STATISTICAL ANALYSIS PLAN
PHASE II

VERSION: 1.0
DATE OF PLAN: OCTOBER 31, 2017

BASED ON: PROTOCOL APPROVED ON JUNE 14, 2016

STUDY DRUG:

LONGSURF

PROTOCOL NUMBER: TO-TAS102-203

STUDY TITLE:

A Phase 2 Study with Safety Lead-in, Evaluating TAS-102 Plus Nivolumab in Patients with Microsatellite-Stable Refractory Metastatic Colorectal Cancer

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This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

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TECHNICAL SUMMARY REPORT (TSR)

Name of Sponsor/Company Taiho Oncology, Inc.	**Individual Study Table Referring to Part of the Dossier:** **Volume:**	***(For National Authority Use Only)*:**
Name of Finished Product: LONGSURF	**Page:**	
Name of Active Ingredient: trifluridine (FTD) and tipiracil hydrochloride (TPI)	**Protocol:** TO-TAS-102-203	
Title Of Study: **A Phase 2 Study with Safety Lead-in, Evaluating TAS-102 Plus Nivolumab in Patients with Microsatellite-Stable Refractory Metastatic Colorectal Cancer**		
Investigators: Study Center(s): about 10		

Studied period (years): Patients will be treated until the patient meets the discontinuation criteria (Section 7.5 of the Study Protocol). For the purpose of final analyses, the study will be considered completed when all patients have discontinued from treatment or 12 months after the first day of treatment with TAS-102 plus nivolumab of the last patient enrolled, whichever occurs first. Upon data cutoff, patients ongoing with study treatment may continue with their treatment and be followed for safety. Measurements of efficacy and data collection may be reduced.	**Phase of development: Phase 2**

Objectives:

To evaluate the following objectives in patients with mCRC receiving TAS-102 in combination with nivolumab:

Primary Objective

- To estimate the immune-related overall response rate (irORR) of TAS-102 and nivolumab combination therapy in mCRC patients

Secondary Objectives

- To confirm the recommended Phase 2 dose for the combination therapy of TAS-102 and nivolumab
- To assess the safety of TAS-102 and nivolumab given as combination therapy
- To estimate the ORR using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
- To estimate the PFS based on immune-related response criteria (irRC) and RECIST
- To estimate the disease control rate (DCR) using irRC and RECIST
- To estimate the OS

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Methodology: Open Label Study with Safety Lead-in

Number of Subjects (planned and analyzed): Approximately 30 to 35 evaluable patients will be enrolled in a Simon's 2-stage design.

Diagnosis and main criteria for inclusion (see Protocol Section 7.3.1):

Patient with confirmed histologically proven metastatic or locally advanced colorectal adenocarcinoma who is MSS (ie, not MSI) based on either an analysis of tissue from a prior biopsy or based on tissue from a new biopsy.

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

In addition, patients will receive nivolumab 3 mg/kg intravenously over 60 minutes every 2 weeks on Day 1 and Day 15 of each cycle. The investigator will attempt to keep the nivolumab schedule on the same schedule as TAS-102, even if there is a delay in dosing of TAS-102.In addition, patients will receive nivolumab 3 mg/kg intravenously over 60 minutes every 2 weeks on Day 1 and Day 15 of each cycle. The investigator will attempt to keep the nivolumab schedule on the same schedule as TAS-102, even if there is a delay in dosing of TAS-102.

Duration of treatment: Patients will be treated until the patient meets the discontinuation criteria (Section 7.5 of the Study Protocol).

Reference therapy, dose and mode of administration: Not applicable, as it is open label study and there is no randomization.

Criteria for evaluation (see Protocol Sections 10.2 and 10.3):

Efficacy:

Computed tomography scans will be performed at baseline and then every 2 cycles. On-site tumor assessments will be performed by the investigator/local radiologist.

Tumor scans will be assessed using irRC and RECIST criteria. Overall response rate, DCR, PFS, and OS will be determined for all patients.

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Safety:

Adverse events (AEs) will be graded using the NCI CTCAE.

Statistical methods:

Study Populations

The study populations for all analyses are defined as follows:

- Safety Population: Includes all patients who received at least 1 dose of study drug. It will be the primary population for safety analyses.
- DLT Evaluable Population: Includes all patients in the safety population in Stage 1, prior to confirming the recommended dose, who completed at least 1 cycle (28 days) of study treatment with at least 80% of the study treatment administered, unless the treatment was interrupted because of a DLT.
- Efficacy Population: Includes all patients in the safety population who completed at least 6 months of tumor follow-up (evaluable irRC and/or RECIST assessments), unless the patient progressed or died before the 6-month follow-up.

Efficacy Analyses

Tumor response assessments and disease progression will be evaluated in this study using the irRC and RECIST criteria. The RECIST and irRC response assessments will be performed by the investigators for the study. Descriptive statistics, such as incidence of responses (ORR and DCR), Kaplan-Meier estimates for PFS and OS, and associated 95% confidence intervals will be provided.

Safety Analyses

Simple descriptive statistics will be provided for safety endpoints, demographic/baseline characteristics, and study drug exposure. Safety endpoints will primarily include incidence of AEs and changes from baseline (grade changes) in clinical laboratory tests.

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LIST OF TABLES

1. LIST OF ABBREVIATIONS

Sample text is provided in the table below. The list should be tailored to the specific requirements of the protocol and the terminology used in the analysis plan.

Table 1: List of Abbreviations

Abbreviation	Term
µmol or mkmol	Micromole
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
b.i.d.	Twice Daily
BP	Blood Pressure
BSA	Body Surface Area
bpm	Beats per Minute
BUN	Blood Urea Nitrogen
C	Center
°C	Degrees Celsius
Ca	Calcium
Cl	Chloride
CrCl	Creatinine Clearance
CMH	Cochran Mantel-Haenszel
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
DCR	Disease Control Rate
DL	Deciliter
DLT	Dose-Limiting Toxicity
DOB	Date of Birth
dy	Days
EOS	End of Study
ºF	Degrees Fahrenheit

g	Grams
GCP	Good Clinical Practices
GGT	Gamma-Glutamyl Transferase
HGB	Hemoglobin
ICD-9	International Classification of Diseases – 9th Edition
In	Inches
IR	Immediate Release
IRB	Institutional Review Board
ITT	Intent-to-Treat Population
irCR	Immune-related complete response
irOR	Immune-related overall response
irORR	Immune-related overall response rate
irPD	Immune-related progressive disease
irPR	Immune-related partial response
irRC	Immune-related response criteria
irSD	Immune-related stable disease
IU	International units
K	Potassium
Kg	Kilogram
L	Liter
Lb	Pounds
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal
LOCF	Last Observation Carried Forward
mAb	Monoclonal antibody
mCRC	Metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities Terminology
meq	Milliequivalent
mg	Milligrams
mL	Milliliter
mmHg	Millimeters of Mercury
mo	Months
MRI	Magnetic resonance imaging

MSI	Microsatellite instability
MSS	Microsatellite stable
N	Total Sample Size
Na	Sodium
ng	Nanograms
NIMH	National Institute of Mental Health
OC	Observed Cases
OTC	Over the Counter Medication
PCS	Potential Clinical Significance
PP	Per-Protocol Population
PFS	Progression free survival
PR	Partial response
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)
RBC	Red Blood Cell Count
S	Sex
s.d.	Standard Deviation
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SI	System International
SD	Stable disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SR	Sustained Release
TG	Treatment Group
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
VEGF	Vascular endothelial growth factor
WBC	White Blood Cell Count
WHO	World Health Organization
yr	Years

2. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and data displays to be included in the Clinical Study Report (CSR) for Protocol #TO-TAS102-203

Protocol Revision Chronology:		
Protocol	14 June 2016	Original

This SAP was developed per standard operating procedure S-CS-001 and guidance document G-CS-001, G-CS-018, G-CS-020.

All decisions regarding final analysis, as defined in this SAP document, will be made prior to Database Freeze (unblinding) of the study data.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

To evaluate the following objectives in patients with mCRC receiving TAS 102 in combination with nivolumab:

3.1.1. Primary Objective

- To estimate the immune-related overall response rate (irORR) of TAS-102 and nivolumab combination therapy in mCRC patients

3.1.2. Secondary Objective

- To confirm the recommended Phase 2 dose for the combination therapy of TAS 102 and nivolumab.
- To assess the safety of TAS 102 and nivolumab given as combination therapy.
- To estimate the ORR using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.
- To estimate the PFS based on immune-related response criteria (irRC) and RECIST.
- To estimate the disease control rate (DCR) using irRC and RECIST.
- To estimate the OS.

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3.2. Study Endpoints

3.2.1. Primary Endpoints

The primary efficacy endpoint is to estimate immune-related overall response rate (irORR) which is defined as the incidence of complete (irCR) and partial (irPR) responses in the efficacy population.

3.2.2. Secondary Endpoints

Secondary endpoints will include:

- DLTs of the combination therapy
- Incidence of AEs and laboratory test abnormalities
- RECIST ORR defined as the incidence of complete (RECIST CR) and partial (RECIST PR) responses in the efficacy population
- PFS defined as the time from the first dose of study drug to disease progression based on irRC and RECIST in the efficacy population
- DCR defined as the incidence of no-PD patients, based on the irRC and RECIST in the efficacy population
- OS defined as the time from the first dose to death in the safety population. Patients alive at the time of study discontinuation will be censored. Additional censoring rules will be defined in the SAP.

4. STUDY DESIGN

4.1. Summary of Study Design

This is a multi-center, single arm, safety lead-in, Phase 2 study evaluating the safety and efficacy of TAS-102 plus nivolumab in patients with MSS refractory mCRC.

Patients will undergo screening to assure eligibility. Screening will include confirmation of MSS status based on an analysis of either archived or fresh biopsy tissue.

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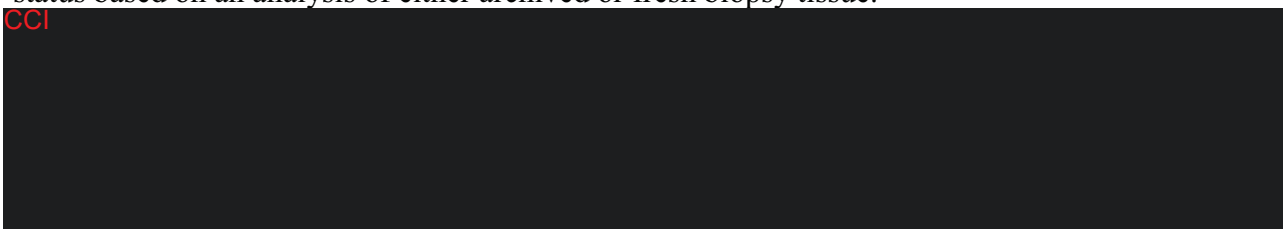

The study is a Simon's 2-stage design. Patients who are eligible will be enrolled sequentially in the following stages:

Stage 1: The first 6 patients will be enrolled and after Cycle 1 treatment, they will be evaluated for the safety and tolerability of the combination therapy. TAS-102 and nivolumab are not expected to have significant overlapping toxicities. A safety team comprised of the medical monitor and treating investigators will review safety data from these first 6 patients after they have undergone Cycle 1 treatment. If 2 or more patients experience a dose-limiting toxicity (DLT), then the dose of TAS-102 will be reduced (after discussion between the investigator and Sponsor) and an additional 6 patients will be enrolled. If the DLT is considered related to TAS 102, the investigator should follow the recommended dose modifications in Section 8.2.4. If the DLT is considered related to nivolumab, the investigator should follow the discontinuation/withhold criteria listed in Section 8.2.6. If the DLT relationship is unclear to either TAS-102 or nivolumab, but is not disease related, then both TAS-102 and nivolumab should be interrupted and the TAS-102 dose should be reduced at the next dose cycle.

Accrual will not be halted while the review is being conducted if no DLTs are identified. Any outcome of this safety review will be communicated in a timely manner to the participating investigators so that they may notify their Institutional Review Boards (IRBs).

Assuming a tolerated dose is confirmed (up to 1 DLT in 6 patients), at least 9 additional patients evaluable for response will be enrolled and followed for a minimum of 6 months. At the point that the ninth patient is enrolled (or a total of at least 15 patients evaluable for response assessment at the target dose), enrollment will stop, and there will be an interim analysis to assess the safety and efficacy to determine whether the second stage will open for enrollment. To proceed to Stage 2, two or more patients out of the 15 patients in Stage 1 will need to demonstrate a PR or complete response (CR) within a 6 month tumor follow-up period. If there are fewer than 2 responders in Stage 1, then the study will be stopped.

Stage 2: An additional 10 patients evaluable for response assessment will be enrolled and followed for a minimum of 6 months.

The following TAS-102 related AEs will be considered DLTs (only AEs occurring in Cycle 1 will be DLT evaluable):

Hematological toxicities

1. Grade 4 neutropenia lasting > 7 days
2. Grade 4 febrile neutropenia and fever ≥ 38°C for over 1 hour
3. Grade 4 thrombocytopenia or grade 3 thrombocytopenia associated with bleeding or requiring transfusions

Non-hematological toxicities

1. Grade 3 or grade 4 non-hematologic toxicity (excluding alopecia, nausea, vomiting, diarrhea)
2. Grade 3 or grade 4 nausea/vomiting lasting > 48 hours and uncontrolled by aggressive anti-emetic therapy, including serotonin 5-HT3 receptor antagonists (e.g., ondansetron)
3. Grade 3 or grade 4 diarrhea lasting > 48 hours and unresponsive to antidiarrheal medication

Drug-related toxicities

1. Any drug-related toxicity resulting in > 2 weeks delay in initiation of Cycle 2 (ie, cannot start Cycle 2 until Day 43 or later)
2. Any drug-related toxicity that prevents completion of 80% compliance for either drug in Cycle 1

The combination of TAS-102 and nivolumab is expected to trigger immune mediated responses, which require activation of the immune system before the observation of clinical responses. Such immune activation may take weeks to months to become evident. Some patients may have an objective volume increase of tumor lesions or other disease parameters within weeks after the start of dosing. Such patients may not have had sufficient time to develop immune system activation or, in some patients, tumor volume or other disease parameter increases may represent infiltration of lymphocytes into the original tumor. Therefore, tumors will be evaluated with both RECIST and irRC to determine objective responses.

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, repeated every 4 weeks. Nivolumab (3 mg/kg/dose) will be administered intravenously over 60 minutes every 14 days on Day 1 and Day 15.

A contrast-enhanced computed tomography (CT) scan of the chest and abdomen (pelvis if clinically indicated) within 28 days before Day 1 of Cycle 1 and every 2 cycles thereafter will be performed during study treatment. On-site tumor assessments will be performed by the investigator or local radiologist. Tumor assessments will be analyzed using RECIST and irRC. 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 before the start of new anticancer therapy. Patients that discontinue treatment for reasons other than disease progression should continue to be followed for tumor response every 2 cycles until the patient develops radiologic disease progression (or death) or initiation of new anticancer therapy (whichever occurs first). Tumor assessments should be performed according RECIST and irRC. If the CT scan was obtained

before the patient signed the informed consent form (ICF), the CT scan may be used if the date of the scan is within 28 days before Day 1 of Cycle 1.

Survival status (alive or dead) should be obtained at scheduled 8-week time intervals until study discontinuation criteria are met.

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

Table 2: Study Schedule

	Baseline Period		On-Treatment Period								End of Treatment/ End of Study Period		
	Baseline Day		CYCLE 1 Day of Cycle[2]				SUBSEQUENT CYCLES Day of Cycle[2]						
Visit ID / Procedure	**-28 to -1**	**-7 to -1**	**1**	**12**	**15**	**End of Recovery**	**1**	**12**	**15**	**End of Recovery**	**End of Treatment[1]**	**30-Day Safety Follow-up Visit[2]**	**Survival Follow-up**
Sign ICF	X[3]												
Enrollment	X[4]												
Medical History	X												
Histological Confirmation	X												
Physical Examination[5]		X					X[6]				X	X	
Baseline Signs and Symptoms		X											
Height		X											
Vital Signs[7]		X					X[6]				X	X	
Weight		X			X		X[6]		X		X	X	
ECOG Performance Status[8]	X		X		X		X[6]		X		X	X	
Hematology[9]		X			X		X[6]		X		X	X	
Serum Chemistry[9]		X			X		X[6]		X		X	X	
Urinalysis[9]		X											
Pregnancy Test[10]		X									X	X	
Tumor Measurements[11]	X									X[11]	X[11]		X[11]
Concomitant Medications[12]	X	→	→	→	→	→	→	→	→	→	→	→	X[13]
AE/SAE Assessment[14]	X	→	→	→	→	→	→	→	→	→	→	→	
TAS-102 Treatment[15]			X D 1-5	X D 8-12			X D 1-5	X D 8-12					
Nivolumab –every 2 weeks			X		X		X		X				
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Table 2: Study Schedule (Continued)

Visit ID / Procedure	Baseline Period		On-Treatment Period								End of Treatment/ End of Study Period		
			CYCLE 1				SUBSEQUENT CYCLES						
	Baseline Day		Day of Cycle[2]				Day of Cycle[2]						
	-28 to -1	-7 to -1	1	12	15	End of Recovery	1	12	15	End of Recovery	End of Treatment[1]	30-Day Safety Follow-up Visit[2]	Survival Follow-up
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Survival Status			→				→				→		X[18]

[1] End of Treatment: Assessments will be performed at time of treatment discontinuation of both study drugs (TAS-102 and nivolumab). If the decision to discontinue study drugs 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 drugs 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 and the information at the End of Treatment visit will be entered into the 30-day Safety Follow-up visit.

[2] Assessment Windows: A window of ± 3 days is allowable for study procedures (± 7 days allowable for computerized tomography [CT] scans), as long as the proper order is maintained.

[3] Sign Informed Consent Form (ICF): Written informed consent should be obtained before the performance of any study procedure.

[4] Enrollment: Enroll patient by entering baseline data into the electronic case report form in order to receive a unique 6-digit patient number.

[5.] Physical Examination: Beginning with Cycle 2, and for all subsequent cycles, perform a physical examination within 24 hours before Day 1 study drug administration.

[6.] Subsequent Cycles ≥ 2: Obtain within 24 hours before Day 1 study drug administration. Before starting subsequent cycles, verify that patients with toxicities have met resumption criteria before administering study drug.

[7.] Vital Sign Measurements: Blood pressure, heart rate, body temperature, respiratory rate; beginning with Cycle 2, and for all subsequent cycles; collect within 24 hours before Day 1 study drug administration.

[8.] ECOG Performance Status: Collect within 24 hours before Day 1 and Day 15 study drug administration for all cycles.

[9.] Hematology, Serum Chemistry, Urinalysis: Hematology and serum chemistry will be performed at baseline (within 7 days before Day 1 of Cycle 1), Day 15 Cycle 1 and Day 1 and Day 15 of each subsequent cycle before administration of study drug. Urinalysis is required at Baseline and thereafter as clinically indicated. Laboratory test results obtained before signing ICF may be used if the results were obtained within 7 days before Day 1 of Cycle 1.

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

[11.] Tumor Measurements: Obtain a contrast-enhanced CT scan of the chest and abdomen (and pelvis, if clinically indicated) within 28 days before Day 1 of Cycle 1 and every 2 cycles thereafter during study treatment. If a patient discontinues treatment because of 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 before 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 2 cycles 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 Response

Evaluation Criteria in Solid Tumors [RECIST] (version 1.1) as well as immune-related response criteria (irRC). Computerized tomography scans obtained before signing the ICF may be used if the date of the scan is within 28 days before Day 1 of Cycle 1.

[12] Concomitant Medications: Collect concomitant medications from time of signed ICF through the 30-day Safety Follow-up visit, including any medications used to treat adverse events (AEs) or serious AEs (SAEs). At the 30-day safety follow-up period, collect date of initiation of any new anticancer therapy.

[13] Concomitant Medications: Collect anticancer therapies.

[14] AE/SAE Assessment: Monitor patients for any untoward medical events from the time of signed ICF through the 30-day safety follow-up period or until initiation of new anticancer treatment, whichever comes first.

[15] Study Drug Treatment: Patients will be dispensed with sufficient quantities of TAS-102 to self-administer twice daily on Days 1 through 5 and 8 through 12 of each cycle. Patients will be instructed to return all unused TAS-102 and used kits to their next clinic visit. Nivolumab will be administered intravenously once

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[18] Survival Status: Obtain survival status (alive/dead) at scheduled 8-week time intervals until study discontinuation criteria are met.

1. Abbreviations: AE = adverse event; ECOG = Eastern Cooperative Oncology Group; ICF = informed consent form; SAE = serious adverse event.

4.2. Sample Size Considerations

4.2.1. Sample Size Justifications

Sample size considerations are based on a 2-stage minimax Simon's design, testing a null hypothesis (poor response) of 10% or less immune-related overall response (irOR) versus an alternative hypothesis (promising response) of 30% or greater irOR at an approximate 5% 1-sided significance level and 80% power. In Stage 1 (futility assessment), enrollment will include 15 evaluable patients for irOR assessment and accrual will continue to Stage 2, if at least 2 of 15 (13%) patients respond (PR or CR). The probability of early stopping assuming poor response is about 55%. In Stage 2, if the Stage 1 futility boundary is exceeded, an additional 10 patients evaluable for irOR assessment will be enrolled, for a total of at least 25 evaluable patients. Further development will be considered promising if at least 6 of 25 (24%) patients respond.

If the initial dose is not tolerated in the first 6 patients in Stage 1, an additional 6 DLT-evaluable patients will be enrolled at the reduced dose. Assuming a 10-15% non-evaluability for DLT and/or irRC assessment rate, a total of 30 to 35 patients is expected to be enrolled in the study.

4.3. Randomization

No randomization will be performed because it is the single arm Study.

4.4. Clinical Assessments

4.4.1. Height, Weight and Vital Signs

Patient's vital signs (blood pressure, heart rate, body temperature, and respiration rate), height and body weight will be collected at the time points presented in the Study Schedule (Table 2). All the vital signs will be taken in a position that is consistent for all time points for each patient.

4.4.2. ECOG Performance Status

An ECOG performance status score will be collected at the following time points (refer to Table 2):

- Within 28 days before study drug administration on Day 1 of Cycle 1
- Obtain within 24 hours before the start of study drug administration on Day 1 in every cycle and Day 15
- End of Treatment visit (if applicable)

- 30-day Safety Follow-up visit

4.4.3. Laboratory Evaluations

Clinical laboratory assessments will include hematology, serum chemistry and urinalysis tests described below.

4.4.3.1. Hematology

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

- Within 7 days before Day 1 of Cycle 1 (Laboratory results obtained before signing the ICF may be used if the results were obtained within 7 days before Day 1 of Cycle 1.)
- Day 15 of each cycle
- Beginning with Cycle 2, obtain blood samples within 24 hours before the start of study drug administration on Day 1 of every cycle
- End of Treatment visit (if applicable)
- 30-day Safety Follow-up visit

In addition, the criteria for repeat testing will be followed as needed. Hematology parameters that will be measured are listed in Section 11.3.1.

4.4.3.2. Serum Chemistry

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

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

Hematology parameters that will be measured are listed in Section 11.3.2.

4.4.3.3. Urinalysis

Urine samples for qualitative (dipstick) analysis will be collected to run tests for protein, glucose, urobilinogen, red blood cell count, and white blood cell count, at the time points listed below:

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

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

5. PLANNED ANALYSES

5.1. Interim Analyses

An interim analysis for efficacy and futility is planned for the study after Stage 1 enrollment is completed. At the point that at least 15 patients are enrolled evaluable for response assessment at the target dose, enrollment will stop, and there will be an assessment of safety and efficacy to determine whether the second stage of an additional 10 patients evaluable for response will be enrolled.

5.2. Final Analyses

Final analysis (once the decision is made to proceed with Stage 2) will be performed according to the instructions presented in the current version of SAP

6. STUDY POPULATIONS

6.1. Safety Population

The "Safety (SAF) Population" is defined as all subjects who receive at least one dose of study medication. This population will be used in the assessment and reporting of safety data.

6.2. DLT Evaluable (DLTE) Population

DLT Evaluable (DLTE) Population is defined as all subjects in the safety population in Stage 1, prior to confirming the recommended dose, who completed at least 1 cycle (28 days) of study treatment with at least 80% of the study treatment administered, unless the treatment was interrupted because of a DLT.

6.3. Efficacy Population

Efficacy Population is defined as all subjects in the safety population who completed at least 6 months of tumor follow-up (evaluable irRC and/or RECIST assessments), unless the patient progressed or died before the 6-month follow-up. This population will be used for efficacy analyses.

7. DERIVED AND TRANSFORMED DATA

7.1. Age (relatively to the first dose taken)

Subject's age in years (whole number, no decimals) will be calculated using date of the first dose taken as the reference point. An appropriate SAS expression recommended by SAS Institute for calculation of a correct age of a person will be applied to calculate the age. The expression is supposed to take into account leap years and other peculiarities of the Gregorian calendar. The formula reads as follows:

Age (year) = INT(INTCK("MONTH", date of informed consent – date of birth)/12)

IF MONTH(date of birth) = MONTH(date of informed consent)

THEN Age = Age - (DAY(date of birth) > DAY(date of informed consent));

where INT( ) function (SAS) returns the integer part of the result, INTCK("MONTH", DATE2 – DATE1) function (SAS) returns a number of months between DATE1 and DATE2, MONTH( ) and DAY( ) – standard SAS functions returning month and day of the month of the argument, correspondingly.

7.2. Study Day

If the date of interest (e.g., start of the cycle #*i*, onset of SAE, lab test date, etc.) occurs on or after the first dose date then study day will be calculated as (date of interest – date of first dose) + 1. If the date of interest occurs prior to the first dose date then study day will be calculated as (date of interest – date of first dose). There will be no study day 0.

7.3. Baseline

Baseline assessment is defined as the last valid/non-missing measurement obtained prior to administration of the first dose of study medication. If the time of the medication and/or time of the assessment is not available, baseline is defined as last valid measurement obtained prior to or on the date of administration of the first dose of study medication

If the multiple results are available that were obtained at the same date and there is no reasonable way to uncover their chronological order, the average value will be used as a baseline (for continuous variables).

All recorded valid data will be considered for analysis of baseline values (including test performed at unscheduled visits).

7.4. Change From Baseline

Change from baseline is calculated as (post-baseline result – baseline result).

Percent change from baseline is calculated as (change from baseline/baseline result * 100).

If either the baseline or the post-baseline result is missing, the change from baseline and/or percentage change from baseline is set to missing as well.

7.5. Day 1

The date of first administration of study medication (first dosing) is defined as Day 1 of treatment (D1). The date of first administration of study medication (first dosing) within the Cycle N is defined as Day 1 of the Cycle N (CND1).

7.6. End of Study Day

If the date of End of Study (EOS) occurs on or after the first dose date then EOS day will be calculated as (EOS date – date of first dose) + 1. If the EOS date occurs prior to the first dose date then EOS day will be calculated as (EOS date – date of first dose).

7.7. Visit Windows

Windows mentioned in the protocol of the present study are used for operational purposes only and they will not be utilized for any analysis.

For the purpose of analysis lab tests, vital examinations, ECOG performance status, tumor assessments, etc. will be assigned to an appropriate cycle according to the start date of this cycle and the start date of the next one. In general, Cycle N will be defined as all days starting with Day 2 of the Cycle N until the Day 1 (including) of the Cycle (N+1). Detailed instructions how an assignment should be performed will be presented under the "Data Handling and Programming Specifications" document.

For the purpose of presentation of AE and/or CM in the listings an assignment to the appropriate cycle will be performed. In general, Cycle N will be defined as all days starting with Day 1 of the Cycle N till the day (including) before Day 1 of the Cycle (N+1). For the last cycle a standard 30 days window after the last dose will be applied. Detailed instructions how an assignment should be performed will be presented under the "Data Handling and Programming Specifications" document.

7.8. Multiple Assessments

When valid multiple assessments within the same cycle (refer to) are available their presentation will depend on the specific output. Detailed instruction for analysis will be presented in the "Data Handling and" document.

8. GENERAL ANALYSIS

8.1. Subject Disposition

A complete accounting of subject participation in the study will be presented according to requirements provided by ICH Guideline for Industry, 1996 (Structure and Content of Clinical Study Reports [CSR]). The purpose of this table is to track subjects from informed written consent through their exit from the study and to account for subject evaluation in major analyses of efficacy and safety, including reasons for early study termination or withdrawal.

8.2. Dose-Limiting Toxicity

The following TAS-102 related AEs will be considered DLTs (only AEs occurring in Cycle 1 will be DLT evaluable):

Hematological toxicities

1. Grade 4 neutropenia lasting > 7 days.
2. Grade 4 febrile neutropenia and fever ≥ 38°C for over 1 hour.
3. Grade 4 thrombocytopenia or grade 3 thrombocytopenia associated with bleeding or requiring transfusions.

Non-hematological toxicities

1. Grade 3 or grade 4 non-hematologic toxicity (excluding alopecia, nausea, vomiting, diarrhea).
2. Grade 3 or grade 4 nausea/vomiting lasting > 48 hours and uncontrolled by aggressive anti-emetic therapy, including serotonin 5-HT3 receptor antagonists (e.g., ondansetron).
3. Grade 3 or grade 4 diarrhea lasting > 48 hours and unresponsive to antidiarrheal medication.

Drug-related toxicities

1. Any drug-related toxicity resulting in > 2 weeks delay in initiation of Cycle 2 (i.e., cannot start Cycle 2 until Day 43 or later).
2. Any drug-related toxicity that prevents completion of 80% compliance for either drug in Cycle 1.

8.3. Demographic and Baseline Characteristics

The demographic and baseline characteristics will be summarized and tabulated. The list of characteristics that will be summarized include but are not limited to the following:

- Gender

- Age (years) (#)
- Age group (<65 years, >=65 years)
- Race (White, Black, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Not Collectable, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Collectable, Unknown)
- ECOG status at baseline (0, 1)
- Height (cm) (#)
- Weight (kg) (#)
- BSA (m^2) (#)

(#) indicates a continuous variable to be summarized.

8.4. Subject Inclusion and Exclusion Criteria

Information regarding subject's inclusion and exclusion criteria will be listed on an individual subject basis.

Patients who were dosed but have not met all inclusion and/or exclusion criteria will be identified and listed and inclusion/exclusion criteria that were not met.

Listings only.

8.5. Medical History

8.5.1. Cancer Medical History

- Primary Cancer Type (colon, rectum, colorectal)
- Location of primary tumor (Cecum, Ascending colon, Transverse colon, Descending Colon, Sigmoid colon, Rectum, Unknown, Other)
- Histology type (refer to appropriate CRF page)
- Time from initial diagnosis to the first dose (#)
- Time from confirmed first metastases to the first dose (#)
- Number of metastatic sites (1-2, ≥3)
- RAS status at baseline (Wild, Mutant)
- KRAS status at baseline (Wild, Mutant)
- NRAS status at baseline (Wild, Mutant)
- BRAF status at baseline

8.5.2. Non-Cancer Medical History

All information regarding subjects non-cancer medical history will be presented in the listings only.

8.6. Prior, Concomitant, and Survival Follow-up Medications and Therapies

8.6.1. Prior Anti-Cancer Therapies

Prior anti-cancer therapies will be summarized for the safety population and will include the following:

- Number of prior regimens (<2, 2, 3, 4≤)
- Prior surgery (Yes, No)
- Prior Radiotherapy (Therapeutic, Palliative, None)

8.6.2. Prior and Concomitant Medications

Prior and concomitant medications will be listed for the safety population. All concomitant medications and therapies will be coded using WhoDDE (September 2015) and summaries will use the system organ class and preferred term codes, as appropriate.

8.6.3. Post-study Anti-cancer Treatment

Post-study anti-cancer treatments initiated during the follow-up period (ref Figure 2) will be listed. The time to start of the new anti-cancer treatment will be defined as the start date of the new anti-cancer therapy minus the date of last dose of study medication + 1. If the start date of the new anti-cancer treatment is missing, the time to start of anti-cancer therapy will be missing for that patient.

8.7. Exposure to Study Medication

Exposure will be summarized and tabulated for the safety population for each study drug. Study drug administration for number of cycles initiated will be summarized by cycle and overall for each study drug. Dose level by cycle will be summarized for each study drug. Patients with at least one dose reduction and first cycle with target dose reduction will be summarized for each study drug. The total dose administered (mg/m^2), dose intensity (mg/m^2/wk), relative dose intensity (ratio to planned) will be summarized.

9. EFFICACY ANALYSES

9.1. General Considerations

The efficacy analyses of antitumor study therapy will be based on objective tumor assessments made by the investigator/local radiologist according to the irRC and revised RECIST criteria of unidimensional evaluation. The reporting tables/listings will be presenting both sets of the criteria.

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9.3. Primary Efficacy Endpoint

This Section will present instructions for statistical analysis and presentation of primary efficacy endpoint.

9.3.1. Immune Related Overall Response Rate

The primary efficacy point (irORR) will be defined as the proportion of incidence of confirmed complete (irCR) and partial (irPR) responses (if any) in the efficacy population. irCR and irPR will be listed.

9.4. Secondary Efficacy Endpoints

This section will describe ways of statistical analysis and presentation of the secondary efficacy endpoints.

9.4.1. RECIST ORR

This efficacy endpoint (RECIST-based ORR) will be defined as the incidence of complete (CR) and partial (PR) responses (if any) in the efficacy population, where the responses are based on RECIST criteria. CR and PR will be listed.

9.4.2. Immune-related Progression-Free Survival (irPFS)

Immune-related progression free survival is defined as the time (in months) from the date of first dose of TAS-102 until the date of the investigator-assessed radiological disease progression (based on irRC) or death due to any cause. Patients who are alive with no disease progression at the moment of the analysis cut-off date will be censored at the date of the last tumor assessment. Patients with clinical but not radiologic evidence of progression will be censored at the date of the last radiologic tumor assessment. An additional analysis using clinical progression as an event will be performed in addition to the main examination described above.

PFS in the safety population will be summarized using Kaplan Meier estimates and further characterized in terms of the median and survival probability at 2, 4, 6, 8 months, along with the corresponding 2-sided 95% CI for the estimates. Confidence intervals for median survival are based upon the methods of Brookmeyer and Crowley.

9.4.3. RECIST Progression-Free Survival (RECIST PFS)

RECIST-based progression free survival is defined as the time (in months) from the date of first dose of TAS-102 until the date of the investigator-assessed radiological disease progression (based on RECIST 1.1) or death due to any cause. Results will be summarized in the same manner as it was described in Section 9.4.2 above for the irPFS.

9.4.4. Disease Control Rate (DCR)

Disease Control Rate will be presented for immune response evaluation and RECIST-based evaluation. DCR is defined as the proportion of patients with objective evidence of radiologic CR, PR or SD and is based on the Overall Best Response from each patient as determined from investigator response assessments. Disease control rate (DCR) will be analyzed using the same methodology as that for ORR.

9.4.5. Overall Survival (OS)

Overall Survival (OS) is defined as the time from the first dose of the study treatment to the death in the safety population. Patients alive at the time of the study discontinuation will be censored. Survival results will be listed only.

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11. SAFETY AND TOLERABILITY

11.1. Adverse Events

11.1.1. Definition of Adverse Event

An *adverse event* (AE) is defined as any untoward medical occurrence in a clinical investigation of a patient that may or may not have casual relationship with treatment (21 CFR 312.32(a)). An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the clinical study, independent of the relationship to the investigational product.

Any AE that started after signing of informed consent and before treatment start date will be presented in the Medical History section of the summary tables.

Any adverse event starting more than 30 days after the last dose of study medication will be excluded from the summary analyses, unless the event caused patient discontinuation from the study.

11.1.2. Definition of Treatment Emergent Adverse Event

Treatment-emergent adverse events (TEAEs) will be defined as those events, which meet one of the two criteria:

- started on or after treatment start date (first dose of study medication ⇔ Cycle1, Day 1) through 30 days after treatment end date (last dose of study medication)
- started before treatment start date and became worse (more severe) after treatment start date (first dose of study medication ⇔ Cycle1, Day 1) through 30 days after treatment end date (last dose of study medication)

Only treatment-emergent adverse events will be summarized, non-treatment emergent AEs will be listed only.

11.1.3. Definition of Serious Adverse Event

SAE, as per FDA regulations defined in 21 CFR 312.32(a), is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant /incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may or may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

If either the Sponsor or Investigator believes that the event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting (21 CFR 312.32(a) and 312.32(c)(1)).

11.1.4. Definition of Treatment Emergent Adverse Event of Special Interest

The TEAEs of special interest (TEAESI) will be selected based on the list of appropriate MedDRA terms provided by the Sponsor. The TEAESI will include, but will not be limited by, following items: Hepatobiliary Abnormality-Related, Renal Impairment, Hematologic Impairment-Related or Infection-Related adverse events. The full list will be provided before the database of the study is locked. The lists of terms (PTs) will be located in Appendices.

11.2. Summaries of Adverse Event

All adverse event verbatim text will be coded and classified by system organ class (SOC) and preferred term (PT) using the MedDRA (Version 18.1). AE summary tables will use the following algorithms for counting subject events within the summary tables:

- Preferred term rows: Each subject is counted once within each unique preferred term at the maximum grade. Subjects experiencing the same AE preferred term several times with different grades would only be counted once with the maximum grade.
- System organ class rows: Each subject is counted only once in the maximum grade at each system organ class level, although they may have several different preferred term events within the same SOC.
- Any event row: Each subject with an event is counted only once at the maximum grade although they may have several events. For drug related AE table, each subject with an event is counted only once at the most related although they may have several events.

Unless specified otherwise, the summaries of adverse events will be based on the safety population.
TEAEs will be presented in alphabetical order of System Organ Class and within each System Organ Class, in decreasing order of the total number of combined TAS-102 patients who experienced each TEAE at the preferred term level.

11.2.1. Overview of Adverse Events

AE incidence will be calculated by the worst CTCAE grade at every level of summarization (SOC or PT), i.e., if a patient has multiple occurrences of the same AE with different toxicity grades during a period, the patient will be accounted for in AE frequency tabulation in the worst grade. An overall summary table (overview) of all adverse events will be presented, summarizing:

- Total number of TEAE
- Total number of TESAE
- Total number of DLT
- Total number and percentage of subjects with at least one TEAE

- Total number and percentage of subjects with at least one TEAE, related to either TAS-102 or Nivolumab
- Total number and percentage of subjects with at least one TEAE, related to TAS-102
- Total number and percentage of subjects with at least one TEAE, related to Nivolumab
- Total number and percentage of subjects with at least one DLT
- Total number and percentage of subjects with at least one TESAEs
- Total number and percentage of subjects with at least one related TESAE, related to either TAS-102 or Nivolumab
- Total number and percentage of subjects with at least one TESAE, related to TAS-102
- Total number and percentage of subjects with at least one TESAE, related to Nivolumab
- Total number and percentage of subjects with at least one severe (Grades 3 - 5) TEAE
- Total number and percentage of subjects with at least one TEAE leading to dose modification
- Total number and percentage of subjects with at least one TEAE leading to discontinuation of the study treatment
- Total number and percentage of subjects with at least one TEAE leading to death

11.2.2. Summaries of Adverse Events

The primary AE summary will also be all TEAE by SOC and PT regard to the relationship to study medication (SAF population).

In addition to the overview table, a number of the summaries will be created. The primary AE summary will tabulate all TEAEs by SOC and PT (Safety population and CCI - Section 4.1). Other summaries will present various aspects of collected AEs. Calculations in the tables will follow the basic principles of counting described in the beginning of Section 11.2. The following summaries will be created:

- TEAEs (all and grades 3-5) summarized by SOC and PT (SAF population)
- TEAEs (all and grades 3-5) related to study drug summarized by SOC and PT, (two separate table – for TAS-102 and Nivolumab; SAF population)
- TEAEs summarized by SOC and PT, by CTCAE grades (SAF population)
- TEAEs (all and grades 3-5) leading to dose modification summarized by SOC and PT (SAF population; listing only)
- TEAEs (all and grades 3-5) leading to treatment discontinuation summarized by SOC and PT (SAF population; listing only)

- TEAEs (all and grades 3-5) leading to death summarized by SOC and PT (SAF population; listing only)
- Serious TEAEs (all and grades 3-5) summarized by SOC and PT (SAF population)
- Serious TEAEs (all and grades 3-5) related to study drug summarized by SOC and PT, (two separate table – for TAS-102 and Nivolumab; SAF population)

11.2.3. DLT of the Combination Therapy

Dose-Limiting Toxicity are defined according to the criteria described in the Study Protocol. All DLT results (if any) will be presented in the form of listings.

11.3. Clinical Laboratory Data

All laboratory values will be converted to SI units and classified as normal, low, or high based on normal ranges (converted to SI units if needed) supplied by the laboratory performed the test. Laboratory categories will be expressed in terms of the L (below LLN), N (between LLN and ULN) and H (above ULN) classifications for numerical measurements and normal, abnormal for characteristic measurements. Additionally, abnormal laboratory values will be presented according to the NCI CTCAE v4.3 laboratory toxicity grades. All laboratory data will be coded with CTCAE grade, where CTCAE grading is available. Local laboratory ranges will be used for grading. In the event a range is not available a standard set of lab ranges as detailed in [redacted] will be utilized and flagged in the database.

Changes in the NCI CTCAE grade from baseline to the worst grade recorded post-baseline (by visit and overall) will be tabulated in the form of shift tables. Applicable bi-directional laboratory tests will be represented by two one-directional separate tests (hypo- and hyper-). The definition of hypo- and hyper-toxicity grades follows the definition provided by the NCI CTCAE v4.3 definition document. Laboratory tables with CTCAE grading will only be produced for laboratory parameters for which CTCAE grading is available. An overall shift summary will also be provided comparing baseline to worst post-dose toxicity observed across all visits.

The number and percentage of patients with laboratory abnormalities of Grade 3 or Grade 4 that worsened from baseline by ≥ 1 grade or are missing at baseline will be summarized. For patients with more than 1 value recorded in a cycle/group of cycles, the abnormality with the highest grade will be selected for tabulation.

If multiple results of an arbitrary test of clinical labs are reported for within analysis window then the reported value will be derived as follows (hypo- and hyper- directions for bi-directional tests will be presented separately):

- For CTCAE Laboratory Toxicity Grade the result with the highest CTCAE grade will be reported. If there are two or more results of the same CTCAE grade then the

largest/smallest result will be used for summary tables. If there are two or more results of the same CTCAE grade and the same values then the latest result will be used.

- For the following clinical lab tests (Hematocrit - having no appropriate CTCAE grading) the result with the largest/smallest (i.e., most abnormal) value will be reported in hyper/hypo one-directional version of the test, correspondingly. If there are two or more results showing the same value then the latest result will be used.
- For other bi-directional clinical lab tests the result with the abnormal value will be reported in final output. If there are two or more abnormal results then the latest result will be used
- For one-directional clinical lab tests the result with the most abnormal value (largest/smallest – depending on test direction) will be reported in final output. If there are two or more abnormal results showing the same value then the latest result will be used.

All observed (including unscheduled) laboratory parameters will be listed. The supportive listings for hematology, serum chemistry, and urinalysis will include the subject number, subject age and sex; laboratory test, lab test units, lab test result, and the lower and upper limits of normal (provided by the local laboratory where the test was performed); sample collection date, time of collection, and relative day; type of visit. The listing will be sorted by laboratory parameter, subject number, and by time points within laboratory parameter and subject number. Abnormal results will be flagged based on the categories mentioned above.

11.3.1. Hematology

The following tests (Table 4) will be summarized and tabulated, all other hematology tests will be listed only:

Table 3: Hematology Laboratory Parameters

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

11.3.2. Serum Chemistry

The following tests (Table 4) will be summarized and tabulated, all other serum chemistry tests will be listed only:

Table 4: Serum Chemistry Laboratory Parameters

ALT	Creatinine	Chloride
AST	Blood urea nitrogen	Calcium
Alkaline phosphatase	Sodium	Albumin
Bilirubin	Potassium	Glucose
Thyroid stimulating hormone	Thyroxine 4 (T4)	

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

11.3.3. Urinalysis

Urinalysis (qualitative [dipstick] analysis) will include tests for protein, glucose, urobilinogen, RBC, and WBC. If a new abnormality is identified during the Study, quantitative urinalysis should be performed.

11.4. Vital Signs, Height, Weight

Height, weight and vital signs will be listed only. Vital signs (VS) will include: systolic/diastolic blood pressure, body temperature, heart rate and respiratory rate.

11.5. Physical Examination

According to the recent updates in CDISC “Guide for implementation” the results of physical examination (abnormalities only) are collected as part of adverse events or medical history (based on the appropriate dates and time).

11.6. ECG

ECG data were not collected and will not be analyzed in any way.

12. INTERIM ANALYSIS

An interim analysis for efficacy and futility is planned for the study after Stage 1 enrollment is completed. At the point that the ninth patient is enrolled (or a total of at least 15 patients evaluable for response assessment at the target dose), enrollment will stop, and there will be an assessment of safety and efficacy to determine whether the second stage of an additional 10 patients evaluable for response will be enrolled.

The planned interim analysis will be performed according to the algorithms presented in the current SAP. No separate document (e.g., SAP for Interim Analysis) for the interim analysis will be produced.