - 2.29	55	110	1	2
	≥ 2.30	60	120	0	3
Level 3 Dose Reduction: From 25 mg/m^2 to 20 mg/m^2					
20 mg/m^2	< 1.14	20	40	0	1
	1.14 – 1.34	25[a]	50[a]	2 (PM)[a]	1 (AM)[a]
	1.35 – 1.59	30	60	2	0
	1.60 – 1.94	35	70	1	1
	1.95 – 2.09	40	80	0	2
	2.10 – 2.34	45	90	3	0
	≥ 2.35	50	100	2	1

[a] At a total daily dose of 50 mg, patients should take 1 x 20-mg tablet in the morning and 2 x 15-mg tablets in the evening.

BSA=body surface area (calculate to 2 decimal places)

If dose modification fails to result in achieving minimal criteria to resume treatment, the Investigator should discontinue study medication.

Should the toxicities that require dose reduction recur after dose reduction to 20 mg/m^2, study medication should be discontinued.

9.2.4.2. Dose Modification in Response to Non-hematologic Toxicities

Rules for study medication dosing modifications for treatment-related non-hematologic AEs are provided in Table 4. At the discretion of the Investigator, patients may continue on study medication at the same dose without reduction or interruption for drug-related AEs (irrespective of grade) considered unlikely to become serious or life-threatening (including, but not limited to, fatigue, alopecia, changes in libido, and dry skin).

Table 4: TAS-102 Dose Modification Criteria for Non-hematologic Toxicities

Grade[a]	Dose Hold/Resumption within a 28-day Treatment Cycle	Dose Adjustment for Next Cycle
Grade 1 or 2		
Any occurrence	Maintain treatment at the same dose level	None
Grade 3[a] or Higher		
1st, 2nd, or 3rd occurrence	Suspend treatment until Grade 0 or 1	Reduce by 1 dose level from the previous level
4th occurrence	Discontinue treatment	Discontinue treatment

[a] Except for Grade 3 nausea and/or vomiting controlled by aggressive antiemetic therapy or diarrhea responsive to antidiarrheal medication.

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

9.2.4.3. Dose Modification in Response to Hematologic Toxicities

Criteria for dose hold and resumption in response to hematologic toxicities related to myelosuppression are described in Table 5 and Table 6, respectively.

NOTE: 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 6 are met; these resumption criteria apply to the start of the next cycle for all patients regardless of whether or not the hold criteria were met.

Table 5: TAS-102 Dose Hold Criteria for Hematologic Toxicities Related to Myelosuppression

Parameter	Hold Criteria	
	Conventional Units	SI Units
Neutrophils	$<500/mm^3$	$<0.5 \times 10^9/L$
Platelets	$<50,000/mm^3$	$<50 \times 10^9/L$

SI=International System

Table 6: TAS-102 Resumption Criteria for Hematologic Toxicities Related to Myelosuppression

Parameter	Resumption Criteria[a]	
	Conventional Units	SI Units
Neutrophils	≥1500/mm^3	≥1.5 × 10^9/L
Platelets	≥75,000/mm^3	≥75 × 10^9/L

[a] These resumption criteria apply to the start of the next cycle for all patients regardless of whether or not the hold criteria were met.
SI=International System

Criteria for dose reduction in response to hematologic toxicities are as follows:

- Uncomplicated neutropenia or thrombocytopenia ≤Grade 3 do not require a reduction in dose of study medication.
- Patients who experience uncomplicated Grade 4 neutropenia or thrombocytopenia that results in a ≤1 week delay of the start of the next cycle should start the next cycle at the same dose level.
- Patients who experience uncomplicated Grade 4 neutropenia or thrombocytopenia that results in a >1 week delay of the start of the next cycle should start the next cycle at one reduced dose level as described in Table 3.

Patients who experience complicated ≥Grade 3 neutropenia or thrombocytopenia should be considered for administration of hematopoietic growth factors, or for a dose reduction in the next cycle or both, dependent on the severity of the complication.

In the event of febrile neutropenia:

- Interrupt dosing until toxicity resolves to Grade 1 or baseline
- When resuming dosing, decrease the dose level by 5 mg/m^2/dose from the previous dose level (as per Table 3).

9.2.4.4. Dose Resumption

If the patient recovers from toxicities requiring dose delay during the 2-week treatment period of a cycle (treatment Days 1 through 5, 8 through 12), and no dose reduction is required, study medication may be resumed during that cycle. If a dose reduction is required, study medication should be resumed at the start of the next cycle at the appropriate dose level as shown in Table 3. Do not increase study medication dose after it has been reduced.

If the patient recovers from toxicities requiring dose delay during the recovery period (Days 13 through 28), start the next cycle on schedule at the appropriate dose level based on Section 9.2.4.2 and Section 9.2.4.3 above. 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 28 days from the scheduled start date of the next cycle. If resumption criteria are met by this maximum 28-day delay, start the next cycle at the appropriate dose level.

Patients who require more than a 28-day delay in the scheduled start date of the next cycle will have study medication discontinued.

9.3. Open-label TAS-102

After completion of the primary analysis, if the primary endpoint of the study was met and efficacy, as well as safety, support a favorable benefit/risk ratio for TAS-102, and after site notification and unblinding, patients currently being treated with placebo and those previously treated with placebo who continue to meet study eligibility criteria will be offered the option to receive open-label TAS-102. The decision to crossover to open-label TAS-102 should be made within 3 months of notification that the patient was receiving placebo. Patients who are currently receiving double-blind TAS-102 will also be switched to open-label TAS-102 at that time.

For patients who receive open-label TAS-102, open-label study medication kits will be assigned by IXRS based on the patient's BSA at the time of initiation of open-label TAS-102.

Patients who receive open-label TAS-102 treatment after conclusion of survival follow-up should be followed for safety and tumor response according to the site standard of care. Study medication and dose modification procedures described in Section 9.2 should continue to be followed.

Adverse events leading to treatment discontinuation, serious AEs (SAEs) and deaths should continue to be documented in the eCRF and reported to the Sponsor as described in Section 12.1. Date and reason for treatment discontinuation should also be recorded in the eCRF.

The end of study is defined as completion of safety follow-up (for any AEs leading to treatment discontinuation, SAEs or deaths) for the last patient who discontinues study treatment.

9.4. Treatment Compliance

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

9.5. Study Drug Accountability

In accordance with International Council for Harmonisation (ICH) and local regulatory requirements, the Investigator and/or the person responsible for dispensing investigational drug must be able at all times to account for all investigational product provided to the site. Prior to drug dispensation, the person responsible for dispensing the drug must call/login to the IXRS, complete the information required on the labels of study medication, and update study logs with the required information (eg, kit number and expiration date).

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

All used and unused study medication shipped to the Investigator must be destroyed by the site or returned to the Sponsor or its representative. Destruction by the site is the preferred method for disposing study medication. Sites must provide the institution's Standard Operating Procedure (SOP) to the Sponsor or its representative for review. If on-site destruction is not allowed, the return of study medication will be arranged regionally. No study medication is to be used outside of this study.

10. STUDY ASSESSMENTS

The study assessments are described by procedure in Section 10.1 and by visit in Section 10.2. 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 is maintained, and a window of ±7 days is allowable for CT scans, and follow-up visits. During the Baseline period (up to 28 days prior to randomization), these windows are not applicable.

10.1. All Study Procedures

10.1.1. Informed Consent

Obtain signed and dated ICF from the patient prior to the implementation of study procedures required by the protocol. A copy of the signed and dated ICF should be given to the patient.

10.1.2. Randomization/Start of Treatment

Following confirmation of eligibility, patients will be randomized via IXRS and should receive the first dose of study treatment (Day 1 of Cycle 1) within 3 calendar days after randomization. The maximum screening period is 28 days; eligible patients must be randomized by Day 29 of screening.

10.1.3. Medical History

Obtain a complete medical history within 28 days prior to study medication administration. Record the patient's medical history on the Medical History section of the eCRF.

Any AEs/SAEs reported from the time of signed ICF until the first dose of study medication should be recorded on the Medical History section of the eCRF.

10.1.4. Histologic Confirmation

Obtain confirmation of gastric adenocarcinoma via pathology report at Baseline (pathology may be from primary tumor or metastasis). The pathology report should be available in the patient's source documents.

10.1.5. Human Epidermal Growth Factor Receptor 2 (HER2) Status

Record the patient's HER2 status at Baseline, if available.

10.1.6. Physical Examination

Perform a complete physical examination at the time points listed below:

- Within 7 days prior to Day 1 of Cycle 1
- Beginning with Cycle 2, obtain within 24 hours prior to start of study treatment in every cycle

- End of Treatment Visit (if applicable)
- 30-day Safety Follow-up Visit

10.1.7. Baseline Signs and Symptoms

Signs and symptoms present following signature of ICF and within 7 days prior to study treatment on Day 1 of Cycle 1 should be recorded in the patient's source documents.

10.1.8. Height, Vital Signs, Weight

Obtain the patient's height within 7 days prior to Day 1 of Cycle 1.

Collect the patient's vital signs (blood pressure, heart rate, body temperature, and respiration rate) and body weight at the time points listed below. Obtain all the vital signs in a position that is consistent for all time points for each patient.

- Within 7 days prior to Day 1 of Cycle 1
- Beginning with Cycle 2, obtain within 24 hours prior to start of study treatment in every cycle
- End of Treatment Visit (if applicable)
- 30-day Safety Follow-up Visit

10.1.9. Performance Status (ECOG)

Obtain an ECOG performance status score at the following time points:

- Within 28 days prior to Day 1 of Cycle 1
- At time of randomization (within 3 calendar days prior to start of study treatment on Day 1 of Cycle 1)
- Beginning with Cycle 2, obtain within 24 hours prior to start of study treatment in every cycle
- End of Treatment Visit (if applicable)
- 30-day Safety Follow-up Visit

10.1.10. Clinical Laboratory Evaluations

10.1.10.1. Hematology

Collect blood for hematological assessments at the following time points and when clinically indicated:

- Within 7 days prior to Day 1 of Cycle 1 (Laboratory results obtained prior to signing ICF may be used if the results were obtained within 7 days prior to Day 1 of Cycle 1.)
- Day 15 of Cycle 1
- Beginning with Cycle 2, obtain within 24 hours prior to start of study treatment in every cycle

- End of Treatment Visit (if applicable)
- 30-day Safety Follow-up Visit

In addition, follow the criteria for repeat testing listed in Section 12.2.2 as needed.

Measure the following hematology parameters:

Red blood cell (RBC) count	White blood cell (WBC) count with differential (automated):
Hemoglobin	Neutrophils
Hematocrit	Lymphocytes
Platelets	Monocytes
	Eosinophils
	Basophils

10.1.10.2. Serum Chemistry

Collect blood at the following time points for serum chemistry assessments:

- Within 7 days prior to Day 1 of Cycle 1 (Laboratory results obtained prior to signing ICF may be used if the results were obtained within 7 days prior to Day 1 of Cycle 1.)
- Day 15 of Cycle 1
- For all subsequent cycles, obtain within 24 hours prior to start of study treatment in every cycle
- End of Treatment Visit (if applicable)
- 30-day Safety Follow-up Visit.

In addition, follow the criteria for repeat testing listed in Section 12.2.2 as needed.

Measure the following serum chemistry parameters:

ALT (SGPT)	Creatinine	Chloride
AST (SGOT)	Blood urea nitrogen (BUN)	Calcium
Alkaline phosphatase	Sodium	Albumin
Bilirubin[a]	Potassium	Glucose

[a] In case of elevation in total bilirubin, fractionation (direct/indirect) should be performed.

10.1.10.3. Urinalysis

Collect urine samples for qualitative (dipstick) analysis, to include tests for protein, glucose, urobilinogen, RBC, and WBC, at the time points listed below:

- Within 7 days prior to Day 1 of Cycle 1 (Laboratory results obtained prior to signing ICF may be used if the results were obtained within 7 days prior to Day 1 of Cycle 1.)
- As clinically indicated thereafter

If a new abnormality is identified, quantitative urinalysis should be performed.

In addition, follow the criteria for repeat testing listed in Section 12.2.2 as needed.

10.1.11. Pregnancy Testing

For patients who are female and of childbearing potential, perform pregnancy testing with serum or urine beta-human chorionic gonadotrophin (β-HCG) at the following time points and record the date, time, and test results in the patient's source documents (Note: More frequent pregnancy assessments should be performed if required by local law):

- Within 7 days prior to Day 1 of Cycle 1
- End of Treatment and 30-day Safety Follow-up Visit

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

10.1.12. Quality of Life

Patients should complete the EORTC Quality of Life Questionnaire - Core Questionnaire (EORTC QLQ-C30) and Gastric-specific module (QLQ-STO22)[8] (see Appendix D) at the following time points:

- Within 7 days prior to randomization
- Prior to dose administration on Day 1 of Cycles ≥2
- At the 30-day Safety Follow-up Visit if not performed within the previous 4 weeks

10.1.13. Tumor Measurements

Computed tomography tumor assessments/imaging studies of the chest and abdomen (and pelvis if clinically indicated) must be obtained at each time point listed below for all patients:

- Within 28 days prior to Day 1 of Cycle 1. Scans obtained prior to patient ICF may be used if the date of the scan is within 28 days of randomization.
- Every 8 weeks during study treatment
- For patients who discontinue treatment for reasons other than radiologic disease progression, every effort should be made to perform a tumor assessment prior to the start of new anticancer therapy.
- For patients who discontinued treatment for reasons other than radiologic disease progression, every 8 weeks until the patient develops radiologic progression or the start of new anticancer treatment (whichever occurs first)

On-site tumor assessments will be performed by the Investigator/local radiologist according to RECIST criteria (version 1.1, 2009). Results of these assessments including response for target and non-target lesions and appearance of new lesions will be the basis for the continuation or discontinuation of study medication. Response definitions are provided in Section 11.

If the Investigator determines that a patient develops 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. Every effort should be made to document objective progression even after discontinuation of treatment.

If a patient is withdrawn due to radiologic disease progression, additional CT scans are not required at the end of treatment.

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

All patients' files and radiological assessments must be available for source verification. Results of any unscheduled evaluations should be recorded in the patient's source documents.

10.1.14. Concomitant Medications and Therapies

Collect all therapies and medications, prescription and over-the-counter, from the time of signed ICF through the 30-day Safety Follow-Up Visit, including any medication used to treat AEs or SAEs during the safety follow-up period. Use of concomitant medication should be documented in the patient's source documents.

At the 30-day Safety Follow-Up Visit, collect any new anticancer therapy and the date of initiation.

During the survival follow-up period, collect only anticancer therapies.

10.1.15. Adverse Event Assessment

Any untoward medical events (AEs or SAEs) that occur from the first dose of study medication (Day 1, Cycle 1) through 30 days after last dose of study medication should be recorded in the AE section of the eCRF. Any AEs/SAEs that occur from the time of signed informed consent until the first dose of study drug should be reported on the Medical History section of the eCRF.

SAEs should be reported to Taiho Pharmacovigilance or designee. If any medical occurrences **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 medication, it is the Investigator's responsibility to record those events on the eCRF and, if any of those events are serious, then the Investigator has to report this occurrence to Taiho Pharmacovigilance or designee.
See Section 12.1.1 and Section 12.1.2, respectively, for definitions and detailed reporting of AEs and SAEs.

10.2. Assessments by Visit

See Section 10.1 for details about specific assessments.

10.2.1. Baseline Procedures Prior to Randomization

10.2.1.1. Day -28 through Day -1

- Signature of Informed Consent Form
- Medical history

- Histological confirmation of gastric adenocarcinoma from either the primary or metastatic site of disease
- HER2 status (if available)
- ECOG performance status
- Tumor measurement (by CT scan)
- Concomitant medication

10.2.1.2. Day -7 through Day -1

- Physical examination
- Baseline signs and symptoms
- Height
- Vital signs (blood pressure, heart rate, body temperature, respiration rate) and body weight
- Blood samples for hematology and serum chemistry
- Urine sample for urinalysis
- Quality of life assessment (EORTC QLQ-C30, QLQ-STO22)
- Pregnancy test

10.2.2. Cycle 1 Day 1

Contact the IXRS when the patient meets the minimum criteria for initiation of study treatment to randomize the patient. Instructions for randomization are described in detail in the IXRS Instructions Manual. Study treatment should be started within 3 calendar days after randomization.

- ECOG performance status (confirmation of eligibility)
- Dispense study medication
- Concomitant medication
- AE/SAE assessment

10.2.3. Cycle 1 Day 15

- Blood samples for hematology and serum chemistry
- Concomitant medication
- AE/SAE assessment

10.2.4. Subsequent Cycles - Cycle X Day 1

Obtain within 24 hours prior to Day 1 study drug administration. Prior to starting subsequent cycles, verify that patients with toxicities have met resumption criteria prior to administering study drug.

- Physical examination
- Vital signs (blood pressure, heart rate, body temperature, respiration rate) and body weight
- ECOG performance status
- Blood samples for hematology and serum chemistry
- Dispense study medication
- Concomitant medication
- AE/SAE assessment
- Quality of life assessment (EORTC QLQ-C30, QLQ-STO22) prior to administration of study medication

10.2.5. Every 8 Weeks from Start of Treatment

- Tumor measurement/assessment (CT scan)

10.2.6. End of Treatment Visit

If the decision to discontinue blinded study medication 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 study medication (due to proven radiologic disease progression or other reasons) is made more than 2 weeks after the last treatment visit, an End of Treatment Visit is required. If this visit occurs within 2 weeks of the 30-day Safety Follow-up Visit, the 2 visits can be combined.

Perform the following assessments:

- Physical examination
- Vital signs (blood pressure, heart rate, body temperature, respiration rate) and body weight
- ECOG performance status
- Blood samples for chemistry and hematology
- Pregnancy test
- For patients who discontinue treatment for reasons other than radiologic disease progression, every effort should be made to perform an end of treatment tumor assessment prior to the start of new anticancer therapy.

- Concomitant medication, including any new anticancer therapy and time of initiation
- AE/SAE assessment

10.2.7. 30-Day Safety Follow-up Visit

A Safety Follow-up visit will be conducted 30 days after the patient's last dose of study medication. If the patient will be starting new anticancer therapy within the 30-day window after the last dose of study medication, the 30-day Safety Follow-up Visit should be performed prior to the start of new anticancer therapy. If the patient is unable to return to the site prior to the initiation of new treatment, a follow-up phone call can be conducted by the site to collect any new safety information that occurred between the end of study treatment and the initiation of the new treatment.

Perform the following assessments:

- Physical examination
- Vital signs (blood pressure, heart rate, body temperature, respiration rate) and body weight
- ECOG performance status
- Blood samples for chemistry and hematology
- Pregnancy test
- Quality of life assessment (EORTC QLQ-C30, QLQ-STO22) if not performed within the previous 4 weeks
- Concomitant medication, including any new anticancer therapy and time of initiation
- AE/SAE assessment

10.2.8. Survival Follow-up after 30-Day Safety Visit

The following assessments should be obtained at scheduled 4-week (±7 days) time intervals during the survival follow-up period:

- Tumor measurement (by CT scan, see Section 11) every 8 weeks until radiologic disease progression (for patients who discontinued treatment for reasons other than disease progression) or initiation of new anticancer therapy (whichever occurs first)
- Concomitant medications – collect antitumor therapies only
- Contact patient/caregiver to determine survival status (alive/dead)
- SAE collection only if the SAE is related to study medication

Patients will be followed for survival until the target number of events is reached. The Investigators will be informed when this target is reached.

11. EFFICACY ASSESSMENT CRITERIA

The determination of antitumor efficacy will be based on objective tumor assessments made by the Investigator/local radiologist according to the revised RECIST criteria (version 1.1, 2009) of unidimensional evaluation.[12] Treatment decisions by the Investigator will also be based on these criteria.

11.1. Method of Imaging

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 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). 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 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.

An additional fluorodeoxyglucose positron emission tomography (FDG-PET) scan may help confirm the diagnosis of suspicious lymph nodes as needed. A "positive" FDG-PET scan lesion is one that is FDG avid "with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image." However, this scan is not mandatory. FDG-PET scan alone cannot replace a MRI or contrast-enhanced CT.

For additional guidance refer to revised RECIST criteria (version 1.1, 2009), specifications for standard anatomical radiological imaging.

11.2. 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: Non-measurable lesions include:

1. 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.
2. Abnormal and suspected metastatic lymph nodes that are ≥10 mm to <15 mm in the short axis.
3. 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 per 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 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
- 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).

11.3. Response Criteria

On-site assessments will include the assessment of:

1. Target and non-target tumor responses.
2. Overall response.

The above assessments will be made as per the time points identified in Section 10.1.13.

11.3.1. Target and Non-target Response Assessments

11.3.1.1. Criteria for Assessment of Tumor Response

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)	The disappearance of all non-target lesions. All lymph nodes must be non-pathological morphologically (ie, <10 mm in short axis in size).
Non-CR/Non-PD	A persistence of ≥1 non-target lesion(s)/ not reaching the extent of 'unequivocal progression.'
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions (see definition below).

Progression in Non-target Disease:

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

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

11.3.1.2. Additional Criteria to Consider When Assessing Tumor Response

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.

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.

11.3.2. Overall Response Assessment

Assessments will be based on the definitions provided in Table 7 and Table 8 below.

Table 7: 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

Table 8: 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	Non-CR/Non-PD
Not all evaluated	No	Not evaluable
Unequivocal PD	Yes or No	PD
Any	Yes	PD

11.4. Best Overall Response Assessment

The best overall response as per RECIST criteria (version 1.1, 2009) is the best response recorded from the start of the study treatment until the end of treatment.

12. REPORTING SAFETY INFORMATION

12.1. Adverse Events/Serious Adverse Events

12.1.1. Adverse Events

An **adverse event** (AE) is any untoward medical condition that occurs in a patient while participating in a clinical study and does not necessarily have a causal relationship with the use of the study medication.

Treatment emergent AEs are AEs that occur from the initiation of any study treatment administration, and do not necessarily have a causal relationship to the use of the study treatment.

Provide a complete and specific clinical diagnosis as an AE verbatim term. If a diagnosis is not available, then report signs and symptoms. The Common Terminology Criteria for Adverse Events (CTCAE Version 4.03) terms are to be used to assess severity/provide the grade for each AE that is reported.

Refer to Section 12.1.5, Section 12.1.6, and Section 12.1.7 for definitions and reporting of pregnancy, medication errors, and overdose, respectively.

Any untoward medical event that occurs outside the period of patient follow-up (30 days after the last dose of study treatment or until the start of new antitumor therapy, whichever is earlier) is not considered an AE unless determined by the Investigator to have a causal relationship with the study treatment.

If any SAEs are observed after the patient follow-up period has ended, only those SAEs determined to have a causal relationship with the study medication will be recorded in the case report form.

Symptoms or laboratory or instrumental (eg, electrocardiographic) abnormalities of a pre-existing disease, such as cancer or other disease, 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 medication dose reduction, treatment delay, treatment discontinuation, requires treatment due to abnormal values, or is considered medically important by the Investigator) is considered an AE, unless it is considered part of clinical manifestations to a clinical diagnosis that is already reported as an AE.

AEs will be reported from the first dose of study medication through the period of patient follow-up (30 days after the last dose of study medication or until the start of new antitumor therapy, whichever is earlier). Document all AEs in the source documents. Documentation should include onset and resolution/stabilization dates, severity/grade, relationship to study medication, and outcome of the event.

Causal relationship:

1. Reasonably Possible: The AE is related if it follows a reasonable temporal sequence from administration of study medication and, one of the following conditions is true:
   - A positive de-challenge. This means that the event resolves when the drug is stopped.
   - A positive re-challenge. This means that the event reappears when the drug is restarted.
   - Or, the event cannot be reasonably explained by the patient's clinical state and/or other administered therapies.
2. Not Reasonably Possible: The AE is not related when there is no reasonable possibility that the study medication caused the event. 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.

   Reasonable possibility is provided by the following examples of types of evidence that would suggest a causal relationship between drug and AE:
   - A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (eg, angioedema, hepatic injury, Stevens-Johnson syndrome)
   - One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to drug (eg, tendon rupture)

Outcome:

- Resolved without sequelae
- Resolved with sequelae
- Resolving (can only be used for SAEs and cannot be a final outcome)
- Unresolved
- Death

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

- AE has resolved.
- AE has stabilized. An AE cannot be considered stabilized while the patient is on study medication. Ongoing AEs must be assessed for stabilization 30 days post study medication discontinuation.
- The start of new antitumor therapy.

12.1.2. Serious Adverse Events (SAE)

A **Serious Adverse Event** (experience) or reaction is any untoward medical occurrence that at any time:

a. Results in death (see Section 12.1.3).
b. Is life-threatening.

   NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization. The following are not considered hospitalizations for the purposes of assessing seriousness:

   – Emergency room visits less than 24 hours.

   – Hospitalizations for preplanned procedures.

   – Hospitalization for study-related treatment and procedures.

d. Results in persistent or significant incapacity or disability, 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 are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Serious adverse events 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/SAE 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 medication 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 investigational product, it is the Investigator's responsibility to report this occurrence to Taiho Pharmacovigilance or designee.

A **serious adverse reaction** (SAR) is any event that meets the definition of an SAE and is considered related to the administration of study medication. An unexpected SAR is defined as any SAR, the nature or severity of which is not consistent with the applicable product information (eg, Investigator's Brochure for an unauthorized investigational product or summary of product characteristics for an authorized product).

All SAEs, SARs and **suspected unexpected serious adverse reactions** (SUSARs) will be reported as per European Union (EU) reporting requirements and local laws and regulations.

12.1.3. Reporting of Deaths

All deaths occurring through the 30-day follow-up period must be reported in the eCRF within 24 hours.

1. Death due to disease progression:

   Disease progression (radiologic or clinical) with the outcome of death will not be reported as an SAE. However, relevant signs, symptoms and complications of disease progression (radiologic or clinical) must be reported as an AE or SAE if it meets the serious criteria. It should be indicated that the signs, symptoms and complications are related to disease progression.

2. Death due to other causes:

   Deaths due to reasons other than disease progression must be reported as an SAE.

   Death is not an acceptable AE/SAE term. Death is an outcome of an SAE.

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

- Toxicity for study drug
- Radiologic disease progression
- Clinical disease progression
- Other causes

12.1.4. Disease Progression

1. How to report events related to non-fatal disease progression:
   a. Disease progression is not an acceptable AE term. In cases of non-fatal disease progression, the relevant signs, symptoms and complications should be reported as an AE unless they meet the serious criteria. If any of the signs, symptoms and complications meets any of the serious criteria, they should be reported as an SAE. In both cases it should be indicated whether the signs, symptoms and complications are related to disease progression.
   b. Radiologic disease progression without relevant signs, symptoms and complications will not be reported as an AE or SAE.

2. How to report events related to fatal disease progression:
    a. See Section 12.1.3, Reporting of Deaths.

12.1.5. Pregnancy

If a patient becomes pregnant while in the study, the study treatment must be immediately discontinued. Pregnancy information for 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 initial Pregnancy Form must be submitted by faxing an updated Pregnancy Form to Taiho Pharmacovigilance or designee.

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

12.1.6. Medication Errors

A **medication error** is defined as any 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 as specified in this protocol (including omission of one or more administrations).

- Medication errors with study medication and concomitant medication treatment will not be recorded in the eCRF unless they result in an AE.
- Medication errors with study medication that result in an overdose will be captured as an AE in the eCRF.
- Medication errors with study medication that do not result in an AE should be handled as follows:
    - If it results in the omission of an administration, an incorrect dose (relative to that specified in this protocol), or the administration of more than the prescribed dose (but does not meet the overdose criteria), it will be identified through the recording of study drug accountability data in the eCRF and does not need to be reported as an AE.
    - If it results in an overdose, incorrect route of administration, or administration of an incorrect study drug, it will be reported as an AE.

Based on the above criteria, medication errors that are captured as an AE on the eCRF should be reported to Taiho Pharmacovigilance or designee **within 24 hours** from the time the Investigator first becomes aware of its occurrence following the same process as described for the SAEs even if it does not meet any of the criteria of an SAE.

12.1.7. Overdose

An overdose with TAS-102 for this clinical trial is defined as:

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

An accidental or intentional overdose with TAS-102 regardless of whether it is associated with an AE (even if not fulfilling a seriousness criterion) is to be captured as an AE on the eCRF and reported to Taiho Pharmacovigilance or designee **within 24 hours** from the time the Investigator first becomes aware of its occurrence following the same process as described for the SAEs.

There is no known antidote available in case of TAS-102 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 medication should only be reported if it is associated with an AE.

12.1.8. Breaking the Study Blind

Prior to completion of the final analysis, unblinding of the study treatment will not occur unless it is needed to manage a patient's medical condition.

- In an emergency, when specific knowledge of the patient's treatment assignment is needed to manage a patient's medical condition, the Investigator can unblind the patient by calling the IXRS to obtain the patient's treatment assignment. It is recommended that the Investigator then informs the Sponsor's Medical Monitor of the case.
- In a non-emergent situation, the Investigator should attempt to contact the Sponsor's Medical Monitor to discuss the case prior to unblinding.

Irrespective of emergent or non-emergent situations, if unblinding occurs, the Investigator must record the date and the reason for unblinding. The Investigator must not disclose the unblinding information.

When a patient has a SUSAR event (see Section 12.1.2), the blind will be broken for that patient by specific Taiho Pharmacovigilance personnel via the IXRS. If the patient is found to be on TAS-102, the SUSAR will be submitted to Regulatory Authorities; if the patient is found to be on placebo, the SUSAR will not be submitted to Regulatory Authorities, unless requested. To maintain the blind, all SUSARs are distributed to site Investigators via a blinded Council for International Organizations of Medical Sciences (CIOMS) report.

12.2. Laboratory Evaluations

12.2.1. Reporting and Evaluation of Laboratory Test Results

Laboratory tests are to be performed as required per 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 study medication.

The laboratory must provide normal reference ranges.

Any laboratory abnormality that has a clinical impact on the patient, eg, results in delay of study medication dosing, study discontinuation, requires treatment due to abnormal values, or is considered by the Investigator to be medically important, must be reported as an AE, unless it is considered a supporting lab to a clinical diagnosis that is already reported as an AE. If there is a question or concern, please call the Sponsor's Medical Monitor. All laboratory data will be analyzed using NCI CTCAE grade criteria (Version 4.03).

12.2.2. Repeat Testing

Repeat the evaluation of any clinically significant laboratory test, as clinically indicated, until the value returns to the baseline level or clinically stabilizes, or until another treatment is given.

12.3. Physical Examination and Performance Status

Perform physical examinations and performance status evaluations as described in the Study Procedures section of the protocol. If changes are observed, determine whether they meet the definition of an AE. Document all observations and evaluations.

12.4. Vital Signs and Body Weight

Verify and document vital signs and body weight. If a clinically significant change is observed, repeat the measurement as clinically indicated and evaluate for its clinical relevance and whether it meets the definition of an AE.

13. STATISTICS

A Statistical Analysis Plan (SAP) that includes a more technical and detailed description (including templates for Tables, Listings, and Figures) of the planned statistical summaries analyses will be prepared.

13.1. Study Populations

The safety and efficacy study populations will be defined as follows:

- Intent-to-Treat (ITT) population: This population includes all randomized patients and is the primary population for all efficacy parameters. All analyses using this population will be based on the treatment assigned by IXRS.
- As-Treated (AT) population: This population includes all patients who took part of any dose of the study treatment. This population will be used for safety analyses. All analyses using this population will be based on the treatment actually received.
- Tumor Response (TR) evaluable population: This population includes all patients in the ITT population with measurable disease (at least one target lesion) at baseline and with at least one tumor evaluation while on treatment (except for early disease progression/cancer-related death). All analyses using this population will be based on the treatment assigned by IXRS.

13.2. Study Endpoints

13.2.1. Primary Efficacy Endpoint – Overall Survival

Survival is the primary endpoint of this study and is defined as the time from the date of randomization to the death date. In the absence of death confirmation or for patients alive as of the OS cut-off date, survival time will be censored at the date of last study follow-up, or the cut-off date, whichever is earlier.

The OS cut-off date used for the primary analysis will be based on the date of the 384th death in the study. With the OS cut-off date being event driven, for operational efficiency, the cut-off date for all other study endpoints will be fixed at close proximity of the OS cut-off date, when the milestone is nearing completion.

13.2.2. Key Secondary Efficacy Endpoint - PFS

Progression free survival is defined as the time from the date of randomization until the date of the investigator-assessed radiological disease progression or death due to any cause. Patients who are alive with no disease progression as of the analysis cut-off date will be censored at the date of the last tumor assessment. Patients who receive non-study cancer treatment before disease progression, or patients with clinical but not radiologic evidence of progression will be censored at the date of the last evaluable tumor assessment before the non-study cancer treatment is initiated. Detailed censoring rules are outlined in the SAP.

13.2.3. Other Secondary Efficacy Endpoints

13.2.3.1. Overall Response Rate (ORR)

The assessment of ORR will be based on Investigator review of the images. ORR is defined as the proportion of patients with objective evidence of CR or PR.

At the analysis stage, the best overall response will be assigned for each patient as the best response recorded from all responses recorded after study randomization. If applicable, responses recorded after disease progression or initiation of non-study cancer treatment will be excluded. A patient's best response assignment of SD needs to be maintained for at least 6 weeks after study randomization. Per RECIST 1.1, responses of PR or CR in studies with survival as the primary endpoint do not have a minimum time requirement to maintain the response.

13.2.3.2. Disease Control Rate (DCR)

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.

13.2.3.3. Time to Deterioration of ECOG Performance Status

The time to deterioration of ECOG performance status is defined as the time from randomization to the first date on which an ECOG performance status score of 2 or higher is observed.

13.2.3.4. Quality of Life

The EORTC QoL questionnaire (QLQ) is an integrated system for assessing the health-related QoL of cancer patients participating in international clinical trials. The core questionnaire, the QLQ-C30, incorporates 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea and vomiting), a global health status scale, and a number of single items assessing additional symptoms commonly reported by cancer patients (dyspnea, loss of appetite, insomnia, constipation and diarrhea) and perceived financial impact of the disease.

The gastric cancer module (QLQ-STO22) is meant for use among gastric cancer patients varying in disease stage and treatment modality.

13.3. Analytical Methods

13.3.1. Patient Disposition, Baseline and Treatment Characteristics

13.3.1.1. Patient Disposition

The number of patients in each study population and the reasons for exclusion, along with any randomization and/or stratification errors will be summarized. In addition, patients that discontinue study treatment or study follow-up will also be summarized, along with reasons for study discontinuation.

13.3.1.2. Patient Baseline Characteristics

Patient demographic and disease characteristics at Baseline will be summarized in frequency tables or with summary statistics for continuous variables.

13.3.1.3. Study Treatment

The study medication administration profile will be summarized descriptively for each treatment arm with respect to number of cycles taken, the cumulative dose, the dose intensity, the relative dose intensity, and dose modifications.

13.3.1.4. Non-Study Treatment in the Study Follow-up Period

The number, type, and extent of use of non-study cancer treatment after study treatment discontinuation will be summarized. Any use of non-study cancer treatment during the study treatment period will also be presented.

13.3.2. Efficacy Analyses

13.3.2.1. Primary Efficacy Analysis

OS in the ITT population will be compared between the 2 treatment groups using the stratified log-rank test. One- and 2-sided p-values will be presented. The estimate of the hazard ratio (HR) and corresponding 95% CI will be provided using a Cox proportional hazards (CPH) model including treatment and the 3 stratifications factors in the model. Survival for each arm will be summarized using Kaplan Meier curves and further characterized in terms of the median and survival probability at 3, 6, 9 and 12 months, along with the corresponding 2-sided 95% CI for the estimates. The stratification factors will be populated as per the IXRS assignment.

13.3.2.2. Supportive Analyses of OS

Supportive analyses for OS, conducted in the ITT population (unless otherwise noted), will include:

a. The unstratified log-rank test and a CPH model (only treatment effect included in the model).
b. Multivariate analysis using the CPH model, including the 3 stratification factors and potential prognostic/predictive factors: age (<65, ≥65 years), race (White, Asian, Other), gender, number of prior regimens (2, 3+), prior therapy, previous gastrectomy, GE junction involvement, presence of peritoneal metastases, presence of liver metastases, number of metastatic sites (1-2, 3+), measurable disease, histology subtype (diffuse, intestinal), and HER2 status. Additional factors may be identified in the SAP.
c. Factors included in the model will be assessed for co-linearity and a stepwise selection process will be applied to identify a final subset of prognostic/predictive factors in the model. Once the subset has been established, treatment will be added to the final model to assess its effect in the presence of the identified covariates.
d. An exploratory analysis of treatment by factor interactions using the CPH model will be conducted, using the factors identified in the final model above.

e. Subgroup analyses will also be conducted for each of the stratification factors and the potential prognostic/predictive factors identified in Section 13.3.2.2b above. The HR and associated 95% CI will be presented for each subgroup.
f. The primary efficacy analysis, as outlined in Section 13.3.2.1, will also be run excluding any patients who did not have documented refractory metastatic gastric cancer, as defined in inclusion criteria #2 and #3 in Section 8.3.1.
g. Additional sensitivity analyses will be defined in the SAP.

13.3.2.3. Secondary Endpoint Analyses

All secondary endpoints comparisons will be made at the 2-sided 0.05 significance level. Since PFS is the only key secondary endpoint for regulatory registration purposes, no further multiplicity adjustments will be made. Assuming that OS demonstrates significance at the 1-sided 0.025 level, PFS can subsequently be tested at the 2-sided 0.05 level.

PFS

PFS will be analyzed with the methodology specified in Section 13.3.2.1 and Section 13.3.2.2a, c, and d. Additional sensitivity analyses, as detailed in the SAP, will account for clinical progression as a PFS event.

ORR and DCR

The treatment comparison for ORR and DCR will be based on the TR population using Fisher's exact test. Treatment estimates and differences will be presented along with the associated 95% CIs.

Time to Deterioration of ECOG Performance Status

Time to deterioration of ECOG performance status to a score of 2 or higher will be analyzed using methodology described in Section 13.3.2.1. Patients not reaching an ECOG of 2 or more (3, 4 or 5) will be censored at the last recorded ECOG assessment.

Quality of Life

Questionnaire compliance rates, for both scales, will be assessed at each measurement time point (baseline, prior to cycle 2, 3, 4, etc.).

Descriptive statistics, for both scales, for the summary scores, as well as the subscale scores will be provided for each assessed time point. In addition, change in QoL scores at representative time points will be determined for the summary, all domains and single items by subtracting each patient's score from their corresponding baseline score. Representative time points will be prior to cycle 2, 3 and 4, chosen based on expected patient compliance to be adequate to allow meaningful analyses, considering the expected treatment duration in the two study groups.

For each domain, the proportion of patients with deteriorating, stable or improving scores prior to cycles 2, 3 and 4 will be compared using Fisher's exact test. In addition, time to QoL deterioration will be evaluated for each arm using Kaplan-Meier estimates and compared using the log-rank test. The criteria for deteriorating, stable or improving scores will be detailed in the SAP.

Additional exploratory analyses will also be detailed in the SAP, including any internal consistency assessments between the two scales, as well as any association between the QoL change scores and OS and PFS.

13.3.3. Safety Analyses

The safety evaluations will focus on AEs and laboratory assessments. All patients included in the AT Population will be evaluated by treatment arm 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 criteria, v4.03, where applicable. Concomitant medications will be coded according to the World Health Organization Drug Dictionary (WHODD). Hematological and chemistry laboratory parameters will be graded according to the NCI CTCAE v.4.03 criteria, where applicable.

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

Absolute values and changes from baseline for hematology and serum chemistry parameters will be summarized by cycle. In addition, worst severity grade, and time to event will also be summarized.

13.4. Justification of Sample Size

The study is designed to detect with 90% power a hazard ratio for death of 0.70 (30% risk reduction) in the TAS-102 arm compared with the placebo arm with an overall 1-sided type 1 error of 0.025. A variable accrual period of 18 months and a 5%/year loss to survival follow-up rate has been assumed. Using a treatment allocation of 2:1 (TAS-102:placebo) of 500 patients, 384 deaths will be targeted for the final OS analysis.

Based on these design operating characteristics and assuming a median survival time of approximately 5 months in the control arm, the primary analysis target events milestone will be reached approximately 8 months after the last patient is randomized in the study. The median OS in the control arm was estimated based on the observed median OS of 3.8 months in the placebo arm of the 2nd line Phase 3 ramucirumab (REGARD) study, and the observed median OS of 4.3 months in the placebo arm of the 2nd & 3rd line Phase 3 everolimus (GRANITE) study.[13] The estimate was further increased to 5 months to account for the higher control median projected in the Japanese population.

13.5. Interim Analyses

An independent DMC will periodically assess the safety data (see Section 15.4).

In addition, one interim analysis for efficacy and futility is planned for the study after approximately 1/2 of the total target events are observed (192 deaths). The Lan-DeMets alpha-spending approach will be used with O'Brien-Fleming stopping boundaries to guide the efficacy evaluation at the interim and final OS analysis. This approach will account for multiple

testing and preserve the overall 1-sided study significance level of 0.025. A fixed HR boundary will be used to assess futility (non-binding). Additional details will be provided in the DMC charter.

14. ETHICS

14.1. Ethical Considerations

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

14.2. Informed Consent and Patient Information

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

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

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

14.3. 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.

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, IB, curriculum vitae, etc), 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.

15. ADMINISTRATIVE CONSIDERATIONS

15.1. Protocol Amendments

No change to the protocol may be made without the agreement of Taiho Oncology, Inc. Any amendment to the original protocol will be made by Taiho Oncology, Inc. and will be submitted to the IRB/IEC and appropriate regulatory authorities for approval or notification.

15.2. Curriculum Vitae

All Investigators and any sub-investigator(s) must provide Taiho Oncology, Inc. 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.

15.3. Administrative Structure

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

15.4. Data Monitoring Committee (DMC)

A DMC will be established for this study to provide additional, independent oversight that can enhance safety of study participants and the study conduct. The DMC will comprise of clinicians and a statistician, all independent from the Sponsor and investigative sites and selected as to avoid conflict of interest.

The primary objectives of this DMC are to provide independent safety monitoring comparing safety between the study groups and to provide a recommendation based on the planned interim analysis.

A DMC charter will be written to establish well-defined standard operating procedures including meeting proceedings and structure, data assessments, documentation and record keeping, process for DMC recommendations, and regulatory reporting as applicable. The charter will be written with procedures ensuring the minimization of bias, such as maintaining confidentiality of any interim data.

15.5. Monitoring Procedures

15.5.1. 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.

15.5.2. 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 study site monitor (CRA) is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical, regulatory, and quality in all aspects of the trial.

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

15.5.3. 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, subject'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, subject 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 use of pencil and correction fluids is not accepted for recording clinical research information. Corrections in source documents must be done by crossing out with a single line, then initialing and dating and recording the corrected information.

15.5.4. Case Report Form

Electronic CRFs will be provided by the Sponsor.

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 entry of data via eCRFs may generate additional requests via electronic 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 included in the eCRFs held by the Investigator and Sponsor.

15.5.5. 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.

15.6. Archiving of Records

The Investigator is responsible for the retention of all study documents according to institutional policies, local laws, ICH guidelines E6 – GCP, Sections 4.9.4 and 4.9.5 and, for studies conducted under an Investigational New Drug (IND) application, the USA Code of Federal Regulation (CFR) Title 21 part 312.62. For more information on USA requirements and ICH Guidelines, please go to http://www.fda.gov and http://www.ema.europa.eu.

The Investigator agrees to inform the Sponsor in writing of the intention to remove or destroy any study-related records. Prior to contacting the Sponsor, the Investigator must ensure that institutional and local requirements (for example, ICH Guidelines) have been satisfied. The Sponsor will evaluate the Investigator's request and 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 the Sponsor requests that the Investigator maintain the records for a longer period of time, additional arrangements will be made.

15.7. 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.

15.8. Use and Publication of Study Results

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. Data from this study must not be published without prior authorization from the Sponsor.

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.

15.9. Financial Disclosure

Financial disclosure for clinical Investigators will be obtained and record keeping of financial records will be in accordance with local regulatory requirements and CFR Title 21 part 54.

15.10. Termination of the Study

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.

16. 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 is 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 that 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.

17. SIGNATURES OF SPONSOR AND INVESTIGATOR

Protocol TO-TAS-102-302: RANDOMIZED, DOUBLE-BLIND, PHASE 3 STUDY EVALUATING TAS-102 PLUS BEST SUPPORTIVE CARE (BSC) VERSUS PLACEBO PLUS BSC IN PATIENTS WITH METASTATIC GASTRIC CANCER REFRACTORY TO STANDARD TREATMENTS

a. Declaration of Sponsor

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

- The current risk-benefit evaluation of the investigational product
- The moral, ethical, and scientific principles governing clinical research as set out in the protocol, Good Clinical Practice (GCP), International Council for Harmonisation (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 adverse events (AEs), relating to treatment with the investigational product.

Date:_____ Signature:_____

Robert E. Winkler, MD
Senior Vice President, Head of Clinical Development
Taiho Oncology, Inc.
101 Carnegie Center, Suite 101
Princeton, NJ 08540
USA

b. Declaration of Investigator

I have read the above protocol, appendices, and referenced documents. I understand the contents and intend to fully comply with all requirements. No changes will be made without formal authorization by Taiho Oncology, Inc./Taiho Pharmaceutical Co., Ltd. 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, Good Clinical Practice (GCP), International Council for Harmonisation (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):_____

18. LIST OF REFERENCES

[1] Muro K, Doi T, Bando H, Yasui H, Nishina T, Yamaguchi K et al. Multicenter phase 2 study of TAS-102 monotherapy in patients with pretreated advanced gastric cancer. Manuscript in preparation.

[2] Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr

[3] National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Gastric cancer. V.3.2015. http://www.nccn.org.

[4] Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. The Lancet. 2010;376:687-97.

[5] Fuchs CS, Tomasek J, Yong CJ, Dumitru F, Passalacqua R, Goswami C, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2014;383:31-39.

[6] Wilke H, Muro K, Van Cutsem E, Oh S-C, Bodoky G, Shimada Y, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol. 2014;15:1224–35.

[7] Mayer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med 2015;372:1909-19.

[8] Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organisation for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. Journal of the National Cancer Institute 1993;85:365-76.

[9] Aapro MS, Bohlius J, Cameron DA, Dal Lago L, Donnelly JP, Kearney N, et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. Eur J Cancer. 2011;47(1):8-32.

[10] Benson AB 3rd, Ajani JA, Catalano RB, Engelking C, Kornblau SM, Martenson JA Jr, et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. J Clin Oncol. 2004;22(14):2918-26.

[11] American Society of Clinical Oncology, Kris MG, Hesketh PJ, Somerfield MR, Feyer P, Clark-Snow R, et al. American Society of Clinical Oncology guidelines for antiemetics in oncology: update 2006. J Clin Oncol. 2006;24:2932-47.

[12] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-47.

[13] Ohtsu A, Ajani JA, Bai Y-X, Bang Y-J, Chung H-C, Pan H-M, et al. Everolimus for previously treated advanced gastric cancer: results of the randomized, double-blind, phase III GRANITE-1 study. J Clin Oncol. 2013;31:3935-43.

19. APPENDICES

APPENDIX A
ECOG PERFORMANCE STATUS

GRADE	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead
From: Oken MM, Creech, RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649-55.	

APPENDIX B
NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION

The Stages of Heart Failure NYHA Classification

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

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

APPENDIX C
BENEFIT AND RISK ASSESSMENT

TAS-102 is comprised of an antineoplastic thymidine-based nucleoside analogue, trifluridine (FTD), and the thymidine phosphorylase inhibitor, tipiracil hydrochloride (TPI), at a molar ratio 1:0.5 (weight ratio, 1:0.471).

Mechanism of Action

Following uptake into cancer cells, FTD is phosphorylated by thymidine kinase, further metabolized in cells to a deoxyribonucleic acid (DNA) substrate, and incorporated directly into DNA, thereby interfering with DNA function to prevent cell proliferation.

However, FTD is rapidly degraded by thymidine phosphorylase (TPase) and readily metabolized by a first-pass effect following oral administration. The inclusion of the thymidine phosphorylase inhibitor, TPI, was shown to increase the half-life of FTD and hence, the two drugs are used in combination.

In nonclinical studies, FTD/TPI demonstrated antitumor activity against both 5-fluorouracil (5-FU) sensitive and resistant colorectal cancer (CRC) cell lines.

The cytotoxic activity of FTD/TPI against several human tumor xenografts correlated highly with the amount of FTD incorporated into DNA, confirming this as the primary mechanism of action.

Nonclinical Toxicology

In toxicology assessments of FTD/TPI performed in rats, dogs and monkeys, the target organs identified were the lymphatic and hematopoietic systems and the gastrointestinal tract. The approximate lethal dose after a single administration was 2000 mg/kg and the gastrointestinal tract was identified as the primary target organ. Similarly, in repeated dose toxicity studies, the gastrointestinal tract was again identified as one of the primary target organs, in addition to the lymphatic and hematopoietic systems. All changes, i.e., leukopenia, anemia, bone marrow hypoplasia, atrophic changes in the lymphatic and hematopoietic tissues and the gastrointestinal tract, were reversible within 9 weeks of drug withdrawal.

Whitening, breakage, and malocclusion (degeneration and disarrangement in the ameloblasts, papillary layer cells and odontoblasts) were observed in teeth of rats treated with FTD/TPI. This finding was not evident in young adult monkeys, and therefore may be rodent-specific.

Trifluridine/tipiracil hydrochloride was shown to be genotoxic in a reverse mutation test in bacteria, a chromosomal aberration test in mammal-cultured cells, and a micronucleus test in mice.

Trifluridine/tipiracil hydrochloride caused embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when given at dose levels lower than the clinical exposure. TAS-102 was administered orally once daily to female rats during gestation (GD7 to GD17) at dose levels of 15, 50, and 150 mg/kg. Inhibition of fetal growth was observed after administration at doses of 50 mg/kg or higher, and a lethal effect on embryos and a teratogenic effect were observed at 150 mg/kg. Maternal rats exhibited suppressed body weight gain at doses ≥50 mg/kg/day and decreased food consumption at doses of 150 mg/kg/day. The AUCs of FTD in rats at these dose levels were lower than that in humans at the recommended dose of TAS-102.

Radioactivity was excreted in the milk of nursing rats dosed with TAS-102 containing ^{14}C-FTD or ^{14}C-TPI indicating elimination of TAS-102 and/or its metabolites by this route.

Results of animal studies did not indicate an effect of FTD and TPI on male fertility in rats. In female rats, increases in the corpus luteum count and implanting embryo count were observed at high doses, but female fertility was not affected.

Clinical Experience/Extent of Exposure

As of 19 January 2015, a total of 1093 patients have received TAS-102 in clinical trials (Taiho-sponsored or Investigator-initiated). An additional 287 patients have been enrolled on the ongoing Phase 3 trial in Asia (TERRA); however, this study remains blinded so treatment allocation to TAS-102 or placebo is unknown.

TAS-102 (Lonsurf®) has been marketed in Japan for the treatment of metastatic colorectal cancer (mCRC) since 26 May 2014. Based on unit sales, it is estimated that 3873 patients have been exposed to TAS-102 in the post-marketing setting as of the end of December 2014.

Clinical Efficacy and Safety

The clinical efficacy and safety of TAS-102 were evaluated in an international, randomized, double-blind, placebo-controlled Phase 3 study (RECOURSE; TPU-TAS-102-301) in patients with previously treated mCRC. The primary efficacy endpoint was overall survival (OS), and the supportive secondary endpoint was progression-free survival (PFS).

In total, 800 patients were randomized 2:1 to receive TAS-102 (N=534) plus best supportive care (BSC) or matching placebo (N=266) plus BSC. TAS-102 dosing was based on body surface area (BSA) with a starting dose of 35 mg/m^2/dose, administered orally BID after morning and evening meals for 5 days a week with 2 days rest for 2 weeks, followed by 14-day rest, repeated every 4 weeks. Patients continued therapy until disease progression or unacceptable toxicity.

Of the 800 randomized patients, the median age was 63 years, 61% were male, 58% and 35% were White and Asian respectively, and all patients had baseline ECOG performance status of 0 or 1. The primary site of disease was colon (62%) or rectum (38%). KRAS status was wild type (49%) or mutant (51%) at study entry. The median number of prior lines of therapy for metastatic disease was 3. All patients received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. All but one patient received bevacizumab, and all but two patients with KRAS wild type tumors received panitumumab or cetuximab.

Efficacy Results

As shown in the following table, treatment with TAS-102 plus BSC resulted in a statistically significant improvement in OS and PFS in comparison to placebo plus BSC. In addition, TAS-102 was shown to demonstrate a statistically significant delay versus placebo in time to deterioration of the patients' ECOG performance status, suggesting that quality of life (QoL) was maintained while on TAS-102 treatment.

Efficacy Results (Intent-To-Treat Population) from RECOURSE

	TAS-102 (N=534)	**Placebo (N=266)**
Overall Survival		
Number of deaths, N (%)	364 (68.2)	210 (78.9)
Median OS (months)[a] [95% CI][b]	7.1 [6.5, 7.8]	5.3 [4.6, 6.0]
Hazard ratio [95% CI]	0.68 [0.58, 0.81]	
P-value[c]	<0.0001 (1-sided and 2-sided)	
Progression-Free Survival		
Number of Progression or Death, N (%)	472 (88.4)	251 (94.4)
Median PFS (months)[a] [95% CI][b]	2.0 [1.9, 2.1]	1.7 [1.7, 1.8]
Hazard ratio [95% CI]	0.48 [0.41, 0.57]	
P-value[c]	<0.0001 (1-sided and 2-sided)	

[a] Kaplan-Meier estimates
[b] Methodology of Brookmeyer and Crowley
[c] Stratified log-rank test (strata: KRAS status, time since diagnosis of first metastasis, region)

Subgroup analyses for OS and PFS according to all major prespecified subgroups including race, geographic region, age (<65; ≥65), sex, performance status, and KRAS status, demonstrated a treatment effect favoring the TAS-102 regimen over the placebo regimen.

Safety Results

In the RECOURSE study, the mean duration of therapy was 12.7 weeks for patients receiving TAS-102 and 6.8 weeks for placebo.

The most frequently observed adverse drug reactions (≥30%) in patients receiving TAS-102 were asthenia/fatigue, nausea, decreased appetite, and diarrhea. In the TAS-102 group, adverse events (AEs) were indicated as the primary reason for treatment discontinuation in 3.6% of patients (AEs leading to discontinuation in ≥2 patients were fatigue, general physical health deterioration, diarrhea, anemia, and decreased appetite). Dose reduction due to AEs occurred in 13.7% of patients receiving TAS-102 (AEs requiring dose reduction in ≥1% of patients were neutropenia related, anemia, fatigue, and diarrhea). Dose delay/interruption due to AEs occurred in 51.8% of patients receiving TAS-102 (primarily neutropenia-related events).

Adverse drug reactions regardless of causality reported in ≥10% of the patients treated in the TAS-102 group and at a rate that exceeded the rate in patients receiving placebo are shown in the following table.

Adverse Drug Reactions (≥10%) Reported in Patients Treated with TAS-102 in the RECOURSE Study and Reported More Commonly than in Patients Receiving Placebo

Adverse Reactions	TAS-102 (N=533)			Placebo (N=265)		
	Grade			Grade		
	All %	3 %	4[a] %	All %	3 %	4 %
Gastrointestinal disorders						
Nausea	48	2	N/A	24	1	N/A
Diarrhea	32	3	<1	12	<1	0
Vomiting	28	2	0	14	<1	0
Abdominal pain	21	2	N/A	18	4	N/A
General disorders and administration site conditions						
Asthenia/fatigue	52	7	N/A	35	9	N/A
Pyrexia	19	1	<1	14	<1	0
Metabolism and nutrition disorders						
Decreased appetite	39	4	0	29	5	0

[a] No Grade 4 definition for nausea, abdominal pain, or fatigue in Common Terminology Criteria for Adverse Events (CTCAE), v4.03

Adverse drug reactions that occurred more frequently with TAS-102 in the RECOURSE study with a frequency of 5-10% (frequency of placebo in parentheses) included: upper respiratory tract infection 8% (3%); dysgeusia 7% (2%); and alopecia 7% (1%).

In the RECOURSE study, TAS-102 caused an increase in the incidence of Grade 3/4 cytopenias including anemia, neutropenia, and thrombocytopenia as shown in the following table.

Laboratory Test Abnormalities in the RECOURSE Study

Laboratory Parameter	TAS-102 (N=533[a])			Placebo (N=265[a])		
	Grade[b]			Grade[b]		
	All %	3 %	4 %	All %	3 %	4 %
Blood and lymphatic system disorders						
Neutropenia	67	27	11	1	0	0
Lymphocytopenia	66	18	3	40	9	1
Anemia[c]	77	18	N/A[d]	33	3	N/A
Thrombocytopenia	42	5	1	8	0	<1

[a] % based on number of patients with post-baseline samples, which may be less than 533 (TAS-102) or 265 (placebo)
[b] Common Terminology Criteria for Adverse Events (CTCAE), v4.03
[c] Anemia: No Grade 4 definition for this laboratory parameter in CTCAE, v4.03
[d] One Grade 4 anemia adverse reaction based on clinical criteria was reported.

Febrile neutropenia was reported in 3.8% of patients treated with TAS-102. There was one (0.2%) drug-related death, which was due to neutropenia-related infection/sepsis. In the TAS-102 group, 9.4% of patients received granulocyte colony-stimulating factor (G-CSF).

Other clinically important adverse drug reactions reported in TAS-102 clinical trials (open-label or placebo-controlled) include:

- **GI**: Stomatitis, ileus, colitis
- **General disorders**: Mucosal inflammation
- **Infection**: Pelvic infection, pneumonia, urinary tract infection
- **Metabolism**: Dehydration
- **Respiratory**: Pulmonary embolism

The following adverse reaction has been identified during post approval use of TAS-102 in Japan:

- Interstitial lung disease

Age, Gender, and Race

Based on the results of a population pharmacokinetic (PK) analysis, there is no clinically relevant effect of age, gender or race on the PK of FTD or TPI.

Among the patients who received TAS-102 in the RECOURSE study, 44% were ≥65 years of age, while 8% were ≥75 years. The effect of TAS-102 on OS was similar in patients <65 years and ≥65 years of age.

Patients ≥65 years of age on TAS-102 had a higher incidence of the following AEs and laboratory abnormalities than patients <65 years of age: decreased appetite (42% vs 37%),

Grade 3 or 4 neutropenia (48% vs 30%), Grade 3 anemia (26% vs 12%) and Grade 3 or 4 thrombocytopenia (9% vs 2%).

Ethnicity

In the RECOURSE study, there were no marked differences between Western and Asian subgroups with respect to overall incidence of AEs or ≥Grade 3 AEs in either the TAS-102 or placebo groups.

Renal Impairment

Based on a population PK analysis, the exposure of TAS-102 in patients with mild renal impairment (creatinine clearance [CLcr] = 60 to 89 mL/min) was similar to those in patients with normal renal function (CLcr ≥90 mL/min). A higher exposure of TAS-102 was observed in patients with moderate renal impairment (CLcr = 30 to 59 mL/min).

Of the 533 patients in the RECOURSE study who received TAS-102, renal function subgroups based on CLcr at baseline were as follows (data were missing for 2 patients): 306 (57%) patients had normal renal function; 178 (33%) patients had mild renal impairment; 47 (9%) had moderate renal impairment. Patients with severe renal impairment were not enrolled in the study.

In the TAS-102 group, there was no marked difference between the normal renal function and mild renal impairment subgroups (based on baseline CLcr) with respect to overall incidence of AEs, ≥Grade 3 AEs, or serious AEs. However, patients with moderate renal impairment had a higher incidence (difference of at least 5%) of ≥Grade 3 AEs, serious AEs, and dose delays and reductions compared to the other 2 subgroups.

Hepatic Impairment

Based on the population PK analysis, liver function parameters including ALT, AST, alkaline phosphatase, and total bilirubin were not significant covariates for PK parameters of either FTD or TPI.

Cardiac Safety

TAS-102 (35 mg/m^2 following a single dose and following multiple doses in an open label study in patients with advanced solid tumors) had no clinically relevant effect on QT/QTc prolongation compared with placebo, i.e., none of the upper bounds of the 1-sided 95% CIs in baseline-subtracted QTc exceeded 20 msec, at any time point. There was no clinically relevant relationship between plasma concentrations of FTD, FTY, and TPI and the QTc interval measured as placebo-adjusted change from baseline.

Conclusions

TAS-102 has demonstrated substantial efficacy with a manageable safety profile in heavily pretreated patients with mCRC, including those who were refractory to standard therapies. The dosing regimen of 35 mg/m^2 administered orally BID, within 1 hour after the morning and the evening meal, for 5 days a week with 2 days rest for 2 weeks, followed by a 14-day rest (1 treatment cycle), has been confirmed as tolerable and effective in Phase 2 and 3 studies.

The most common and clinically relevant AEs associated with TAS-102 treatment are myelosuppression and gastrointestinal toxicities. The safety profile of TAS-102 is acceptable and manageable particularly when considering the advanced refractory nature of the patients to

be treated and the safety profile of other chemotherapeutic agents. The significant survival benefit, as well as increase in PFS, and increasing time to ECOG performance status 2 seen in mCRC patients in the RECOURSE study are clear signals of the activity of this TAS-102 regimen. Thus, the evaluation of this TAS-102 dose regimen in refractory gastric cancer patients is indicated.

Hence, based on the large amount of data from both clinical trials and post-marketing use, the benefit risk ratio is deemed positive for this prospective comparative global Phase 3 clinical trial in patients with gastric cancer.

APPENDIX D
QUALITY OF LIFE QUESTIONNAIRES

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____

Your birthdate (Day, Month, Year): ____

Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

Specimen

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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Specimen

EORTC QLQ – STO22

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Have you had problems eating solid foods?	1	2	3	4
32. Have you had problems eating liquidised or soft foods?	1	2	3	4
33. Have you had problems drinking liquids?	1	2	3	4
34. Have you had discomfort when eating?	1	2	3	4
35. Have you had pain in your stomach area?	1	2	3	4
36. Have you had discomfort in your stomach area?	1	2	3	4
37. Did you have a bloated feeling in your abdomen?	1	2	3	4
38. Have you had trouble with acid or bile coming into your mouth?	1	2	3	4
39. Have you had acid indigestion or heartburn?	1	2	3	4
40. Have you had trouble with belching?	1	2	3	4
41. Have you felt full up too quickly after beginning to eat?	1	2	3	4
42. Have you had trouble enjoying your meals?	1	2	3	4
43. Has it taken you a long time to complete your meals?	1	2	3	4
44. Have you had a dry mouth?	1	2	3	4
45. Did food and drink taste different from usual?	1	2	3	4
46. Have you had trouble with eating in front of other people?	1	2	3	4
47. Have you been thinking about your illness?	1	2	3	4
48. Have you worried about your weight being too low?	1	2	3	4
49. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
50. Have you worried about your health in the future?	1	2	3	4
51. Have you lost any hair?	1	2	3	4
52. Answer this question only if you lost any hair: If so, were you upset by the loss of your hair?	1	2	3	4

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Specimen

APPENDIX E
SUMMARY OF CHANGES TO PROTOCOL

Please note that the following pages represent the changes for Amendment 0.1 only. A separate summary of changes is provided for each amendment thereafter.

AMENDMENT 0.1: 16 July 2015

SUMMARY OF CHANGES

PROTOCOL TO-TAS-102-302

RANDOMIZED, DOUBLE-BLIND, PHASE 3 STUDY EVALUATING TAS-102 PLUS BEST SUPPORTIVE CARE (BSC) VERSUS PLACEBO PLUS BSC IN PATIENTS WITH METASTATIC GASTRIC CANCER REFRACTORY TO STANDARD TREATMENTS

RATIONALE

This administrative change to the protocol has been made to update/amend the Medical Monitor information.

Conventions

A detailed summary of all protocol changes, additions, and/or deletions follows. All original text is shown in its original text style. Deleted text is in ~~strikethrough~~. Additions to text are shown in **bold underline**.

Change 1:

Location: TITLE PAGE

Original protocol:

SPONSOR'S MEDICAL MONITORS:

North America: **Europe:** **Japan:**

[redacted]

Changed to:

Change 2:

Location: Section 19. Appendices

Added:

APPENDIX E
SUMMARY OF CHANGES TO PROTOCOL

AMENDMENT 0.1: 16 July 2015