CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1a/1b Study of GS-1423, an Anti-CD73-TGFβ-Trap Bifunctional Antibody, as Monotherapy or in Combination with a Chemotherapy Regimen in Subjects with Advanced Solid Tumors
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number:	142793
EudraCT Number:	2019-004938-41
Clinical Trials.gov Identifier:	NCT03954704
Indication:	Advanced solid tumors
Protocol ID:	GS-US-505-5452
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Original: 25 March 2019 Amendment 1: 19 November 2019 Amendment 2: 29 April 2020

This study will be conducted under US Food and Drug Administration IND regulations (21 CFR Part 312); however, sites located in the European Economic Area, United Kingdom, and Switzerland are not included under the IND and are considered non-IND sites.

CONFIDENTIALITY STATEMENT

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
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Study Title:	A Phase 1a/1b Study of GS-1423, an Anti-CD73-TGFβ-Trap Bifunctional Antibody, as Monotherapy or in Combination with a Chemotherapy Regimen in Subjects with Advanced Solid Tumors
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	142793 2019-004938-41 NCT03954704
Study Centers Planned:	Approximately 35 centers in the United States, Europe, and rest of world
Objectives (Phase 1a):	The primary objectives are: • Part A (dose escalation): To assess safety and tolerability and to define the dose limiting toxicity (DLT) and maximum tolerated dose (MTD) or recommended Phase 2 dose (RP2D) of GS-1423 monotherapy in subjects with advanced solid tumors • Part B (flat dose regimens): To assess safety and tolerability of GS-1423 monotherapy in subjects with advanced solid tumors The secondary objectives are: • To characterize GS-1423 pharmacokinetics (PK) • To evaluate GS-1423 immunogenicity CCI [redacted]

Objectives (Phase 1b):

Cohort 1 (gastric cancer): GS-1423 in combination with a chemotherapy regimen in advanced (unresectable, recurrent or metastatic) gastric and gastroesophageal junction adenocarcinoma

For safety run-in, the primary objective is:

- To assess safety and tolerability and to define the DLT and MTD or RP2D of GS-1423 in combination with a chemotherapy regimen in subjects with advanced gastric or gastroesophageal junction adenocarcinoma

For post safety run-in, the primary objective is:

- To assess the preliminary efficacy of GS-1423 in combination with a chemotherapy regimen in subjects with advanced gastric or gastroesophageal junction adenocarcinoma, as determined by the confirmed objective ORR

For post safety run-in, the secondary objective is:

- To assess safety and tolerability of GS-1423 in combination with a chemotherapy regimen in subjects with advanced gastric or gastroesophageal junction adenocarcinoma

CCI [redacted]

Cohort 2 (paired biopsy): GS-1423 monotherapy in subjects with advanced solid tumors accessible for biopsy

The primary objective is:

- To assess safety and tolerability of GS-1423 monotherapy in subjects with advanced solid tumors

CCI [redacted]

Study Design (Phase 1a)

Part A – Dose escalation

This is an open-label, Phase 1a study to evaluate the safety, tolerability, and PK profiles of GS-1423 and to define the DLT and MTD or RP2D of GS-1423 monotherapy in subjects with advanced solid tumors.

This study will be conducted in an accelerated titration, followed by a 3+3 dose escalation design. GS-1423 will be administered on Day 1 of each 2-week cycle (Q2W) for up to 1 year or until any progressive disease (PD) or unacceptable toxicity. The starting dose was selected to be 0.3 mg/kg derived from minimally anticipated biologic effect level (MABEL). A Safety Review Team (SRT) will be established to assess safety and decide on dose escalation.

Starting at Cohort 4 (10 mg/kg), if no DLT is observed during the 28-day DLT observation period in the first 3 subjects, 3 additional subjects may be enrolled at the respective dose level to obtain more safety, PK, CCI [redacted] data. If ≥ 2 subjects have experienced DLTs in the last 3 (of 6) subjects, dose escalation will halt and up to 3 additional subjects will be enrolled at the preceding dose level (if there were only 3 subjects in that cohort) for DLT assessment. If 6 subjects were already evaluated, the preceding dose level will be considered as MTD.

Part B – Flat dose regimens

Part B will consist of up to 3 adaptive cohorts (every week [QW], Q2W and/or, every 3 weeks [Q3W]) to evaluate the safety, tolerability, and PK profiles of GS-1423 monotherapy with flat dose regimens.

	Based on PK, CCI [redacted] and safety results from the Part A study, the target exposures for the Phase 1b study will be determined. Subsequently, 6 to 12 subjects per cohort may be enrolled to explore the flat dose(s) and dosing interval(s) that will achieve the target exposures. The doses evaluated in these subjects will be selected such that they do not result in exposures that are higher than the maximum tolerated exposures and match the exposures for RP2D determined based on the dose escalation portion of the study. Gilead may choose not to initiate any or all of the adaptive cohorts if it is deemed unnecessary.
Study Design (Phase 1b)	This is an open-label, Phase 1b study with 2 cohorts. **Cohort 1 (Gastric)** Cohort 1 will assess safety and tolerability and define the DLT and MTD or RP2D of GS-1423 in combination with a chemotherapy regimen (oxaliplatin, 5-fluorouracil [5-FU], and leucovorin; mFOLFOX6) in subjects with advanced (unresectable, recurrent or metastatic) gastric or gastroesophageal junction adenocarcinoma who have not previously received systemic therapy for advanced disease. Safety run-in: A standard 3+3 dose escalation design will be used to define the DLT and MTD or RP2D of GS-1423 in combination with mFOLFOX6. An SRT will assess safety and decide on dose escalation. After the MTD or RP2D of GS-1423 in combination with mFOLFOX6 has been determined, the cohort will be expanded by adding approximately 70 subjects to explore the potential efficacy. One futility interim analysis may be performed after approximately 50% of subjects have been enrolled and are able to complete study treatment for at least 6 months post safety run-in. **Cohort 2 (Paired Biopsy)** Cohort 2 will assess safety and tolerability of GS-1423 monotherapy in multiple tumor types. Cohort 2 will enroll subjects until 15 evaluable paired tumor biopsies (baseline and any on treatment) have been collected, including a minimum of 5 biopsies from non-small-cell lung carcinoma (NSCLC) (non-squamous adenocarcinoma) and 5 colorectal cancer (CRC) or pancreatic cancer subjects.

Number of Subjects Planned:	Approximately 213 subjects will be enrolled • Phase 1a: (Part A): Up to 53 subjects (Part B): Up to 40 subjects • Phase 1b: Cohort 1: Up to 90 subjects Cohort 2: Up to 30 subjects
Target Population:	Phase 1a (Parts A and B): Subjects who are ≥ 18 years with a histologically or cytologically confirmed diagnosis of a locally advanced or metastatic solid tumor for which no standard therapy is available or standard therapy has failed Phase 1b: Cohort 1: Subjects who are ≥ 18 years with a histologically or cytologically confirmed advanced (unresectable, recurrent or metastatic) gastric or gastroesophageal junction adenocarcinoma who have not previously received systemic therapy for advanced disease Cohort 2: Subjects who are ≥ 18 years with a histologically or cytologically confirmed diagnosis of a locally advanced or metastatic solid tumor for which no standard therapy is available or standard therapy has failed and from whom biopsies can be obtained prior to study treatment and on-treatment
Duration of Treatment:	Phase 1a (all cohorts) and Phase 1b (Cohort 2): Subjects will continue GS-1423 for up to 1 year (maximum 52 cycles for QW, 26 cycles for Q2W and 17 cycles for Q3W) or until the subject meets study treatment discontinuation criteria. Phase 1b (Cohort 1): Subjects will continue GS-1423 for up to 2 years (maximum 52 cycles) or until PD, unacceptable toxicity, substantial noncompliance with study procedures or study treatment regimen, study discontinuation or withdrawal from study. mFOLFOX6 will be administered for up to 12 cycles with the option of maintenance therapy with 5-FU and leucovorin per Investigator's discretion until the subject meets study treatment discontinuation criteria or for up to 2 years (maximum 52 cycles).

Diagnosis and Eligibility Criteria:

Inclusion Criteria:

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study:

1) Voluntarily agree to participate by giving a signed written informed consent
2) Age ≥ 18 years
3) Diagnosis:
    a) Phase 1a and Phase 1b Cohort 2: Have a histologically or cytologically confirmed diagnosis of a locally advanced or metastatic solid tumor for which no standard therapy is available or standard therapy has failed
    b) Phase 1b Cohort 1 (gastric cancer): Have histologically or cytologically confirmed advanced (unresectable, recurrent or metastatic) gastric or gastroesophageal junction adenocarcinoma who have not previously received systemic therapy for advanced disease (perioperative, neoadjuvant, and adjuvant chemotherapy regimens will not count as a prior regimen, unless PD has occurred during or within 6 months of neoadjuvant/adjuvant chemotherapy). Gastroesophageal junction adenocarcinoma is defined as tumors with epicenters no more than 2 cm into the gastric cardia.
        i) Is human epidermal growth factor receptor 2 (HER2)/neu negative
        ii) Has not received prior treatment with an immune checkpoint inhibitor within 2 years of day 1 of study treatment
4) Have measurable disease on imaging based on Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)
5) Have a life expectancy of at least 3 months and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

6) Have adequate organ function as indicated by the following laboratory values:

System	Laboratory Value[a]
Hematological[b]	
Absolute Neutrophil Count (ANC)	≥ 1.5 x 10^9/L ≥ 2 × 10^9/L (for Phase 1b Cohort 1 only)
Platelets	≥ 100 x 10^9/L
Hemoglobin	≥ 9 g/dL
Renal	
Creatinine clearance	≥ 50 mL/min by the Cockcroft-Gault method
Hepatic	
Total bilirubin	≤ 1.5 x ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 x ULN
Coagulation[c]	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤ 1.5 x ULN unless the subject is receiving anticoagulant therapy
Activated Partial Thromboplastin Time (aPTT)	≤ 1.5 x ULN unless the subject is receiving anticoagulant therapy

a All screening laboratory tests must be reviewed by the investigator and be acceptable prior to randomization.
b Hematologic laboratory values must be met at screening visit and maintained without transfusion and growth factors prior to the first study drug dose
c Subjects on full dose oral anticoagulation, must be on a stable dose (minimum duration 14 days). Subjects on low molecular weight heparin will be allowed. In subjects receiving warfarin, the recommended INR is ≤ 3.0 with no active bleeding (ie, no bleeding within 14 days prior to first dose of study drug).

7) Tissue criteria:

   a) Phase 1a and Phase 1b Cohort 1: Subjects must have available, sufficient, and adequate formalin-fixed tumor tissue sample (as specified in the Laboratory Manual) preferably from a biopsy of a tumor lesion obtained either at the time of or after the diagnosis of advanced disease has been made and from a site not previously irradiated. Alternatively, subjects must agree to have a biopsy taken prior to entering the study to provide adequate tissue. Fine needle aspirates are not acceptable. Core

needle or excisional biopsy or resected tissue is required.

b) Phase 1b Cohort 2: Subjects must have a tumor lesion that biopsies can be obtained from prior to treatment and on-treatment. The biopsies for each subject should be taken from the same lesion.

8) A negative serum pregnancy test is required for female subjects (unless permanently sterile or greater than 2 years postmenopausal as described in Appendix 5).

9) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception and refrain from egg or sperm donation as described in Appendix 5.

10) Lactating females must agree to discontinue nursing before the study drug is administered.

11) Is willing and able to comply with the requirements of the protocol

Exclusion Criteria:

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study:

1) Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigation device within 3 weeks of the first dose of treatment

2) Has received prior systemic cytotoxic chemotherapy, biological therapy, radiotherapy, or major surgery within 3 weeks; a 1-week washout is permitted for palliative radiation to non-central nervous system (CNS) disease with Gilead approval

3) Has persisting toxicity related to prior therapy of National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI CTCAE v5.0) Grade > 1 severity

   Note: Alopecia and sensory neuropathy of Grade ≤ 2 is acceptable.

4) Is expected to require any other form of systemic or localized anticancer therapy while on study (including maintenance therapy with another agent, radiation therapy, and/or surgical resection)

5) Has known severe hypersensitivity reactions (NCI CTCAE Grade ≥ 3) to fully human monoclonal antibodies, GS-1423 formulation excipient, or severe reaction to immuno-oncology agents, such as colitis or pneumonitis requiring treatment with corticosteroids, any history of anaphylaxis, or uncontrolled asthma
6) Is receiving systemic corticosteroid therapy 1 week prior to the first dose of study treatment or receiving any other form of systemic immunosuppressive medication

Note: The following corticosteroid uses are permitted: use as premedication for known hypersensitivity reactions (e.g. IV contrast, IV drug infusions); intraocular, intranasal, inhaled, and/or topical corticosteroids; and/or prednisone at doses of up to 10 mg per day or equivalent.

7) Has concurrent active malignancy other than nonmelanoma skin cancer, carcinoma in situ of the cervix, or superficial bladder cancer who has undergone potentially curative therapy with no evidence of disease. Subjects with other previous malignancies are eligible if disease free for > 2 years
8) Has a known CNS metastasis(es), unless metastases are treated and stable and the subject does not require systemic corticosteroids for management of CNS symptoms at least 7 days prior to study treatment. Subjects with history of carcinomatous meningitis are excluded regardless of clinical stability.
9) Has active or history of autoimmune disease that has required systemic treatment within 2 years of the start of study treatment (ie, with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs)

   Note: Subjects with diabetes type 1, vitiligo, psoriasis, hypothyroid disease, or hyperthyroid disease not requiring immunosuppressive treatment are eligible.
10) Has had an allogeneic tissue/solid organ transplant
11) Has or had interstitial lung disease (ILD)
12) Has a serious systemic fungal, bacterial, viral, or other infection that is not controlled or requires IV antibiotics
13) Has known history of human immunodeficiency virus (HIV)
14) Has known active hepatitis B virus (HBV) and/or hepatitis C virus (HCV)

15) Subjects with cardiovascular disease/abnormalities will be excluded per the following criteria:

    a) Has clinically significant (ie, active) cardiovascular disease: cerebral vascular accident/stroke or myocardial infarction within 6 months of enrollment, unstable angina, congestive heart failure (New York Heart Association class ≥ II), or serious uncontrolled cardiac arrhythmia requiring medication

    b) Has a mean QT interval corrected for heart rate using the Fridericia formula (QTcF) ≥ 470 ms

    c) Has systolic dysfunction defined as ejection fraction < 50% measured by echocardiogram (or multigated acquisition [MUGA] scan) at baseline

16) Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator

17) Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study

18) Is legally incapacitated or has limited legal capacity

19) Taking biotin supplements within 72 hours of screening

20) Positive serum pregnancy test (Appendix 5)

21) Has had prior treatment with anti-cluster of differentiation (CD)73 or transforming growth factor beta (TGFβ) therapies

22) Breastfeeding female

23) Phase 1b Cohort 2: Has melanoma

24) Phase 1b Cohort 2: Has any tumor from which 2 biopsies cannot be obtained. Bone biopsies and ascites are not acceptable tumor samples for the study

Study Procedures/ Frequency:

Screening:

Screening will commence with obtaining the subject's signed informed consent and will occur up to 28 days prior to the first dosing of study drug. Screening procedures will include the following: medical history review, physical examination, vital signs, height and weight, 12-lead electrocardiogram (ECG), echocardiogram (or MUGA scan), ECOG performance status, prior/concomitant medication review, blood collection for pregnancy test (females of childbearing potential), serum chemistry, CCI [redacted],

hematology, endocrine function, coagulation, HBV and HCV serology, urinalysis, adverse event (AE) assessment, computed tomography or magnetic resonance imaging, and tumor tissue. For Phase 1b Cohort 2, screening will include an assessment of if 2 biopsies (pretreatment and on treatment) can be obtained from the same lesion. Baseline tumor lesions will be measured and characterized prior to enrollment to assess the subject's disease status prior to beginning treatment.

Treatment

Phase 1a:

Part A Dose escalation

GS-1423 will be administered Q2W with associated evaluations and procedures that must be performed at specific time points. Each cycle begins with the administration of GS-1423 on Day 1 of a 2-week cycle (timing of doses may be adjusted for management of AEs). Subjects will be treated for up to 1 year or until any PD or unacceptable toxicity.

Part B Flat dose regimens

GS-1423 monotherapy may also be evaluated at a flat dose administered QW, Q2W, and/or Q3W. Based on safety data and available PK CCI [redacted] data from Part A, Part B will be initiated at or below the exposures of the highest dose for which data are available from Part A. Part B cohorts may be initiated in parallel with cohorts from Part A of the study if the dose/exposure under evaluation is at or below a dose/exposure that has already been evaluated and considered as safe.

Phase 1b:

Cohort 1 (gastric): GS-1423 will be administered Q2W for up to 2 years or until PD or unacceptable toxicity. The chemotherapy regimen mFOLFOX6 will be administered Q2W for up to 12 cycles. After 12 cycles, subjects may continue to receive 5-FU and leucovorin at the investigator's discretion until the subject meets study treatment discontinuation criteria.

Cohort 2 (paired biopsy): GS-1423 will be administered every 2 weeks (Q2W) for up to 1 year or until PD or unacceptable toxicity. If an alternate dosing schedule is recommended after Phase 1a, this dosing schedule may also be adapted to this cohort.

Tumor Assessment:

Tumor assessments will be conducted at 6, 12, 18, and 24 weeks (± 7 days) from the first treatment and then every 12 weeks thereafter until PD as assessed by investigator, unexpected toxicity occurs, or a new line of therapy is initiated for up to 1 year (Phase 1a and Phase 1b Cohort 2) or 2 years (Phase 1b Cohort 1).

Test Product, Dose, and Mode of Administration:

Phase 1a

Part A Dose escalation

GS-1423 will be administered through IV infusion over 60 minutes. The planned dose cohorts are 0.3, 1, 3, 10, 20, 30, and 45 mg/kg as monotherapy.

The dose escalation will be conducted in an accelerated titration, followed by a 3+3 dose escalation design. At each of the first 2 dose levels of 0.3 mg/kg and 1 mg/kg, if 2 or more drug-related AEs of Grade 2 or higher or at least 1 DLT are observed during the 28-day DLT observation period, the 3+3 escalation scheme will be used at that dose and subsequent doses. Gilead may choose not to enroll any cohort if it is deemed unnecessary.

Part A: GS-1423 Dose Levels and Cohorts

Cohort	No. of Subjects	Escalation Type	Dose of GS-1423 (mg/kg)
1	1 or 3 6	Accelerated titration	0.3
2	1 or 3 6	Accelerated titration	1
3	3 6	3+3	3
4	3 6	3+3	10
5	3 6	3+3	20
6	3 6	3+3	30
7	3 6	3+3	45

An additional 6 subjects may be enrolled at a dose level at or below maximum tolerated dose to obtain additional safety, pharmacokinetics, and CCI information.

Part B Flat dose regimens

After the target exposures for the Phase 1b study has been determined, an additional 6 to 12 subjects per cohort may be enrolled to explore the RP2D at flat dose(s) and dosing interval(s) that will achieve the target exposures from Part A. The doses/schedules evaluated in these subjects will be selected as such that the expected exposures will not exceed the maximum tolerated exposures determined in the dose

escalation portion of the study. Gilead may choose not to initiate any or all of the adaptive cohorts if it is deemed unnecessary.

Part B: GS-1423 Dose Levels and Cohorts

Adaptive Cohort	No. of Subjects	Dose of GS-1423 (mg)
8	6 12	Dose 1 (Q2W)
9	6 12	Dose 2 (QW)
10	6 12	Dose 3 (Q3W)

QW every week; Q2W every 2 weeks; Q3W every 3 weeks

Phase 1b

Cohort 1 (Gastric)

Safety run-in: The planned starting dose of GS-1423 will be targeted to achieve the exposure at -1 dose level of RP2D monotherapy (Q2W) determined from Phase 1a. GS-1423 will be administered in combination with mFOLFOX6.

Phase 1b Cohort 1 Safety Run-in GS-1423 Dose Levels and Cohorts

Regimen	No. of Subjects	Escalation Type	Dose of GS-1423 (mg)
GS 1423 + mFOLFOX6	3 6	3+3	1 Dose 1 Q2W
GS 1423 + mFOLFOX6	3 6	3+3	Dose 1 Q2W

5 FU 5 fluorouracil; Q2W every 2 weeks;
The mFOLFOX6 regimen consists of *l* leucovorin/*dl* leucovorin 200/400 mg/m^2 and oxaliplatin 85 mg/m^2 followed by bolus 5 FU 400 mg/m^2 and a 46 hour infusion of 5 FU 2400 mg/m^2. Administration of mFOLFOX6 will follow administration of GS 1423 on Day 1 of each cycle.
1 Dose 1: Will be targeted to achieve the exposure at 1 dose level of RP2D monotherapy (Q2W) determined based on cumulative data from Phase 1a.
Dose 1: Will be targeted to achieve the exposure at the dose level of RP2D monotherapy (Q2W) determined based on cumulative data from Phase 1a.

An additional 6 subjects may be enrolled at a dose level at or below MTD to obtain additional safety, PK, [redacted] information.

Following the safety run-in, approximately 70 subjects will be enrolled to receive GS-1423 at the dose level determined from the safety run-in period, in combination with mFOLFOX6 regimen.

Cohort 2 (Paired Biopsy)

GS-1423 is planned to be administered at Dose 1 Q2W in this cohort. However, other dose/dosing schedule may be selected upon review of cumulative data from Phase 1a. The planned dose/dosing schedule of GS-1423 will be targeted to achieve the exposure at the dose level of the RP2D monotherapy (Q2W) determined from Phase 1a.

Regimen	No. of Subjects	Dose of GS-1423 (mg)
GS 1423	15 with evaluable paired biopsies	Dose 1

Reference Therapy, Dose, and Mode of Administration:

The mFOLFOX6 dosing regimen consists of *l*-LV 200 mg/m^2 or *dl*-LV 400 mg/m^2 and oxaliplatin 85 mg/m^2 followed by bolus 5-FU 400 mg/m^2 and a 46-hour infusion of 5-FU 2400 mg/m^2. Administration of mFOLFOX6 will follow administration of GS-1423 on Day 1 of each 2-week cycle.

Criteria for Evaluation:

Safety:

Safety will be assessed by evaluating occurrence of DLTs in subjects in dose escalation during the first 28 days of treatment, incidence of AEs for all dose groups for the duration of the study, assessment of clinical laboratory test findings, physical examination, 12-lead ECG, echocardiogram or MUGA scan, ECOG performance status, and vital signs measurements. Adverse events will be graded using NCI CTCAE v5.0.

Efficacy:

Response assessment will be performed according to RECIST 1.1. Radiology assessment will be performed at 6, 12, 18, and 24 weeks (± 7 days) from first treatment dose, and then every 12 weeks thereafter.

Pharmacokinetics:

Plasma drug concentrations will be analyzed. The PK parameters to be estimated and reported may include, but may not be limited to, maximum observed drug concentration (C_{max}), area under the concentration versus time curve over the dosing interval (AUC_{tau}), observed drug concentration at the trough (C_{trough}), time to maximum observed concentration (T_{max}), systemic clearance (CL), volume of distribution (V_d), if applicable.

The immunogenicity assessment will be conducted to detect and measure anti-drug antibodies against GS-1423 (ADA).

CCI [redacted]	[redacted]

Statistical Methods:

Analysis Methods

Safety and efficacy data will be summarized by dose level/cohort for subjects in the Safety Analysis Set and the Full Analysis Set, respectively. In general, for categorical and ordinal data, count and percent of subjects will be summarized. For continuous data, sample size, mean, standard deviation, minimum, quartiles, median, and maximum values will be summarized. Time-to-event endpoints, such as progression-free survival (PFS), overall survival (OS) and duration of response (DOR), will be analyzed using Kaplan-Meier methods.

The plasma concentration data and the PK parameters will be summarized using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, % coefficient of variation, standard deviation, median, minimum, and maximum) by dose level/cohort for subjects in the PK Analysis Set.

Number and percentage of positive or negative ADA results at each specified time point will be summarized by dose level/cohort for subjects in the Immunogenicity Analysis Set.

Sample Size

Phase 1a

Part A Dose escalation

Assuming that up to 7 planned dose levels for escalation will be tested with up to 6 subjects per dose level (42 subjects for escalation) and 10% of subjects are not evaluable, and 6 additional subjects may be enrolled at a dose level at or below MTD to obtain additional safety, PK, and CCI [redacted], up to 53 subjects will be enrolled.

Part B Flat dose Regimens

Assuming 10% of subjects are not evaluable for PK CCI [redacted] assessments in the first 28 days on and after the first dosing of GS-1423, up to 40 subjects may be enrolled to obtain 12 evaluable subjects per cohort.

Phase 1b

Cohort 1 (gastric) safety run-in: Assuming that up to 2 planned dose levels for escalation will be tested with up to 6 subjects per dose level (12 subjects for escalation) and 10% of subjects are not evaluable, and 6 additional subjects may be enrolled at a dose level at or below MTD to obtain additional safety, CCI [redacted] information, up to 20 subjects will be enrolled.

Cohort 1 (gastric) post safety run-in: In a randomized Phase 3 study, the ORR of mFOLFOX6 as first-line treatment in subjects with advanced gastric or gastroesophageal junction adenocarcinoma was approximately 40%. Phase 1b Cohort 1 post safety run-in will be a single-arm study. The null hypothesis of a 35% confirmed ORR will be tested against the alternative hypothesis of a 50% confirmed ORR with GS-1423 in combination with mFOLFOX6. A sample size of 70 subjects will provide at least 85% power at a 1-sided significance level of 0.1 using a binomial test.

Cohort 2 (paired biopsy): This cohort will enroll subjects until evaluable paired biopsies from at least 15 subjects are obtained, with at least 5 of which NSCLC subjects and 5 CRC or pancreatic cancer subjects.

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

β-hCG	beta-human chorionic gonadotropin
5-FU	5-fluorouracil
ADA	anti-drug antibody against GS-1423
ADL	activities of daily living
AE	adverse event
AJCC-8	eighth edition of the American Joint Committee on Cancer staging manual
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AR	accumulation ratio
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC_{tau}	area under the concentration versus time curve over the dosing interval
BUN	blood urea nitrogen
C1D1	Cycle 1 Day 1
CD	cluster of differentiation
CFR	Code of Federal Regulations
CI	confidence interval
CL	systemic clearance
CLcr	estimated creatinine clearance
C_{max}	maximum observed drug concentration
CNS	central nervous system
CR	complete response
CRC	colorectal cancer
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CRS	cytokine release syndrome
CT	computed tomography
C_{trough}	observed minimal drug concentration during the dosing interval
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid

DOR	duration of response
EC_{90}	90% effective concentration
ECD	extracellular domain
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EMT	epithelial-to-mesenchymal transition
EOT	End of Treatment
FIH	first-in-human
Free T4	free thyroxine
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GGT	gamma-glutamyltransferase
GLP	Good Laboratory Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HED	human equivalent dose
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
IB	investigator's brochure
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IEC	independent ethics committee
IgG1	immunoglobulin G1
IHC	immunohistochemistry
ILD	interstitial lung disease
INR	international normalized ratio
irAE	immune-related adverse event
IRB	institutional review board
ISH	in situ hybridization
IV	intravenous(ly)
IXRS	interactive voice/web response system
KM	Kaplan-Meier
LDH	lactate dehydrogenase
LFT	liver function test

LLN	lower limit of normal
MABEL	minimally anticipated biologic effect level
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mFOLFOX6	oxaliplatin, 5-fluorouracil, and leucovorin
MRI	magnetic resonance imaging
MRSD	maximum recommended starting dose
MTD	maximum tolerated dose
MUGA	multigated acquisition
NCI	National Cancer Institute
NHP	non-human primate
NOAEL	no observed adverse effect level
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small-cell lung carcinoma
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	ligand 1 of programmed cell death protein 1
PFS	progression-free survival
PK	pharmacokinetic(s)
PLT	platelet
PO	orally
PR	partial response
PT	prothrombin time
PVE	Pharmacovigilance and Epidemiology
QW	every week
Q2W	every 2 weeks
Q3W	every 3 weeks
QTcF	QT interval corrected for heart rate using the Fridericia formula
RBC	red blood cell
RECIST 1.1	Response Evaluation Criteria in Solid Tumors Version 1.1

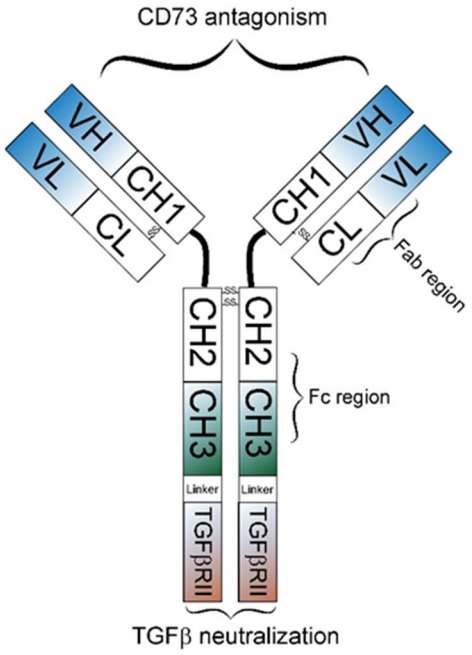
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SmPC	Summary of Product Characteristics
SOP	standard operating procedure
SSR	Special Situations Report
SRT	Safety Review Team
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal elimination half-life
TGFβ	transforming growth factor beta
T_{max}	time to maximum observed concentration
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
Vd	volume of distribution
Vd_{ss}	volume of distribution at steady-state
WBC	white blood cell

1. INTRODUCTION

1.1. Background

GS-1423 is a bifunctional humanized aglycosylated immunoglobulin G1 (IgG1)κ antibody that selectively antagonizes 2 prominent resistance pathways for cancer immunotherapy: Cluster of differentiation (CD)73-adenosine and transforming growth factor beta (TGFβ). GS-1423 is comprised of a high-affinity adenosinergic anti-CD73 antibody with a single TGFβRII extracellular domain (ECD) fused to the CH_3 constant region of each antibody heavy chain via a glycine-serine $(G_4S)_4G$ linker (Figure 1-1).

Figure 1-1. GS-1423 Design



CD cluster of differentiation; ECD extracellular domain; TGFβ transforming growth factor beta
An illustration of the anti CD73 and TGFβ cytokine trap bifunctional antibody GS 1423. The ECD of TGFβRII is fused to the CH_3 domain of each anti CD73 heavy chain via a $(G_4S)_4G$ linker. The anti CD73 antibody portion of GS 1423 is aglycosylated using a single asparagine to alanine mutation at position 297 to reduce the potential for undesired effector function.

1.2. Investigational Medicinal Product GS-1423

1.2.1. General Information

For further information on GS-1423, refer to the current investigator's brochure (IB).

1.2.2. Preclinical Pharmacology and Toxicology

CD73-generated adenosine (referred to as CD73-adenosine) and TGFβ represent 2 major immunoregulatory and pro-tumorigenic mechanisms responsible for therapeutic resistance and progressive disease (PD) in a wide range of cancer patients {Massague 2008}. Extracellular adenosine is produced via a cascade of enzymatic reactions with soluble and membrane-bound CD73 (ecto-5' nucleotidase, NT5E) rate-limiting the catalysis of adenosine monophosphate into adenosine {Ohta 2001}. TGFβ proteins are multipotent growth factors present in a variety of tissues that become activated following proteolytic release from latent complexes {Morikawa 2016}. CD73-adenosine and TGFβ mediate regulatory effects through interactions with a distinct set of cell surface receptors, namely adenosine receptors (ie, A_1R, $A_{2A}R$, $A_{2B}R$, and A_3) and TGFβ receptors (ie, TGFβRI, TGFβRII, and TGFβRIII), each with differential expression patterns and affinities for cognate ligands {David 2018, Sheth 2014}. Under physiological conditions, CD73-adenosine and TGFβ are highly regulated and serve to maintain tissue homeostasis {Antonioli 2013, Arjaans 2012, Li 2006}. However, under conditions of stress, both pathways are utilized to combat excessive inflammatory responses and tissue damage. These functional characteristics are often co-opted by cancers, leading to a pro-tumor microenvironment resulting in abrogated antitumor immune responses, and subsequent tumor escape {Bullen 2016, Massague 2008, Massague 2000, Reinhardt 2017, Ryzhov 2014, Samanta 2018}.

The potential clinical utility of antagonizing the CD73-adenosine and TGFβ pathways for the treatment of cancer is supported by several lines of preclinical evidence. Several studies support the use of anti-CD73 antibodies or small molecule inhibitors targeting individual or multiple adenosine receptors to enhance conventional (ie, radiotherapy and chemotherapy), targeted therapies, and immunotherapeutic interventions for cancer {Allard 2013, Stagg 2010, Young 2016}. Similarly, a myriad of preclinical studies underscores the importance of TGFβ inhibition for effective anticancer treatment, and the prevention of therapeutic resistance {Holmgaard 2018, Lan 2018, Ravi 2018, Takaku 2010}. Consistent with these findings, evaluation of the independent pathways has been an active area of clinical interest {Barnhart 2016, Geoghegan 2016, Knudson 2018, Siu 2018, Strauss 2018}.

While the evidence for intervention of the CD73-adenosine and TGFβ pathways is encouraging, it is important to consider that due to the prevalence of both in human cancers, targeting just one of these pathways may not be sufficient to enable effective therapeutic responses.

GS-1423 binds to both CD73 and TGFβ with high affinity. The anti-CD73 portion of GS-1423 binds to human CD73 with an estimated affinity (KD) of 0.07 nanomolar (nM). The TGFβRII cytokine trap moiety of GS-1423 binds human TGFβ1, TGFβ2, and TGFβ3 with estimated affinities (KD) of 0.002, 1.6, and 0.004 nM, respectively. Importantly, binding to CD73 or TGFβ is not compromised by the presence of TGFβRII or anti-CD73 domains, respectively. GS-1423 acts as a potent functional antagonist with the capacity to attenuate CD73 enzymatic activity, TGFβ signaling, and associated invasive properties of cancer cells, as well as rescue of T-cell functional activity under immunosuppressive and exhaustive conditions. Similar to its effects on human cells, GS-1423 binds to non-human primate (NHP) cynomolgus monkey CD73 with a

less than 2-fold difference and demonstrates similar inhibition of cynomolgus monkey CD73 enzymatic activity. The active forms of TGFβ1, TGFβ2, and TGFβ3 are 100% conserved between humans and NHP. Thus, GS-1423 exhibits analogous binding and function in humans and NHP. GS-1423 also binds rodent TGFβ with a similar affinity to that of humans. By contrast, GS-1423 demonstrates reduced (> 60-fold vs. human) cross-reactivity to rat and no cross-reactivity to mouse CD73, therefore cynomolgus monkey NHP was considered the most relevant species to evaluate the pharmacological and toxicological impact of GS-1423.

Consistent with an engineered, aglycosylated human IgG1 Fc region, GS-1423 shows reduced binding to cell-expressed FcγRs as compared to conventional IgG1. A fresh human whole blood cytokine release assay was used to evaluate the potential risk of GS-1423 eliciting adverse pro-inflammatory infusion reactions in soluble and complexed (plate-bound) formats. GS-1423 does not induce cytokines in whole blood that in vivo would be predictive of cytokine release syndrome (CRS) in patients. Taken together, the pharmacologic properties of GS-1423 illustrate its suitability for clinical development.

Two repeat dose toxicology studies have been undertaken in the most appropriate species, the cynomolgus monkey. The first study was a dose range finding investigation, which facilitated the design of a Good Laboratory Practice (GLP) study. The test and control articles were administered to the 20 female cynomolgus monkeys at dose levels of 0, 25, or 75 mg/kg, via slow bolus intravenous (IV) injection once weekly on Days 1, 8, 15, and 22 (unpublished data TRL-0175). There were no GS-1423-related mortalities, nor were there any effects noted in clinical observations, body weight, urinalysis, hematology, gross pathology, organ weights or histopathology. At the highest dose (75 mg/kg/week), decreased total protein, calcium, and albumin:globulin ratio in serum were noted with no known toxicological consequences. The no observed adverse effect level (NOAEL) was considered to be 75 mg/kg/week for 4 doses in 4 weeks.

A 4-week GLP toxicology study was conducted in 20 male and 20 female cynomolgus monkeys administered 5 weekly IV bolus infusions of GS-1423 or vehicle control over 29 days at doses of 0, 10, 25, or 75 mg/kg/dose and included a 4-week recovery period (unpublished data TRL-0179).

There were no treatment related effects on macroscopic appearance or organ weights for brain, heart, kidney, liver, lung, spleen, and thymus. There were no GS-1423-related microscopic changes noted.

GS-1423 caused no ocular effects, abnormal electrocardiographic findings, changes in body temperature, blood pressure, or heart rate during this study. There were no changes in any of the neurological parameters evaluated.

In a human tissue cross-reactivity study (unpublished data TRL-0165), GS-1423 produced widespread immunoreactivity in the human tissue panel examined. However, the majority of the staining was cytoplasmic in nature, and monoclonal antibody binding to cytoplasmic sites in tissue cross-reactivity studies generally is considered of little to no toxicologic significance due to the limited ability of antibody drugs to access the cytoplasmic compartment in vivo.

Although the subcellular localization of the neuropil staining in the spinal cord could not be identified at the resolution of a light microscope, this staining is also not anticipated to be toxicologically significant.

Membrane binding with GS-1423 was only evident in decidual cells in the placenta and spindloid cells in the cervix, which was considered expected reactivity of the test article due to the reported expression of TGFβ in placental decidual cells and both CD73 and TGFβ in fibroblasts.

1.2.3. Clinical Studies of GS-1423

This is a first-in-human (FIH) clinical study conducted with this investigational product.

1.3. Information About Comparator or Reference Products

Not applicable.

1.4. Rationale for This Study

1.4.1. Rationale for Phase 1a and Phase 1b Cohort 2 (Dose Escalation, Flat Dose Regimens and Paired Biopsy)

GS-1423 is a novel bifunctional molecule comprised of an anti-CD73 antibody fused to a TGFβRII-based cytokine trap. Analogous to the format of GS-1423, neutralization of TGFβ using TGFβRII-ECD fusion ("cytokine trap") molecules have yielded promising results in preclinical tumor models and in cancer patients {Knudson 2018, Lan 2018, Ravi 2018, Strauss 2018}. Inhibition of both pathways will be leveraged to address these 2 prominent cancer-associated pathways, potentially providing an advantage over strategies targeting individual therapeutic resistance pathways by addressing this issue from multiple angles.

These parts of the study aim to evaluate the safety and preliminary efficacy of GS-1423 as monotherapy in subjects with advanced solid tumors[redacted]. Nonclinical pharmacology and toxicology data of GS-1423 justify its investigation in clinical studies for the development of a potential treatment for subjects with advanced solid tumors. The evaluation of various dose schedules of GS-1423 is important in the Phase 1a dose finding part of the study to identify an optimal recommended Phase 2 dose (RP2D) regimen for future clinical development of GS-1423.

1.4.2. Rationale for Phase 1b Cohort 1 (Gastric Cancer)

Gastric cancer remains one of the most common and deadly cancers worldwide, accounting for the third leading cause of cancer deaths worldwide, especially among older males {Rawla 2019}. The 5-year survival rate for all gastric cancer is 31% in the United States (US) and Stage IIIC tumors treated with surgery had a 5-year survival rate of 18%. Current first-line treatment for metastatic gastric cancer consists of combination chemotherapy, most often including doublet or triplet platinum/fluoropyrimidine combinations. Response rates of combination chemotherapies

in these patients are generally in the range of 40% to 50%, and median overall survival (OS) is approximately 10 to 12 months {Kim 2012}. Despite recent advancement in treatment, the clinical outcome for patients with advanced (unresectable, recurrent or metastatic) disease has remained unsatisfactory and alternative treatment options with improved efficacy are sought to address this unmet medical need.

GS-1423 has the potential to cooperate or synergize with a range of approved cancer therapies including radiotherapy, chemotherapy, and immune-based therapies {Allard 2013, Samanta 2018}. Treatment of cancer cells with certain chemotherapies (such as platinum based) has been shown to induce immunogenic cell death, characterized by increased extracellular adenosine triphosphate levels and upregulation of CD73, leading to the enhanced generation of adenosine (commonly referred to as the "purinergic halo") {Stagg 2010}. Consistent with this immunosuppressive mechanism, CD73 expression, potently transcriptionally regulated via hypoxia-inducible factor-1, has been established as a negative prognostic marker across a range of tumor indications, including gastric carcinoma, and is also associated with chemotherapy resistance. High TGFβ levels have been associated with PD, lymph node metastasis, and poor prognosis in gastric cancer. TGFβ, together with hypoxia in the tumor microenvironment, has been implicated in inducing gastric tumor cell epithelial-to-mesenchymal transition (EMT), a process by which epithelial cells lose their polarity and cell-cell adhesion and gain migratory and invasive properties {Syed 2016}. GS-1423 is designed to inhibit CD73-mediated adenosine production and neutralize active TGFβ signaling within the tumor microenvironment. Dual antagonism of these broadly immunosuppressive barriers is anticipated to facilitate antitumor immunity and inhibit tumor intrinsic proliferation and EMT transition (unpublished data).

The mFOLFOX6 regimen (oxaliplatin, 5-fluorouracil [5-FU], and leucovorin) is commonly used and is acceptable in the first-line setting to treat advanced gastric and gastroesophageal junction adenocarcinoma {Kim 2012}. In this Phase 1b study, GS-1423 in combination with mFOLFOX6 will be evaluated in subjects with advanced gastric and gastroesophageal junction adenocarcinoma who have not received prior systemic therapy for advanced disease.

1.5. Rationale for Dose Selection of GS-1423 in Phase 1a Dose Escalation

The Phase 1a dose escalation part of this study is proposed for GS-1423 with a starting dose of 0.3 mg/kg once every 2 weeks (Q2W). The estimate for the starting dose for the proposed GS-1423 FIH study (GS-US-505-5452) is based on minimally anticipated biologic effect level (MABEL; International Council for Harmonisation [of Technical Requirements for Pharmaceuticals for Human Use] [ICH] S9) derived from 90% effective concentration (EC_{90}) from the most biologically-relevant assay. An EC_{90} value was selected because GS-1423 is not expected to directly stimulate the immune system, but rather relieve suppression mediated by CD73-adenosine and TGFβ pathways. Thus, EC_{90} may provide the most favorable benefit-to-risk ratio for patients in balancing unforeseen toxicity that may result from a high starting dose versus a non-effective dose that misses an opportunity to provide clinical benefit to patients. This is supported by an 83.3-fold safety margin as compared to the human equivalent dose (HED) derived from the NOAEL, which is described in detail below.

The single dose plasma GS-1423 toxicokinetic data from a cynomolgus monkey non-GLP toxicology study were analyzed by noncompartmental analysis using the software WinNonlin. Pharmacokinetic (PK) parameters were allometrically scaled to obtain estimates of human volume of distribution at steady-state (Vd_{ss}), half-life, and accumulation ratio (AR). MABEL (EC_{90} geometric mean of 3.28 µg/mL) and volume of distribution (Vd) (7840 mL of standard 70 kg human body weight) were converted to a calculated human dose of 0.367 mg/kg. This dose was rounded down to a final GS-1423 starting dose of 0.3 mg/kg (Table 1-1). Further, 25.0 mg/kg is the HED based on a NOAEL of 75 mg/kg in cynomolgus monkey (ie, determined to be the most appropriate species for toxicological evaluation) and scaling using the mean 2.5 kg cynomolgus monkey body weight to a 70 kg human body weight. The difference between HED (at NOAEL) and MABEL-derived starting dose demonstrates that the starting dose provides an 83.3-fold margin-of-safety (Table 1-1). For this FIH study, the proposed GS-1423 dosing interval of Q2W is supported by the predicted 9.06-day half-life scaled to human and the calculated AR of 1.52.Thus, the proposed GS-1423 starting dose of 0.3 mg/kg Q2W takes into consideration of the acceptable risk-to-benefit profile outlined in this protocol and is expected to be pharmacologically active in humans as demonstrated by the EC_{90} values in a human in vitro assay.

The highest dose of GS-1423 to be evaluated in subjects is 45 mg/kg Q2W, which is projected to provide exposure margins corresponding to ≥ 4.7-fold of the rat NOAEL/STD10 and ≥ 4.0-fold of the monkey NOAEL/HNSTD, assuming dose proportionality after 10 mg/kg.

Table 1-1. Calculation of GS-1423 Starting Dose from MABEL and Determination of Safety Margin

Starting Dose MABEL	
Relevant assay	**Cell proliferation**
EC_{90}	0.00328 mg/mL
Vd_{ss} for 70 kg human	7840 mL
Calculated dose/70 kg human	25.7 mg
Calculated MABEL dose	0.367 mg/kg
MRSD-MABEL, rounded down	**0.3 mg/kg**
HED NOAEL	
NOAEL dose group (cynomolgus monkey)	75 mg/kg
HED based on NOAEL	25 mg/kg
Safety margin (HED/starting dose MABEL)	83.3 fold

EC_{90} 90% effective concentration; GLP Good Laboratory Practice; HED human equivalent dose; MRSD maximum recommended starting dose; MABEL minimally anticipated biologic effect level; NOAEL no observed adverse effect level; starting dose maximum recommended starting dose; Vd_{ss} volume of distribution at steady state.
MABEL calculated from a physiologically relevant assay (Agenus Document TRL 0135). Preliminary plasma GS 1423 toxicokinetic data from a cynomolgus monkey non GLP toxicology study were analyzed by noncompartmental analysis using the software WinNonlin. Pharmacokinetic parameters were allometrically scaled to obtain estimates of human clearance (CL), Vd_{ss}, half life ($t_{1/2}$), and accumulation ratio (AR).
GS-1423 starting dose based on MABEL approach = 0.00328 mg/mL*7840 mL 25.7 mg/70 kg 0.367 mg/kg (rounded down to 0.3 mg/kg).
HED D(a)*(BW(a)/BW(human))^(1 b), where D(a) animal dose in amount/kg, BW(a) animal body weight in kg, BW(human) human body weight in kg, b 0.67. HEDs calculated from cynomolgus monkey doses of 0, 10, and 75 mg/kg (using mean 2.5 kg cynomolgus monkey body weight) were scaled to HED doses of 0, 3.33, and 25mg/kg, respectively. GS 1423 NOAEL derived from 75 mg/kg dose group from a cynomolgus monkey GLP toxicology study.

1.6. Risk/Benefit Assessment for the Study

The proposed Phase 1a dose escalation study aims to evaluate GS-1423 in patients with advanced malignancies as a single agent to evaluate safety and to define a pharmacologically active dose in relation to antibody PK. Nonclinical investigations were conducted in support of the FIH study to provide sufficient evidence that cancer patients administered GS-1423 would not be exposed to unreasonable risks in an early stage.

When tested in vitro, GS-1423 inhibited cell-expressed and soluble CD73 enzymatic activity and promoted internalization of CD73, thereby preventing extracellular functional activity; inhibited TGFβ signaling and its downstream pro-metastatic process of tumor cell EMT; and rescued proliferation of primary T-cells that have been suppressed by adenosine monophosphate and/or TGFβ as compared to anti-CD73 and TGFβ cytokine trap tested individually. Additionally, a package of toxicity studies involving IV administration of GS-1423 to cynomolgus monkey demonstrated that treatment was well-tolerated with an acceptable toxicokinetic profile. GS-1423 did not induce cytokine release in a whole blood cytokine release assay indicating minimal risk of CRS. A human tissue cross-reactivity study showed specific reactivity of GS-1423 with mononuclear cells in a variety of tissues, consistent with the expected expression on T-cell subsets.

Taken together, the pharmacologic properties of GS-1423 demonstrate its suitability for clinical development. No major concerns have been identified that preclude evaluation of GS-1423 in an FIH study to evaluate safety and assess exploratory clinical pharmacology endpoints in cancer patients. An integrated assessment of data from a collection of in vitro and in vivo assays indicates that a safe starting dose for a patient with advanced malignancy would be 0.3 mg/kg Q2W.

The Phase 1b Cohort 1 study will evaluate safety and preliminary efficacy of GS-1423 in combination with mFOLFOX6 regimen. A safety run-in to define the RP2D of GS-1423 in combination with mFOLFOX6 will be conducted prior to the general enrollment (post safety run-in). The addition of GS-1423 to mFOLFOX6 may potentially increase antitumor activity over mFOLFOX6 alone by utilizing a wholly different mechanism of action. However, this combination regimen may introduce other toxicities, such as infusion reactions and dermatologic AEs (e.g., rashes) due to immune-related reactions. Please refer to GS-1423 IB, and oxaliplatin and 5-FU Summary of Product Characteristics (SmPCs) for more information. As summarized in Section 1.4.2, the ORR for mFOLFOX6, the standard of care in gastric cancer, remains low. Although there is a theoretical overlap in toxicities, this combination may offer the potential to improve upon the response in this cancer type. Strategies to mitigate risks for these toxicities include incorporating safety run-in to evaluate dosing of GS-1423 in combination with mFOLFOX6 and close monitoring of lab values and AEs. Parameters for dose delay and discontinuation of study drugs are also defined in the protocol. Based on available information, the benefit/risk balance for this study is considered positive.

1.7. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES

2.1. Phase 1a

The primary objectives are:

- Part A (dose escalation): To assess safety and tolerability and to define the dose limiting toxicity (DLT) and maximum tolerated dose (MTD) or RP2D of GS-1423 monotherapy in subjects with advanced solid tumors
- Part B (flat dose regimens): To assess safety and tolerability of GS-1423 monotherapy in subjects with advanced solid tumors

The secondary objectives are:

- To characterize GS-1423 PK
- To evaluate GS-1423 immunogenicity

CCI [redacted]

2.2. Phase 1b

Cohort 1 (gastric cancer): GS-1423 in combination with a chemotherapy regimen in advanced (unresectable, recurrent or metastatic) gastric and gastroesophageal junction adenocarcinoma

For safety run-in, the primary objective is:

- To assess safety and tolerability and to define the DLT and MTD or RP2D of GS-1423 in combination with a chemotherapy regimen in subjects with advanced gastric or gastroesophageal junction adenocarcinoma

For post safety run-in, the primary objective is:

- To assess the preliminary efficacy of GS-1423 in combination with a chemotherapy regimen in subjects with advanced gastric or gastroesophageal junction adenocarcinoma, as determined by the confirmed ORR

For post safety run-in, the secondary objective is:

- To assess safety and tolerability of GS-1423 in combination with a chemotherapy regimen in subjects with advanced gastric or gastroesophageal junction adenocarcinoma

CCI

[redacted]

Cohort 2 (paired biopsy): GS-1423 monotherapy in subjects with advanced solid tumors accessible for biopsy

The primary objective is:

- To assess safety and tolerability of GS-1423 monotherapy in subjects with advanced solid tumors

CCI

[redacted]

3. STUDY DESIGN

3.1. Endpoints

The endpoints of this study are described in Sections 8.1.2, 8.1.3, and 8.1.4.

3.2. Study Design

3.2.1. Phase 1a

Part A – Dose escalation

This is an open-label, Phase 1a study to evaluate the safety, tolerability, and PK profiles of GS-1423, a novel bifunctional molecule comprised of an adenosinergic anti-CD73 antibody fused to a TGFβRII-based "cytokine trap", and to assess the MTD or RP2D of GS-1423 monotherapy in subjects with advanced solid tumors.

The dose escalation will be conducted in an accelerated titration (Cohorts 1 and 2), followed by a 3+3 dose escalation design starting with Cohort 3 (Figure 3-1 and Figure 3-2). GS-1423 will be administered on Day 1 of each 2-week cycle (Q2W) until the subject meets study treatment discontinuation criteria or for up to 1 year.

The starting dose was selected to be 0.3 mg/kg derived from MABEL.

Part B – Flat dose regimens

Part B will consist of up to 3 adaptive cohorts (every week [QW], Q2W, and/or every 3 weeks [Q3W]) to evaluate the safety, tolerability, and PK profiles of GS-1423 monotherapy with flat dose regimens. GS-1423 will be administered on Day 1 of each cycle (QW, Q2W, or Q3W) until the subject meets study treatment discontinuation criteria or for up to 1 year.

The target exposure for the Phase 1b study will be determined based on PK, CCI [redacted] and safety results from the Part A (dose escalation) study. Subsequently, 6 to 12 subjects per cohort may be enrolled to explore the flat dose(s) and dosing interval(s) that will achieve the target exposure. The doses evaluated in these subjects will be selected as such that they do not result in exposures that exceed the maximum tolerated exposures based on the dose escalation portion of the study. Gilead may choose not to initiate any or all of the adaptive cohorts if it is deemed unnecessary.

3.2.2. Phase 1b

This is an open-label, multi-center, single-arm, Phase 1b study with 2 cohorts.

GS-1423 + mFOLFOX6: Cohort 1 (gastric cancer)

Cohort 1 will assess safety and tolerability and define the DLT and MTD or RP2D of GS-1423 in combination with a chemotherapy regimen (mFOLFOX6) in subjects with advanced (unresectable, recurrent or metastatic) gastric or gastroesophageal junction adenocarcinoma who have not previously received systemic therapy for advanced disease. GS-1423 and mFOLFOX6 will be administered starting on Day 1 of each 2-week cycle (Q2W). GS-1423 will be administered for up to 2 years and mFOLFOX6 will be administered for up to 12 cycles with option to continue leucovorin and 5-FU Q2W at investigator's discretion until the subject meets study treatment discontinuation criteria or for up to 2 years.

A standard 3+3 dose escalation design will be used to determine the DLT and MTD or RP2D of GS-1423 in combination with mFOLFOX6. A Safety Review Team (SRT) will assess safety and decide on dose escalation.

After the MTD or RP2D of GS-1423 in combination with mFOLFOX6 has been determined, the cohort will be expanded by adding approximately 70 subjects to explore the potential efficacy.

One futility interim analysis will be performed after approximately 50% of subjects have been enrolled and are able to complete study treatment for at least 6 months post safety run-in.

GS-1423 Monotherapy: Cohort 2 (Paired Biopsy)

Cohort 2 will assess safety and tolerability of GS-1423 monotherapy in multiple tumor types. GS-1423 will be administered on Day 1 of each cycle until the subject meets study treatment discontinuation criteria or for up to 1 year.

Cohort 2 will enroll subjects until 15 evaluable paired tumor biopsies (baseline and any on-treatment) have been collected, including a minimum of 5 biopsies from non-small-cell lung carcinoma (NSCLC) (non-squamous adenocarcinoma) and 5 colorectal cancer (CRC) or pancreatic cancer subjects.

3.2.3. Dose Escalation

3.2.3.1. Dose Escalation Procedure (Phase 1a Part A)

Subjects with advanced solid tumors who have failed or are intolerant to standard therapy or for whom no standard therapy exists will be sequentially enrolled at progressively higher dose levels to receive GS-1423.

The initial starting dose will be 0.3 mg/kg and the first cohort will be enrolled to confirm safety at this level. Subsequent doses of 1, 3, 10, 20, 30 and 45 mg/kg are planned.

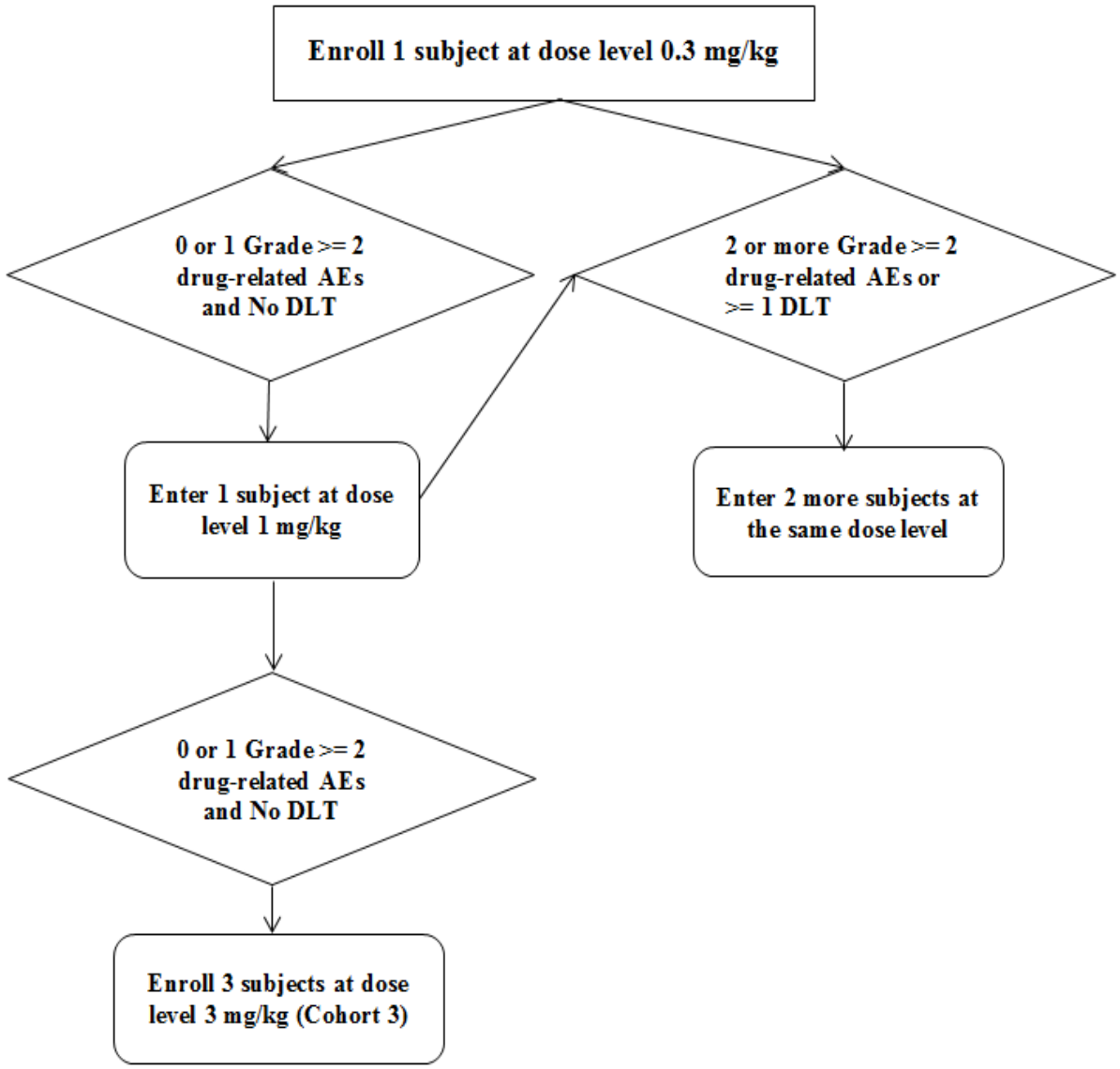
Table 3-1. Phase 1a Part A GS-1423 Dose Levels and Cohorts

Cohort	No. of Subjects	Escalation Type	Dose of GS-1423 (mg/kg)
1 (starting dose)	1 or 3-6	Accelerated titration	0.3
2	1 or 3-6	Accelerated titration	1
3	3-6	3+3	3
4	3-6	3+3	10
5	3-6	3+3	20
6	3-6	3+3	30
7	3-6	3+3	45

Note: An additional 6 subjects may be enrolled at a dose level at or below maximum tolerated dose to obtain additional safety, pharmacokinetics, and CCI information. Gilead may choose not to enroll any cohort if it is deemed unnecessary.

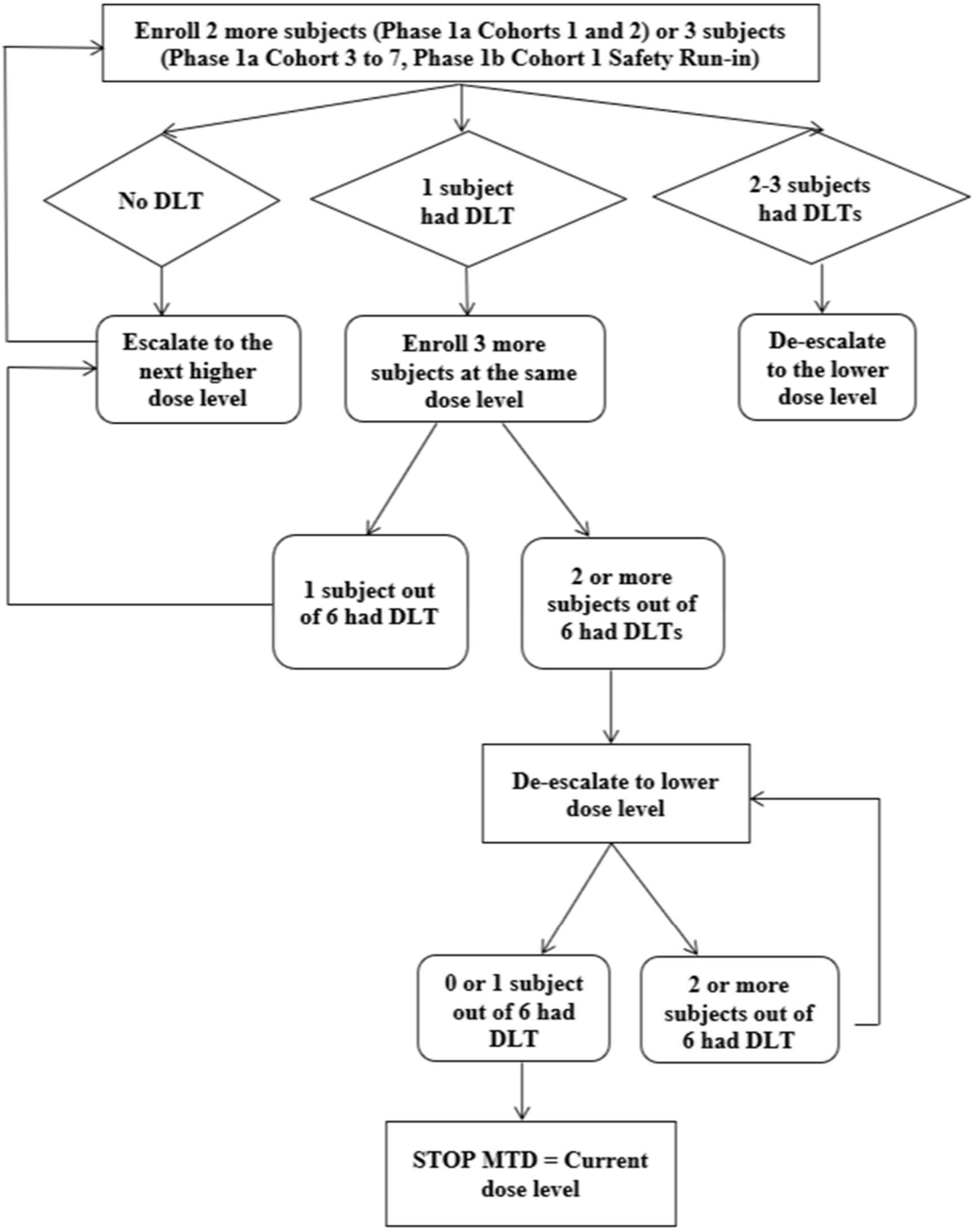
This part of study will utilize an accelerated titration design schema of dosing 1 subject each at the first 2 dose levels of 0.3 mg/kg and 1 mg/kg and with subsequent dosing conducted in a 3+3 dose escalation format (Figure 3-1 and Figure 3-2). At the first 2 dose levels of 0.3 mg/kg and 1 mg/kg, if 2 or more drug-related adverse events (AEs) of Grade 2 or higher or at least 1 DLT are observed during the 28-day DLT observation period, the 3+3 escalation scheme will be used at that dose and subsequent doses. Each subject will stay on the dose level and schedule assigned at study entry.

Figure 3-1. Accelerated Dose Escalation Scheme



AE adverse event; DLT dose limiting toxicity

Figure 3-2. 3+3 Dose Escalation Scheme



DLT dose limiting toxicity; MTD maximum tolerated dose

Note: If MTD is attained at the first dose level, discussion with investigators and medical monitor to change dose or schedules in a protocol amendment

In each dosing cohort of more than 1 subject, the enrollment of the second subject will not proceed unless the first subject tolerated the therapy without DLT within the first 7 days following the first infusion. Thereafter, within each cohort in the dose escalation phase, consecutively enrolled subjects may initiate treatment ≥ 24 hours after the prior enrolled subject initiated treatment. Each subject will be observed for a DLT observation period of 28 days from the initial dose of GS-1423, and 3 subjects must be able to receive and tolerate the first 2 doses of GS-1423 without DLTs during this observation period before the dose will be escalated and the next cohort begins enrollment.

If 1 of the first 3 evaluable subjects enrolled has a DLT within the first 28 days, then 3 additional subjects will be enrolled at the same dose level. If no DLTs are observed in the additional 3 subjects, dose escalation will occur. If a DLT occurs in ≥ 2 subjects in the total cohort of 6 subjects, the MTD will be deemed to be exceeded, and the prior dose level will be evaluated to determine the MTD by increasing enrollment to 6 subjects. If the prior dose level was already deemed to be safe (ie, 0 or 1 DLT) and enrolled 6 subjects, then it will be defined as the MTD. If 2 or more subjects have DLTs within the first 28 days, dose de-escalation to a lower dose will occur. The MTD is the highest dose level with an incidence of DLTs of 0 or 1 out of 6 subjects during the first 28 days of study drug dosing. A minimum of 6 subjects need to be treated at a dose level before this dose level can be deemed as the MTD. A subject who is withdrawn from the study before the completion of the first 28 days for a reason other than a DLT will be replaced.

The SRT will review safety and relevant clinical data after all subjects in a cohort have reached the end of the DLT observation period of 28 days and make the dose escalation/stay/de-escalation decision. Source data verification is not required to be performed prior to dose escalation/SRT meetings. Alternative data quality control checks that are performed on data used to make dose escalation decisions are described in the SRT Charter.

Starting at Cohort 4 (10 mg/kg), if no DLT is observed during the 28-day DLT observation period in the first 3 subjects, 3 additional subjects may be enrolled at the respective dose level to obtain more safety, PK, and CCI [redacted] data. If ≥ 2 subjects have experienced DLTs in the last 3 (of 6) subjects, dose escalation will halt and up to 3 additional subjects will be enrolled at the preceding dose level (if there were only 3 subjects in that cohort) for DLT assessment. If 6 subjects were already evaluated, the preceding dose level will be considered as MTD.

If 0.3 mg/kg exceeds the MTD (ie, does not pass DLT evaluation), Gilead and investigators may consider alternative dose schedules based on available safety data. If needed, PK, and CCI [redacted] data will be reviewed as well; this will require a protocol amendment. If an alternate schedule is tested and determined to be safe, re-escalation of GS-1423 will proceed according to the protocol amendment. Otherwise, dose escalation will continue until the MTD is reached or dosing with the maximum planned dose level (45 mg/kg) is completed without meeting the criteria for MTD.

The RP2D will be determined by Gilead based on all available relevant clinical data. The RP2D will not exceed the maximum tolerated dose evaluated in this study.

3.2.3.2. Dose Escalation/Safety Run-in for Phase 1b

Cohort 1 (gastric cancer)

Safety run-in: This part of study will utilize a 3+3 dose escalation scheme. The planned starting dose of GS-1423 will be targeted to achieve the exposure at -1 dose level of RP2D monotherapy (Q2W) determined from Phase 1a. GS-1423 will be administered in combination with mFOLFOX6. In each dose level, the enrollment of the second subject will not proceed unless the first subject tolerated the therapy without DLT within the first 7 days following the first infusion. Thereafter, within each dose level in the safety run-in phase, consecutively enrolled subjects may initiate treatment ≥ 24 hours after the prior enrolled subject initiated treatment.

Each subject will be observed for a DLT observation period of 28 days from the initial dose of GS-1423, and 3 subjects must be able to receive and tolerate the first 2 doses of GS-1423 in combination with mFOLFOX6 without DLTs during this observation period before the dose will be escalated and the next dose level begins enrollment. The SRT will review safety and relevant clinical data after all subjects at a dose level have reached the end of the DLT observation period of 28 days and make the dose escalation/stay/de-escalation decision.

Table 3-2. Phase 1b Cohort 1 Safety Run-in GS-1423 Dose Levels

Regimen	No. of Subjects	Escalation Type	Dose of GS-1423 (mg)
GS-1423 + mFOLFOX6	3-6	3+3	−1 Dose 1 (Q2W)
GS-1423 + mFOLFOX6	3-6	3+3	Dose 1 (Q2W)

5 FU 5 fluorouracil; Q2W every 2 weeks; RP2D recommended Phase 2 dose
The mFOLFOX6 regimen consists of l LV 200 mg/m^2 or dl LV 400 mg/m^2 and oxaliplatin 85 mg/m^2 followed by bolus 5 FU 400 mg/m^2 and a 46 hour infusion of 5 FU 2400 mg/m^2. Administration of mFOLFOX6 will follow administration of GS 1423 on Day 1 of each cycle.
1 Dose 1: Will be targeted to achieve the exposure at 1 dose level of RP2D monotherapy (Q2W) determined based on cumulative data from Phase 1a.
Dose 1: Will be targeted to achieve the exposure at the dose level of RP2D monotherapy (Q2W) determined based on cumulative data from Phase 1a.

An additional 6 subjects may be enrolled at a dose level at or below MTD to obtain additional safety, PK, and CCI [redacted] information.

3.2.3.3. Definition of Dose Limiting Toxicity

Toxicity will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI CTCAE v5.0). A DLT is a toxicity observed in the first 28 days as defined below and considered possibly related to GS-1423.

A DLT may lead to permanent withdrawal of GS-1423 for the subject after discussion between the Investigator and Gilead.

Hematologic

- Grade 3 thrombocytopenia with clinically significant bleeding (ie, requires hospitalization, transfusion of blood products, or other urgent medical intervention)
- Grade ≥ 3 febrile neutropenia (absolute neutrophil count [ANC] < 1.0×10^9/L and fever > 101°F/38.3°C)
- Any Grade 4 hematologic laboratory abnormalities/AEs regardless of duration will be considered DLTs with the **exception** of

  Grade 4 lymphopenia

  Grade 4 neutropenia lasting ≤ 7 days that is not associated with fever (the use of growth factors is permitted)

  Grade 4 anemia explained by underlying disease

Non-Hematologic

- Grade 4 non-hematologic (laboratory and non-laboratory) AEs will be considered DLT regardless of the duration
- Any ≥ Grade 2 uveitis, blurred vision, eye pain, and/or reduction of visual acuity that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks of the initiation of topical therapy OR requires systemic treatment will be considered as a DLT
- The following Grade 3 non-hematologic AEs **will be considered as DLTs**:

  Any Grade 3 AE of unknown etiology consistent with an immune phenomenon that does not resolve to ≤ Grade 1 or to baseline with immunosuppressive therapy within 3 weeks of its onset

  Any Grade 3 central nervous system (CNS)-related AE of unknown etiology consistent with an immune phenomenon regardless of duration or reversibility

  Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation ≥ 3 × upper limit of normal (ULN), also showing elevation of serum total bilirubin of > 2 × ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

- Any other non immune-related Grade 3 AE **except**:

  Any Grade 3 endocrinopathy that is adequately controlled by hormonal replacement

  Grade 3 AE of tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumor)

  Transient (≤ 3 days) Grade 3 fatigue, local reactions, headache, nausea, emesis, or diarrhea that are controlled with medical management and/or resolves to Grade ≤ 1

  Transient (≤ 3 days) Grade 3 flu-like symptoms or fever, which are controlled with medical management

  An event clearly associated with the underlying disease, PD, a concomitant medication, or comorbidity.

Dosing/procedures-related toxicities

- Inability to receive the first 2 doses of GS-1423 because of related toxicity, even if the toxicity does not meet DLT criteria defined above (regardless of dosing schedule)

  Note: Exceptions include DLT exclusions mentioned above.

- Greater than a 2-week delay in starting the next cycle of therapy due to a treatment-related toxicity, even if the toxicity does not meet the DLT criteria determined above

Grade 5 event (ie, death)

3.2.3.4. Stopping Rules for Toxicity

The SRT will meet to review any cohort under evaluation as well as the safety of all cohorts. In cohorts with more than 1 subject, should > 33% subjects on any dose level have toxicities that meet DLT criteria after the DLT observation period of 28 days or in subjects not included in the DLT analysis, the occurrences will be thoroughly evaluated by the committee. Subjects not included in the DLT analysis set are those who discontinued during the DLT period for reasons other than DLT. The SRT will then make recommendations to initiate any changes in study conduct.

If there is a subject death within 30 days of initial study drug administration (Day 1) for reasons directly related to study treatment, enrollment in the study and/or treatment will be put on hold as appropriate. The SRT will then evaluate the cause of the event and recommend the appropriate change in study conduct to be communicated with health authorities. If the event is determined to be related to study treatment, then a study amendment and/or other corrective action plan will be established by the SRT in conjunction with health authorities.

3.2.4. Safety Review Team

An SRT will be established to assess safety, make decisions on dose escalation, and define the DLT and MTD.

For any given cohort, Gilead may elect to hold dosing, select an intermediate dose, or stop study enrollment at any time based on review of the preliminary safety data.

Based on review of relevant safety data by the SRT, as specified in Section 3.2.3.1, and in discussion with the investigator, escalation to a higher dose will occur only in the absence of > 1 DLTs per dose level and/or meeting any prespecified stopping criteria.

The SRT will consist of at least 1 investigator and the Gilead medical monitor. Others may be invited to participate as members of the SRT if additional expertise is desired (ie, representatives from Pharmacovigilance and Epidemiology [PVE], Clinical Operations, Biostatistics, Clinical Pharmacology and Biomarker Sciences as applicable). The medical monitor serves as the chair of the SRT. An SRT Charter will be agreed by all SRT members prior to the first SRT meeting. The data reviewed at the SRT to make dose escalation decisions will be defined in the SRT Charter. The quality control checks performed on the data reviewed and used for making dose escalation decisions will be described in the SRT Charter.

3.3. Study Treatments

Formulation, packaging, and dosing regimens are further described in Section 5.3.

Phase 1a:

Part A Dose Escalation

This part of the study consists of an accelerated titration design scheme and a 3+3 dose escalation scheme with the following proposed escalating dose levels and schedules of GS-1423: 0.3, 1, 3, 10, 20, 30, and 45 mg/kg administered Q2W.

Part B Flat Dose Regimens

GS-1423 monotherapy may also be evaluated at a flat dose QW, Q2W, and/or Q3W. Based on safety and available PK and CCI [redacted] data from Part A, Part B will be initiated at or below the exposure of the highest dose for which data are available from Part A. Part B cohorts may be initiated in parallel with cohorts from Part A of the study if the dose/exposure under evaluation is at or below a dose/exposure that has already been evaluated and considered as safe. Six to 12 subjects per cohort will be enrolled to explore the flat dose(s) and dosing interval(s). Gilead may choose not to initiate any or all of the adaptive cohorts if it is deemed unnecessary.

Table 3-3. Phase 1a Part B Dose Levels

Adaptive Cohort	No. of Subjects	Dose of GS-1423 (mg)
8	6-12	Dose 1 (Q2W)
9	6-12	Dose 2 (QW)
10	6-12	Dose 3 (Q3W)

QW every week; Q2W every 2 weeks; Q3W every 3 weeks;

Phase 1b:

Cohort 1 (Gastric Cancer): GS-1423 + mFOLFOX6

GS-1423 will be administered on Day 1 of each 14-day cycle via IV infusion. Subjects will also be administered mFOLFOX6 after administration of GS-1423 as described in Section 5.4.

Cohort 2 (Paired Biopsy): GS-1423 Monotherapy

GS-1423 will be administered on Day 1 of each cycle via IV infusion. The planned starting dose of GS-1423 will be targeted to achieve the exposure at the dose level of the RP2D monotherapy (Q2W) determined from Phase 1a.

Regimen	No. of Subjects	Dose of GS-1423 (mg)
GS-1423	15 with evaluable paired biopsies	Dose 1

Dose 1: Will be targeted to achieve the exposure at the dose level of RP2D monotherapy (Q2W) determined based on cumulative data from Phase 1a.

3.4. Duration of Treatment

Cycle lengths are 7 days for QW, 14 days for Q2W, and 21 days for Q3W.

Phase 1a (all cohorts) and Phase 1b (Cohort 2): Subjects will continue GS-1423 for up to 1 year (maximum 52 cycles for QW, 26 cycles for Q2W, and 17 cycles for Q3W) or until the subject meets study treatment discontinuation criteria.

Phase 1b (Cohort 1): Subjects will continue GS-1423 for up to 2 years (maximum 52 cycles) or until PD, unacceptable toxicity, substantial noncompliance with study procedures or study treatment regimen, study discontinuation or withdrawal from study. mFOLFOX6 will be administered for up to 12 cycles with the option of maintenance therapy with 5-FU and leucovorin per investigator's discretion until the subject meets study treatment discontinuation criteria or for up to 2 years (maximum 52 cycles).

3.5. Study Discontinuation Criteria

The entire study may be discontinued in the event of any of the following:

- New information leading to unfavorable risk-benefit judgment of GS-1423
- Gilead's decision
- Poor enrollment of subjects, making completion of the study within an acceptable timeframe unlikely
- Discontinuation of development of GS-1423
- The entire study may be terminated or suspended upon request of health authorities.

Health authorities and institutional review boards or independent ethics committees (IRBs/IECs) will be informed about study discontinuation in accordance with applicable regulations.

Recruitment at a center may be stopped for reason that may include low recruitment, protocol violation, or inadequate data recording quality control and quality assurance.

3.6. Post Study Care

Upon withdrawal from study treatment, subjects will receive the care upon which they and their physicians agree. Subjects will be followed for survival and AEs as specified in Section 6.8.

3.7. Source Data

The source data for this study will be obtained from electronic data capture (EDC), central laboratory, local laboratory, specialty laboratory (for PK and/or CCI data), and interactive voice/web response system (IXRS).

CCI

CCI

CCI [redacted]

[redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

This study will enroll approximately 213 adult subjects with advanced cancer (solid tumors).

- Phase 1a: GS:1423 monotherapy dose escalation and flat dose regimen:

  (Part A dose escalation): Up to 53 subjects

  (Part B flat dose regimen): Up to 40 subjects

- Phase 1b:

  Cohort 1 (gastric cancer treated with GS-1423+mFOLFOX6): Up to 90 subjects

  Cohort 2 (CCI [redacted] GS-1423 monotherapy): Up to 30 subjects

4.1.1. Subject Replacement

Subjects who do not complete the DLT observation period of 28 days after the first dose, for reasons other than a DLT, will be replaced.

For Phase 1a Part B, replacement subjects may be enrolled if subjects do not complete intensive PK and CCI [redacted] collection in the first 28 days on and after the first dosing of GS-1423 (including trough PK and CCI [redacted]

4.2. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study:

1) Voluntarily agree to participate by giving written informed consent

2) Age ≥ 18 years

3) Diagnosis:

   a) Phase 1a and Phase 1b Cohort 2: Have a histologically or cytologically confirmed diagnosis of a locally advanced or metastatic solid tumor for which no standard therapy is available (per local guidance) or standard therapy has failed

b) Phase 1b Cohort 1 (gastric cancer): Have histologically or cytologically confirmed advanced (unresectable, recurrent or metastatic) gastric or gastroesophageal junction adenocarcinoma who have not previously received systemic therapy for advanced disease (perioperative, neoadjuvant, and adjuvant chemotherapy regimens will not count as a prior regimen, unless PD has occurred during or within 6 months of neoadjuvant/adjuvant chemotherapy). Gastroesophageal junction adenocarcinoma is defined as tumors with epicenters no more than 2 cm into the gastric cardia {Rice 2017}.

   i) Is human epidermal growth factor receptor 2 (HER2)/neu negative

   ii) Has not received prior treatment with an immune checkpoint inhibitor within 2 years of day 1 of study treatment

4) Have measurable disease on imaging based on Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) (Appendix 3)

5) Have a life expectancy of at least 3 months and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

6) Have adequate organ function as indicated by the following laboratory values:

System	Laboratory Value[a]
Hematological[b]	
Absolute Neutrophil Count (ANC)	$\geq 1.5 \times 10^9$/L $\geq 2 \times 10^9$/L (for Phase 1b Cohort 1 only)
Platelets	$\geq 100 \times 10^9$/L
Hemoglobin	≥ 9 g/dL
Renal	
Creatinine clearance	≥ 50 mL/min by the Cockcroft-Gault method
Hepatic	
Total bilirubin	$\leq 1.5 \times$ ULN
AST (SGOT) and ALT (SGPT)	$\leq 2.5 \times$ ULN
Coagulation[c]	
International Normalized Ratio (INR) or Prothrombin Time (PT)	$\leq 1.5 \times$ ULN unless the subject is receiving anticoagulant therapy
Activated Partial Thromboplastin Time (aPTT)	$\leq 1.5 \times$ ULN unless the subject is receiving anticoagulant therapy

a All screening laboratory tests must be reviewed by the investigator and be acceptable prior to randomization.
b Hematologic laboratory values must be met at screening visit and maintained without transfusion and growth factors prior to the first study drug dose
c Subjects on full dose oral anticoagulation, must be on a stable dose (minimum duration 14 days). Subjects on low molecular weight heparin will be allowed. In subjects receiving warfarin, the recommended INR is ≤ 3.0 with no active bleeding (ie, no bleeding within 14 days prior to first dose of study drug).

7) Tissue criteria:

   a) Phase 1a and Phase 1b Cohort 1: Subjects must have available, sufficient, and adequate formalin fixed tumor tissue sample (as specified in the Laboratory Manual) preferably from a biopsy of a tumor lesion obtained either at the time of or after the diagnosis of advanced disease has been made and from a site not previously irradiated. Alternatively, subjects must agree to have a biopsy taken prior to entering the study to provide adequate tissue. Fine needle aspirates are not acceptable. Core needle or excisional biopsy or resected tissue is required.

   b) Phase 1b Cohort 2: Subjects must have a tumor lesion that biopsies can be obtained from prior to treatment and on treatment. The biopsies for each subject should be taken from the same lesion.

8) A negative serum pregnancy test is required for female subjects (unless permanently sterile or greater than 2 years postmenopausal as described in Appendix 5).

9) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception and refrain from egg or sperm donation as described in Appendix 5.

10) Lactating females must agree to discontinue nursing before the study drug is administered.

11) Is willing and able to comply with the requirements of the protocol.

4.3. Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study:

1) Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigation device within 3 weeks of the first dose of treatment.

2) Has received prior systemic cytotoxic chemotherapy, biological therapy, radiotherapy or major surgery within 3 weeks; a 1-week washout is permitted for palliative radiation to non-CNS disease with Gilead approval.

3) Has persisting toxicity related to prior therapy of NCI CTCAE v5.0 Grade > 1 severity.

   Note: Alopecia and sensory neuropathy of Grade ≤ 2 is acceptable.

4) Is expected to require any other form of systemic or localized anticancer therapy while on study (including maintenance therapy with another agent, radiation therapy, and/or surgical resection).

5) Has known severe hypersensitivity reactions (NCI CTCAE Grade ≥ 3) to fully human monoclonal antibodies, GS-1423 formulation excipient, or severe reaction to immuno-oncology agents, such as colitis or pneumonitis requiring treatment with corticosteroids, any history of anaphylaxis, or uncontrolled asthma

6) Is receiving systemic corticosteroid therapy 1 week prior to the first dose of study treatment or receiving any other form of systemic immunosuppressive medication.

   Note: The following corticosteroid uses are permitted: use as premedication for known hypersensitivity reactions (e.g. IV contrast, IV drug infusions); intraocular, intranasal, inhaled, and/or topical corticosteroids; and/or prednisone at doses of up to 10 mg per day or equivalent.

7) Has concurrent active malignancy other than nonmelanoma skin cancer, carcinoma in situ of the cervix, or superficial bladder cancer who has undergone potentially curative therapy with no evidence of disease. Subjects with other previous malignancies are eligible if disease free for > 2 years.

8) Has a known CNS metastasis(es), unless metastases are treated and stable and the subject does not require systemic corticosteroids for management of CNS symptoms at least 7 days prior to study treatment. Subjects with history of carcinomatous meningitis are excluded regardless of clinical stability.

9) Has active or history of autoimmune disease that has required systemic treatment within 2 years of the start of study treatment (ie, with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs).

   Note: Subjects with diabetes type 1, vitiligo, psoriasis, hypothyroid disease, or hyperthyroid disease not requiring immunosuppressive treatment are eligible.

10) Has had an allogeneic tissue/solid organ transplant

11) Has or had interstitial lung disease (ILD)

12) Has a serious systemic fungal, bacterial, viral, or other infection that is not controlled or requires IV antibiotics

13) Has known history of human immunodeficiency virus (HIV)

14) Has known active hepatitis B virus (HBV) and/or hepatitis C virus (HCV)

15) Subjects with cardiovascular disease/abnormalities will be excluded per the following criteria:

    a. Has clinically significant (ie, active) cardiovascular disease: cerebral vascular accident/stroke or myocardial infarction within 6 months of enrollment, unstable angina, congestive heart failure (New York Heart Association class ≥ II), or serious uncontrolled cardiac arrhythmia requiring medication

    b. Has a mean QT interval corrected for heart rate (QTc) using the Fridericia formula (QTcF) ≥ 470 ms

    c. Has systolic dysfunction defined as ejection fraction < 50% measured by echocardiogram (or multigated acquisition [MUGA] scan) at baseline

16) Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator

17) Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study

18) Is legally incapacitated or has limited legal capacity

19) Taking biotin supplements within 72 hours of screening

20) Has positive serum pregnancy test (Appendix 5)

21) Has had prior treatment with anti-CD73 or TGFβ therapies

22) Breastfeeding female

23) Phase 1b Cohort 2: Has melanoma

24) Phase 1b Cohort 2: Has any tumor from which 2 biopsies cannot be obtained. Bone biopsies and ascites are not acceptable tumor samples for the study

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Enrollment and Blinding

5.1.1. Enrollment

An IXRS will be employed to manage the conduct of the study. The IXRS will be used to maintain a central log documenting enrollment, to assess current inventories of study drug, to initiate any necessary resupply of study drug, and to document discontinuation of study drug. Subjects who meet eligibility criteria will be enrolled starting on Day 1 and assigned a subject number by IXRS.

5.1.2. Blinding

Blinding of treatment assignments or data will not be performed in this study.

5.2. Description and Handling of GS-1423

GS-1423 is a bifunctional, Fc-engineered (N297A, aglycosylated) IgG1κ antibody that selectively antagonizes 2 prominent resistance pathways for cancer immunotherapy: CD73-adenosine and TGFβ.

GS-1423 consists of 4 polypeptide chains with 2 identical heavy chains of 603 amino acids each and 2 identical kappa light chains of 214 amino acids each. The heavy chains are linked through 2 disulfide bonds, and each heavy chain/light chain pair is linked through a single interchain disulfide bond. Included in each heavy chain is an extracellular domain of TGFβRII (cytokine trap moiety, 136 amino acids), fused to the carboxy-terminus of the CH_3 domain with a glycine-serine linker of 22 amino acids ($(G_4S)_4G$). Additional information may be found in the investigator's brochure.

5.3. Formulation

5.3.1. GS-1423

GS-1423 drug product is supplied as a sterile, single-use solution for IV infusion in a US Pharmacopeia-compliant Type 1 borosilicate glass vial. Each drug product vial contains, at minimum, 50 mg of GS-1423 in a formulation buffer containing 10 mM L-histidine, 145 mM sodium chloride, 0.01% polysorbate 80, pH 6.0. The excipients in the formulation of GS-1423 are compendial, and there are no novel excipients or excipients of human or animal origin used in the production or formulation of GS-1423. Detailed information can be found in the Pharmacy Manual.

5.3.2. mFOLFOX6

The mFOLFOX6 dosing regimen will consist of *dl*-LV or *l*-LV, oxaliplatin, and 5-FU.

5.3.2.1. *dl*-Leucovorin and *l*-Leucovorin

dl-Leucovorin and *l*-LV is commercially sourced. Information regarding the formulation can be found in the current prescribing information.

5.3.2.2. Oxaliplatin

Oxaliplatin is commercially sourced. Information regarding the formulation can be found in the current prescribing information.

5.3.2.3. 5-Fluorouracil

5-Fluorouracil is commercially sourced. Information regarding the formulation can be found in the current prescribing information.

5.3.3. Packaging and Labeling

Packaging and labeling will be in accordance with applicable local and national regulatory requirements and applicable Good Manufacturing Practice guidelines. All study drugs must be kept in a secure place under appropriate storage conditions. Gilead or its representatives must be granted access on reasonable request to check drug storage, dispensing procedures, and accountability records.

MFOLFOX6 may be supplied by Gilead per local country regulations for certain regions.

5.3.4. Storage and Handling

GS-1423 will be shipped frozen in temperature appropriate containers (20°C ± 5°C) that are monitored with temperature-controlled devices.

GS-1423 drug product vials must be stored at 20°C ± 5°C (with a temperature log maintained daily) and protected from light. Caution should be taken to ensure that GS-1423 drug product vials are not placed in freezers set to lower temperatures, in order to avoid cracking of the glass. Storage conditions are specified on the study drug label. Until dispensed to the subject, all study drugs should be stored in a securely locked area, accessible only to authorized site personnel. To ensure stability and proper identification, the study drug should be stored in the containers in which they are supplied until dosing to the subject. Instructions for preparation of GS-1423 drug product for administration can be found in the Pharmacy Manual.

Information regarding the storage and handling of *dl*-LV/*l*-LV, oxaliplatin, and 5-FU can be found in the current prescribing information.

5.4. Dosage and Administration of Study Drugs

Relevant clinical laboratory results essential for subject management decisions (hematology, serum chemistry, coagulation) must be available and reviewed before administration of GS-1423.

Premedications should not be administered routinely prior to dosing of GS-1423. Refer to Section 5.5.3 for subsequent premedication recommendations following GS-1423 related infusion reactions.

GS-1423 should be administered IV over approximately 60 minutes (-10/+20 minutes) at the research clinic by a qualified staff member on Day 1 of each treatment cycle. Infusions will be followed immediately with a saline flush of the IV line, per institutional guidelines. Modifications of the infusion rate due to infusion-related reactions are described in Section 5.5.3.

Subjects receiving GS-1423 should be monitored for infusion reactions. This includes the measurement of vital signs prior to each infusion commencing, at the end of each infusion, and for the first 2 cycles, 1 hour (± 15 minutes) after the end of the GS-1423 infusion. Thereafter, the final vital signs can be taken 30 minutes (-10/+20 minutes) after the end of the GS-1423 infusion. Subjects will remain in the clinic under close supervision for the duration of this monitoring period.

5.4.1. GS-1423 Monotherapy: Phase 1a and Phase 1b Cohort 2

Phase 1a, Part A will consist of dose escalation by an accelerated dosing design and a 3+3 dose escalation scheme with escalating dose levels of GS-1423 (0.3, 1, 3, 10, 20, 30, and 45 mg/kg) administered Q2W. Subjects in Phase 1a, Part B of the study will be administered a flat dose of GS-1423 at QW, Q2W, and/or Q3W. Subjects in Phase 1b Cohort 2 will be administered GS-1423 at a flat dose/dosing schedule that matches the exposure of the RP2D determined based on cumulative data from Phase 1a.

5.4.2. GS-1423 + mFOLFOX6: Phase 1b Cohort 1

GS-1423 will be administered on Day 1 of each 14-day treatment cycle.

Subjects in Phase 1b, Cohort 1 (gastric cancer) will also be administered mFOLFOX6 starting on Day 1 of each 14-day treatment cycle after administration of GS-1423. The mFOLFOX6 dosing regimen will consist of *l*-LV 200 mg/m^2 or *dl*-LV 400 mg/m^2 and oxaliplatin 85 mg/m^2 followed by bolus 5-FU 400 mg/m^2 and a 46-hour infusion of 5-FU 2400 mg/m^2 for up to 12 cycles. After 12 cycles, subjects may continue to receive 5-FU and leucovorin at the Investigator's discretion until the subject meets study treatment discontinuation criteria or up to 2 years. Minor modifications to the duration of the infusion time are permitted as per institutional standard. Adjustments to the dose of mFOLFOX6 are permitted in response to treatment-emergent AEs. Refer to the current prescribing information for care of subjects including contraindications, subject monitoring, and the medicinal products prohibited or to be used with care for all the components of mFOLFOX6.

For Phase 1b Cohort 1, vital signs will be measured as per standard institutional guidelines for mFOLFOX6 infusion.

5.5. Dose Modifications and Treatment Delay

If an AE is considered to be attributed to 1 or more study drugs (ie, GS-1423 or 1 or more component of mFOLFOX6), it is at the investigator's discretion to withhold or discontinue the relevant study drug(s) for the safety of the subject at any time during the study. The subject may continue study treatment with the remainder of study drug regimen.

5.5.1. Dose Modifications

5.5.1.1. GS-1423

Intrasubject dose reduction of GS-1423 is not permitted; the need for a dose reduction is considered a DLT, and the subject will be discontinued from treatment.

Intrasubject dose escalation of GS-1423 is not permitted except for subjects enrolled in Phase 1b Cohort 1 1 Dose 1 Q2W (gastric cohort) where GS-1423 may be increased to RP2D dose with mFOLFOX6, once determined, at Investigator's discretion.

5.5.1.2. mFOLFOX6

Recommended dose modification for the components of mFOLFOX6 is described in Table 5-1 and is based on the tables in Appendix 6. Sites may also follow their institutional practice for dose reductions. Leucovorin doses may be adjusted per institutional guidelines in the event of a supply shortage.

Subjects who permanently discontinue all components of mFOLFOX6 can continue GS-1423 until meeting the discontinuation criteria.

Investigators should contact the Gilead medical monitor with any questions regarding study drug dose modification, interruption, or discontinuation.

Table 5-1. Dose Modification[a] for mFOLFOX6

Drug	Dose Level		
	Starting Dose	**-1**	**-2[b]**
Oxaliplatin	85 mg/m^2	65 mg/m^2	50 mg/m^2
5-FU bolus	400 mg/m^2	OMIT	OMIT
5-FU continuous infusion over 46 hours	2400 mg/m^2	1900 mg/m^2	1500 mg/m^2
l-Leucovorin/*dl*-Leucovorin[c]	200/400 mg/m^2	200/400 mg/m^2	200/400 mg/m^2

5 FU 5 fluorouracil; AE adverse event
a If an AE is believed likely to be due to 1 drug, it is permissible to decrease dose of that drug only.
b Further dose levels (3, 4, etc) will be 20% dose reductions from the previous level for oxaliplatin and 5 FU continuous infusion. In addition, the bolus dose of 5 FU will continue to be omitted, and the *l* leucovorin/*dl* leucovorin dose will remain unadjusted at 200/400 mg/m^2
c Dosing of leucovorin will remain fixed at 100% of recommended dose.

5.5.2. Treatment Delay

For infusion-related reactions and immune-related AEs attributed to GS-1423, please follow Sections 5.5.3 and 5.5.4, respectively, for treatment delay guidance. For AEs attributed to mFOLFOX6, please follow Appendix 6 for guidance.

Study treatment may also be delayed due to any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants a delay.

If an AE is attributed to only one study drug, it is at the Investigator's discretion to determine if the study drug(s) not attributed to the AE will be withheld based on the Investigator's assessment of risk-benefit of withholding one or more study drugs.

Subjects who have drug-related toxicities that meet the criteria for dose delay should have study drug treatment delayed until criteria to resume treatment are met. It is recommended to restart study drug treatment at the next scheduled administration.

Note: GS-1423 should be discontinued in subjects who experience any Grade ≥ 3 skin drug-related AE, suspected/confirmed Stevens-Johnson syndrome, or suspected/confirmed toxic epidermal necrolysis. See Section 5.5.6 for permanent treatment discontinuation criteria due to AEs.

5.5.3. Treatment of Infusion-Related Reactions

Acute infusion reactions (which can include, CRS, angioedema, or anaphylaxis) are different from allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include allergic reaction/hypersensitivity (including drug fever); arthralgia (joint pain); bronchospasm; cough; dizziness; dyspnea (shortness of breath); fatigue (asthenia, lethargy, malaise); headache; hypertension; hypotension; myalgia (muscle pain); nausea; pruritus/itching; rash/desquamation; rigors/chills; sweating (diaphoresis); tachycardia; tumor pain (onset or exacerbation of tumor pain due to treatment); urticaria (hives, welts, wheals); and vomiting.

For individual subjects, once the GS-1423 infusion rate has been decreased by 50% or interrupted due to an infusion-related reaction, it must remain decreased for all subsequent infusions for that subject. If the subject has a second infusion-related reaction that is Grade ≥ 2 at the slower infusion rate, infusion should be stopped, and the subject should discontinue treatment. If a subject experiences a Grade 3 or Grade 4 infusion-related reaction at any time, the subject must discontinue treatment (Table 5-2). If an infusion reaction occurs, all details about drug preparation and infusion must be recorded.

For the gastric cohort (Phase 1b Cohort 1), careful monitoring must be ensured for subjects with a history of allergic reactions to other platinum-based chemotherapy agents. In the event of anaphylactic shock symptoms, interrupt infusion immediately and initiate appropriate treatment. Resumption of oxaliplatin treatment following anaphylactic reaction is contraindicated.

Clinically significant, abnormal 12-lead safety electrocardiograms (ECGs) should be repeated. Subjects who have 2 consecutive ECGs showing a new absolute QTcF (Fridericia correction) duration > 500 ms, or a QTc > 60 ms over the corresponding baseline value must discontinue any medications that could prolong the QT interval (including oxaliplatin). Subject's concomitant medications should be reviewed to determine a potential etiology for the ECG changes. Appropriate intervention (ie, cardiology evaluation, telemetry monitoring, management of electrolyte abnormalities) in response to treatment-emergent QT interval prolongation should be initiated.

Should infusion reaction be considered a significant safety issue by the SRT, the SRT might decide to recommend premedication with an antihistamine and acetaminophen approximately 30 to 60 minutes before each dose of GS-1423 (eg, 25-50 mg diphenhydramine, 500-1000 mg acetaminophen or equivalent dose of antipyretic).). This regimen may be modified based on local treatment standards and guidelines, as appropriate.

Table 5-2 shows treatment guidelines for subjects who experience an infusion reaction associated with administration of GS-1423.

Subjects receiving GS-1423 should be monitored for infusion reactions. This includes the measurement of vital signs prior to each infusion commencing, at the end of each infusion, and for the first 2 cycles, 1 hour (± 15 minutes) after the end of the GS-1423 infusion. Thereafter, the final vital signs can be taken 30 minutes (-10/+20 minutes) after the end of the GS-1423 infusion. Subjects will remain in the clinic under close supervision for the duration of this monitoring period. Subjects with mild or moderate infusion reactions may receive GS-1423 with close monitoring. Premedication with an antipyretic or antihistamine for subsequent treatment administration may be considered. For severe infusion reactions, GS-1423 infusion must be discontinued, and appropriate medical therapy should be administered.

Subjects who do not experience any infusion-related toxicity Grade 1 or higher during or after the infusion may be released from monitoring after 1 hour if they are otherwise stable. Subjects with any infusion-related toxicity must be managed as per the guidelines in Table 5-2, and monitoring will continue until any infusion-related toxicity has abated to less than Grade 1 and at least 1 hour has passed from the completion of the entire infusion and flushing the line. All subjects will be given information on and instructions regarding both infusion-related toxicity, which is expected to be most likely in the hour after completion of the infusion, and immune-related AEs (irAEs) before leaving the study site.

Table 5-2. GS-1423 Infusion-Related Reactions Management Guidelines

CTCAE Grade	Treatment	Premedication at Subsequent Dose Administration
Grade 1 Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None.
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti inflammatory drugs [NSAIDs], narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	Stop infusion and monitor symptoms. Additional appropriate medical therapy may include but is not limited to the following: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate. Otherwise, dose administration will be held until symptoms resolve, and the subject should be premedicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug administration.	Subject may be premedicated prior to infusion with the following: Diphenhydramine 25 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500 1000 mg PO (or equivalent dose of antipyretic).
Grade 3 or 4 Grade 3 Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates). Grade 4 Life threatening; pressor or ventilatory support indicated.	Stop infusion. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressor Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. Subject is permanently discontinued from further study drug administration.	No subsequent dosing.

CTCAE Common Terminology Criteria for Adverse Events; IV intravenous; NSAID nonsteroidal anti inflammatory drug; PO orally

5.5.4. Management of Potential Immune-Related Adverse Events

Immune-related AEs may be associated with immuno-oncology agents such as GS-1423 and will be categorized as AEs of interest in this study. An irAE is defined as an AE of unknown etiology, that is potentially associated with study drug exposure and is consistent with an immune-mediated phenomenon. Efforts should be made to rule out other etiologies prior to labeling an AE of clinical interest. Early recognition and management of irAEs may mitigate

severe toxicity. Investigators should also monitor subjects closely for potential irAEs, which may manifest after weeks of treatment, at the earliest. Such events may consist of persistent rash, diarrhea, colitis, autoimmune hepatitis, pneumonitis, encephalitis, arthritis, glomerulonephritis, cardiomyopathy, or uveitis and other inflammatory eye conditions.

Management algorithms have been developed to assist investigators in assessing and managing the following groups of irAEs: dermatological, gastrointestinal, pulmonary, hepatic, endocrine renal, and neurological, among others.

Adverse events (both non-serious and serious) associated with drug exposure and consistent with an immune phenomenon may represent an immunologic etiology. These irAEs may be predicted based on the nature of the study drugs, their mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. An irAE can occur any time from shortly after the first dose to several months after the last dose of treatment. Particular attention should be paid to AEs that may be suggestive of potential irAEs, as outlined below.

5.5.4.1. Dermatological irAEs

Rule out non-inflammatory causes. If a non-inflammatory cause is identified, treat accordingly and continue therapy per protocol.

Table 5-3. Dermatological irAE Management Algorithm

Dermatological irAEs		
CTCAE Grade of Rash	**Management**	**Follow-up**
Grade 1-2 Covering ≤ 30% body surface area	Symptomatic therapy (eg, antihistamines, topical corticosteroids). Continue GS-1423 therapy per protocol.	**If persists > 1 to 2 weeks or recurs**: Consider skin biopsy. Delay GS-1423 therapy. Consider 0.5-1 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper corticosteroids over ≥ 1 month; consider prophylactic antibiotics for opportunistic infections; and resume GS-1423 therapy per protocol. **If worsens**: Treat as Grade 3-4.
Grade 3-4 Covering > 30% body surface area; life-threatening consequences	Delay or discontinue GS-1423 therapy per protocol. Consider skin biopsy. Dermatology consult 1-2 mg/kg/day methylprednisolone IV or IV equivalent.	**If improves to Grade 1**: Taper corticosteroids over ≥ 1 month; add prophylactic antibiotics for opportunistic infections. Resume GS-1423 therapy per protocol.

CTCAE Common Terminology Criteria for Adverse Events; irAE immune related adverse event; IV intravenous.

5.5.4.2. Gastrointestinal irAEs

Rule out non-inflammatory causes. If a non-inflammatory cause is identified, treat accordingly and continue therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Table 5-4. Gastrointestinal irAE Management Algorithm

Gastrointestinal irAEs		
CTCAE Grade of Diarrhea / Colitis	**Management**	**Follow-up**
Grade 1 Diarrhea: < 4 stools/day over baseline. Colitis: asymptomatic.	Continue GS-1423 therapy per protocol. Symptomatic treatment.	Close monitoring for worsening symptoms. Educate subject to report worsening immediately. Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide. **If worsens**: Treat as Grade 2 or 3-4.
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated < 24 h; not interfering with activities of daily living (ADL). Colitis: abdominal pain; blood in stool.	Delay GS-1423 therapy per protocol. Symptomatic treatment.	**If improves to Grade 1**: Resume GS-1423 therapy per protocol. **If persists > 5 to 7 days or recurs**: 0.5-1 mg/kg/day methylprednisolone or equivalent. When symptoms improve to Grade 1, taper corticosteroids over ≥ 1 month; consider prophylactic antibiotics for opportunistic infections; resume GS-1423 therapy per protocol. **If worsens or persists > 3 to 5 days with oral corticosteroids**: Treat as Grade 3-4.
Grade 3-4 Diarrhea (Grade 3): ≥ 7 stools per day over baseline; incontinence; IV fluids ≥ 24 h; interfering with ADL. Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs. Grade 4: life-threatening, perforation	Discontinue GS-1423 therapy per protocol. 1-2 mg/kg/day methylprednisolone IV or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider lower endoscopy.	**If improves**: Continue corticosteroids until Grade 1, then taper over ≥ 1 month. **If persists > 3 to 5 days or recurs after improvement**: Add infliximab 5 mg/kg (if no contraindication). **Note**: Infliximab should not be used in cases of perforation or sepsis.

ADL activities of daily living; CTCAE Common Terminology Criteria for Adverse Events; irAE immune related adverse event; IV intravenous.

5.5.4.3. Pulmonary irAEs

Rule out non-inflammatory causes. If a non-inflammatory cause is identified, treat accordingly and continue therapy per protocol. Evaluate with imaging and pulmonary consultation.

Table 5-5. Pulmonary irAE Management Algorithm

Pulmonary irAEs		
CTCAE Grade of Pneumonitis	**Management**	**Follow-up**
Grade 1 Radiographic changes only.	Consider delay of GS-1423 therapy per protocol. Monitor for symptoms every 2-3 days. Consider pulmonary and infectious disease consults.	Re-image every ≥ 3 weeks. **If worsens**: Treat as Grade 2 or Grade 3-4.
Grade 2 Mild to moderate new symptoms.	Delay GS-1423 therapy per protocol. Pulmonary and infectious disease consults. Monitor symptoms daily; consider hospitalization. 1 mg/kg/day methylprednisolone IV or oral equivalent. Consider bronchoscopy, lung biopsy.	Re-image every 1-3 days. **If improves**: When symptoms return to near baseline, taper corticosteroids over ≥ 1 month, then resume GS-1423 therapy per protocol, and consider prophylactic antibiotics. **If not improving after 2 weeks or worsening**: Treat as Grade 3-4.
Grade 3-4 Severe new symptoms; new/ worsening hypoxia; life-threatening.	Discontinue GS-1423 therapy per protocol. Hospitalize. Pulmonary and infectious disease consults. 2-4 mg/kg/day methylprednisolone IV or IV equivalent. Add prophylactic antibiotics for opportunistic infections. Consider bronchoscopy, lung biopsy.	**If improves to baseline**: Taper corticosteroids over ≥ 6 weeks. **If not improving after 48 hours or worsening**: Add additional immunosuppression (eg, infliximab, cyclophosphamide, IV immunoglobulin, mycophenolate mofetil).

CTCAE Common Terminology Criteria for Adverse Events; irAE immune related adverse event; IV intravenous.

5.5.4.4. Hepatic irAEs

Rule out non-inflammatory causes. If a non-inflammatory cause is identified, treat accordingly and continue therapy per protocol. Consider imaging for obstruction.

Table 5-6. Hepatic irAE Management Algorithm

Hepatic irAEs		
CTCAE Grade of Liver Test Elevation	**Management**	**Follow-up**
Grade 1 AST or ALT > ULN to 3 × ULN or total bilirubin > ULN to 1.5 × ULN.	Continue GS-1423 therapy per protocol.	Continue liver function tests (LFT) monitoring per protocol. **If worsens**: Treat as Grade 2 or Grade 3-4.
Grade 2 AST or ALT > 3 to ≤ 5 × ULN or total bilirubin > 1.5 to ≤ 3 × ULN.	Delay GS-1423 therapy per protocol. Increase frequency of monitoring to every 3 days. If subject has concurrent AST or ALT > 3 × ULN **and** total bilirubin > 2 × ULN > 7 days, discontinue GS-1423 therapy per protocol.	**If returns to baseline**: Resume routine monitoring; resume GS-1423 therapy per protocol. **If elevations persist > 5 to 7 days or worsen**: 0.5-1 mg/kg/day methylprednisolone IV or oral equivalent. When LFT returns to Grade 1 or baseline, taper corticosteroids over ≥ 1 month, consider prophylactic antibiotics for opportunistic infections, and resume GS-1423 therapy per protocol.
Grade 3-4 AST or ALT > 5 × ULN and/or total bilirubin > 3 × ULN.	Discontinue GS-1423 therapy per protocol. Increase frequency of monitoring to every 1-2 days. 1-2 mg/kg/day methylprednisolone IV or oral equivalent.[a] Add prophylactic antibiotics for opportunistic infections. Consult gastroenterology. Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted.	**If returns to Grade 2**: Taper corticosteroids over ≥ 1 month. **If does not improve in > 3 to 5 days, worsens or rebounds**: Add mycophenolate mofetil 1 g twice daily. If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines.

ALT alanine aminotransferase; AST aspartate aminotransferase; CT computed tomography; CTCAE Common Terminology Criteria for Adverse Events; irAE immune related adverse event; IV intravenous; LFT liver function test; MRI magnetic resonance imaging; ULN upper limit of normal.
a The recommended starting dose for Grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

5.5.4.5. Endocrine irAEs

Rule out non-inflammatory causes. If a non-inflammatory cause is identified, treat accordingly and continue therapy per protocol. Consider visual field testing, endocrinology consultation, and imaging.

Table 5-7. Endocrine irAE Management Algorithm

Endocrine irAEs		
Endocrine Disorder	**Management**	**Follow-up**
Asymptomatic TSH abnormality.	Continue GS-1423 therapy per protocol. **If TSH < 0.5 × lower limit of normal (LLN) or TSH > 2 × ULN, or consistently out of range in 2 subsequent measurements**: Include free thyroxine at subsequent cycles as clinically indicated; consider endocrinology consult.	
Symptomatic endocrinopathy.	Evaluate endocrine function. Consider pituitary scan. **Symptomatic with abnormal lab/pituitary scan**: Delay GS-1423 therapy per protocol; 1-2 mg/kg/day methylprednisolone IV or oral equivalent; initiate appropriate hormone therapy. **No abnormal lab/pituitary MRI scan but symptoms persist**: Repeat labs in 1-3 weeks, MRI in 1 month.	**If improves (with or without hormone replacement)**: Taper corticosteroids over ≥ 1 month and consider prophylactic antibiotics for opportunistic infections. Resume GS-1423 therapy per protocol. Subjects with adrenal insufficiency may need to continue corticosteroids with mineralocorticoid component.
Suspicion of adrenal crisis (eg, severe dehydration, hypotension, shock out of proportion to current illness)	Delay or discontinue GS-1423 therapy per protocol. Rule out sepsis. Stress dose of IV corticosteroids with mineralocorticoid activity. IV fluids. Consult endocrinologist. If adrenal crisis ruled out, treat as above for symptomatic endocrinopathy.	

irAE immune related adverse event; IV intravenous; LLN lower limit of normal; MRI magnetic resonance imaging; TSH thyroid stimulating hormone; ULN upper limit of normal.

5.5.4.6. Renal irAEs

Rule out non-inflammatory causes. If a non-inflammatory cause is identified, treat accordingly and continue therapy per protocol.

Table 5-8. Renal irAE Management Algorithm

Renal irAEs		
CTCAE Grade of Creatinine Elevation	**Management**	**Follow-up**
Grade 1 Creatinine > ULN and > baseline but ≤ 1.5 × baseline.	Continue GS-1423 therapy per protocol. Monitor creatinine weekly.	**If returns to baseline**: Resume routine creatinine monitoring per protocol. **If worsens**: Treat as Grade 2 or Grade 3-4.
Grade 2-3 Creatinine > 1.5 × baseline to ≤ 6 × ULN.	Delay GS-1423 therapy per protocol. Monitor creatinine every 2-3 days. 0.5-1.0 mg/kg/day methylprednisolone IV or oral equivalent. Consider renal biopsy.	**If returns to Grade 1**: Taper corticosteroids over ≥ 1 month, consider prophylactic antibiotics for opportunistic infections, and resume GS-1423 therapy and routine creatinine monitoring per protocol. **If elevations persist > 7 days or worsen**: Treat as Grade 4.
Grade 4 Creatinine > 6 × ULN	Discontinue GS-1423 therapy per protocol. Monitor creatinine daily. 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent. Consult nephrologist. Consider renal biopsy.	**If returns to Grade 1**: Taper corticosteroids over ≥ 1 month and add prophylactic antibiotics for opportunistic infections.

CTCAE Common Terminology Criteria for Adverse Events; irAE immune related adverse event; IV intravenous; ULN upper limit of normal.

5.5.4.7. Neurological irAEs

Rule out non-inflammatory causes. If a non-inflammatory cause is identified, treat accordingly and continue therapy per protocol.

Table 5-9. Neurological irAE Management Algorithm

Neurological irAEs		
CTCAE Grade of Neurological Toxicity	**Management**	**Follow-up**
Grade 1 Asymptomatic or mild symptoms; intervention not indicated.	Continue GS-1423 therapy per protocol	Continue to monitor subject. **If worsens**: Treat as Grade 2 or Grade 3-4.
Grade 2 Moderate symptoms; limiting instrumental ADL.	Delay GS-1423 therapy per protocol. Treat symptoms per local guidelines. Consider 0.5-1.0 mg/kg/day methylprednisolone IV or oral equivalent.	**If returns to baseline**: Resume GS-1423 therapy per protocol. **If worsens**: Treat as Grade 3-4.
Grade 3-4 Severe symptoms; limiting self-care ADL; life-threatening.	Discontinue GS-1423 therapy per protocol. Obtain neurology consult. Treat symptoms per local guidelines. 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent. Add prophylactic antibiotics for opportunistic infections.	**If improves to Grade 2**: Taper corticosteroids over ≥ 1 month. **If worsens or atypical presentation**: Consider IV immunoglobulin or other immunosuppressive therapies per local guidelines.

ADL activities of daily living; CTCAE Common Terminology Criteria for Adverse Events; irAE immune related adverse event; IV intravenous.

5.5.5. Criteria to Resume Treatment

Subjects may resume treatment with GS-1423 when drug-related AE(s) resolve(s) to Grade 1 or baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue.

- Subjects with combined Grade 2 AST/ALT **and** total bilirubin values lasting > 7 days meeting discontinuation parameters (Section 5.5.6) should have treatment permanently discontinued.

- Drug-related Grade 2 pulmonary toxicity or colitis must have resolved to baseline before treatment is resumed.

- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment. (Exception: Study treatment does not need to be delayed/interrupted for subjects who experience immune-related hypothyroidism [Grades 1-2].)

- Subjects who received systemic corticosteroids for management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone ≤ 10 mg/day.

5.5.6. Permanent Treatment Discontinuation

Study drug treatment must be discontinued for drug-related AEs described in Table 5-10. Non-AE reasons for study treatment discontinuation can be found in Section 6.10.1.

Table 5-10. Drug-Related Adverse Events Requiring Discontinuation of GS-1423

Toxicity Category*	Qualifying Severity/Duration
Ophthalmic	• Grade 2 uveitis, blurred vision, eye pain, and/or reduction of visual acuity that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks OR requires systemic treatment • Grade 3 or higher uveitis
Gastrointestinal	• Grade 3 or higher diarrhea, colitis
Neurologic	• Grade 3 or higher neurologic toxicities
Dermatologic	• Grade 3 or higher skin AE, suspected Stevens-Johnson syndrome, or toxic epidermal necrolysis
Pulmonary	• Grade 2 pneumonitis or interstitial lung disease that does not improve after 2 weeks or worsening despite dose delay and systemic corticosteroids (see Table 5-5) • Grade 3 or higher pneumonitis
Endocrinopathies	• Grade 3 endocrinopathies not adequately controlled with physiologic hormone replacement • Grade 4 or higher endocrinopathies
Hypersensitivity	• Grade 3 or higher bronchospasm, hypersensitivity reaction, or infusion-related reaction

Toxicity Category*	Qualifying Severity/Duration
Laboratory	Thrombocytopenia • Grade 3 thrombocytopenia lasting > 7 days or associated with clinically significant bleeding (i.e. requires hospitalization, transfusion of blood products, or other urgent medical intervention) • Grade 4 thrombocytopenia Neutropenia • Grade 4 neutropenia lasting > 7 days Electrolyte Abnormalities • Grade 4 electrolyte abnormalities with clinical sequelae • Grade 4 electrolyte abnormalities unable to be corrected with supplementation/appropriate management within 72 hours of onset Liver Function Abnormalities (see Table 5-6) • AST or ALT > 5 × ULN • Total bilirubin > 3 × ULN • Concurrent AST or ALT > 3 × ULN **AND** total bilirubin > 2 × ULN lasting > 7 days
Other	• Grade 2 or 3 adverse event (laboratory or non-laboratory) that does not resolve in ≤ 12 weeks • Recurrence of Grade 3 or higher adverse event (laboratory or non-laboratory) • Grade 4 non-hematologic adverse event

* AE must be study drug related for discontinuation reasons to apply

5.5.6.1. Treatment Compliance

Treatment delays from the protocol-specified treatment plan for greater than 4 weeks (QW or Q2W) or 6 weeks (Q3W) require consultation between the investigator and Gilead and written documentation of the collaborative decision on subject management.

Administration of study medications will be witnessed by the investigator and/or study staff. The total volume of study treatments infused will be compared with the total volume prepared to determine compliance with each dose administered.

Any reason for noncompliance should be documented. Drug treatment noncompliance is defined as a subject missing > 1 cycle of study treatment for non-medical reasons. If 1 cycle was missed and the interval between the subsequent treatment cycle and the last administered treatment cycle is longer than 4 weeks for non-medical reasons, criteria for insufficient compliance are met.

5.5.7. Treatment Beyond Initial Progressive Disease

Subjects who experience initial radiologic PD and are not doing well clinically will discontinue study drug treatment and no further imaging is required.

Subjects who experience initial radiologic PD and are doing well clinically are considered to have initial RECIST 1.1-defined PD and will be permitted, with Gilead's approval, to continue with study drug treatment. These subjects will be reevaluated using the same imaging modality no less than 4 weeks later to assess whether study drug treatment will be continued. To continue study drug treatment beyond initial RECIST 1.1-defined PD, they must meet the following criteria:

- There is investigator-assessed clinical benefit from the treatment
- Subject is clinically stable
- Subject is tolerating study drug and
- There is agreement with Gilead

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment. The following criteria need to be taken into consideration:

- Absence of clinical symptoms and signs (including worsening of laboratory values) indicating PD,
- No decline in ECOG performance status attributed to underlying malignancy, and
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, spinal cord compression) requiring urgent alternative medical intervention.

5.5.7.1. Subsequent Anticancer Therapy

The investigator or qualified designee will review all new anticancer therapy initiated after the last dose of study treatment. If a subject initiates a new anticancer therapy within 30 days after the last dose of study treatment, the 30-Day Follow-up Visit must occur before the first dose of the new therapy. Once new anticancer therapy has been initiated, subjects will move into the first posttreatment visit at 3 months from last treatment dose, then survival follow-up thereafter.

5.6. Prior and Concomitant Medications

5.6.1. Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. Concomitant medications, including all prescription, over-the-counter, herbal supplements, and IV medications and fluids received within 30 days before the first dose of study treatment through the 30-day follow-up visit should be recorded in the electronic case report form (eCRF). If changes occur during the study period, documentation of drug dosage, frequency, route, and date will also be included on the eCRF.

Palliative and supportive care is permitted during the course of the study for underlying medical conditions and management of symptoms.

Surgery for tumor control or symptom management is not permitted during the study. Palliative radiotherapy is permitted to a single lesion if considered medically necessary by the treating physician as long as the lesion is NOT a RECIST 1.1 defined target lesion and treatment is NOT administered for tumor control. Study therapy should be held during the course of palliative radiotherapy and should be resumed no earlier than the next scheduled administration of study therapy. The specifics of the radiation treatment, including the location, will be recorded.

5.6.1.1. Rescue Medications and Supportive Care

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator including but not limited to the items outlined below.

For guidelines for continuing treatment with GS-1423, see Section 5.5.5.

- Diarrhea: Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic subjects, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered. All subjects who experience diarrhea should be advised to drink liberal quantities of clear fluids or rehydration solutions. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

- Anemia: Transfusions may be utilized as clinically indicated for the treatment of anemia but should be clearly noted as concurrent medications or in a transfusion page. Consider a potential immunologic etiology and follow the American Society of Clinical Oncology (ASCO) guidelines for use of erythropoietin or derivatives.

- Neutropenia: Prophylactic use of colony-stimulating factors including granulocyte colony-stimulating factor (G-CSF), PEGylated G-CSF, or granulocyte macrophage colony-stimulating factor is not allowed in this study. Therapeutic use of G-CSF is allowed in subjects with Grade 3 to 4 febrile neutropenia. Consider a potential immunologic etiology.

- Thrombocytopenia: Transfusion of platelets may be used if clinically indicated. Immune thrombocytopenia purpura should be ruled out before initiation of platelet transfusion.

- Anti-infectives: Subjects with suspected or documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.

- Adverse events with a potential immunologic etiology (irAEs): Follow ASCO or local institutional practice guidelines for identification, evaluation, and management of adverse experiences of a potential immunologic etiology. Depending on the type and severity of an irAE, oral or IV treatment with a corticosteroid should be considered, in addition to appropriate symptomatic treatment of a given condition (see Section 5.5.4 for management algorithms guidance).

5.6.2. Prohibited and/or Restricted Treatments

Subjects are prohibited from receiving the following therapies and treatments during the study. Study treatment will be discontinued in subjects who, in the assessment by the investigator, require the use of any of the following therapies and treatments for clinical management:

- Immunotherapy not specified in this protocol

- Chemotherapy

- Investigational agents other than GS-1423

- Corticosteroids are not permitted with the following exceptions:

  As premedication for known hypersensitivity reactions (e.g. IV contrast, IV drug infusion);

  Note: Premedication should not be administered routinely prior to dosing of GS-1423. Refer to Section 5.5.3 for subsequent premedication recommendations following GS-1423-related infusion reactions. Premedication for mFOLFOX6 should follow local SmPC or institutional guidance.

  Intraocular, intranasal, inhaled, and/or topical corticosteroids; and/or

  Prednisone at doses of up to 10 mg per day or equivalent.

- Live vaccines within 30 days prior to first dose of study therapy and while participating in study

There are no prohibited therapies during the Posttreatment Follow-up Phase.

5.6.3. Other Restrictions and Precautions

The following non-drug therapies must not be administered or performed during the study:

- Major elective surgery
- Herbal remedies with immunostimulating properties (eg, mistletoe extract) or that are known to potentially interfere with major organ function (eg, hypericin)
- Subjects should not abuse alcohol or other drugs during the study

5.7. Accountability for Study Drug

The investigator is responsible for ensuring adequate accountability of all used and unused study drug (kits, vials, diluent ampules, etc). This includes acknowledgment of receipt of each shipment of study drug (quantity and condition) and tracking of vials assigned/utilized for subject dosing.

Each study site must keep accountability records that capture:

- The date received and quantity of study drug vials
- The date, subject number, and the study drug lot number dispensed
- The date and quantity of used and unused study drug, along with the initials of the person recording the information

5.7.1. Investigational Medicinal Product Return or Disposal

Gilead recommends that used and unused study drug supplies be destroyed at the site. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead, the site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for the electronic trial master file. If study drug is destroyed on site, the investigator must maintain accurate records for all study drugs destroyed. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be returned to Gilead.

If the site does not have an appropriate SOP for drug destruction, used and unused study drug supplies are to be sent to the designated disposal facility for destruction. The study monitor will provide instructions for return.

The study monitor will review study drug supplies and associated records at periodic intervals.

Please refer to the current version of the Pharmacy Manuals for return and disposal instructions for GS-1423.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Appendix 2 and described in the text that follows.

The investigator must document any deviation from the protocol procedures and notify Gilead or the CRO.

6.1. Subject Enrollment and Treatment Assignment

Entry into screening does not guarantee enrollment into the study. In order to manage the total study enrollment, Gilead, at its sole discretion, may suspend screening and/or enrollment at any site or study-wide at any time.

6.2. Pretreatment Assessments

6.2.1. Screening

Subjects will be screened within 28 days prior to the first dose of study treatment to determine eligibility for participation in the study. The following will be performed and documented during screening as per Appendix 2:

- Within 28 days prior to first dose of study treatment:

  Administrative procedures including

  - Obtain written informed consent
  - Review of inclusion/exclusion criteria
  - Issue Emergency Medical Support and Subject Card
  - Obtain medical history and demographics
  - Review of baseline symptoms
  - Review of prior and concomitant medications
  - Obtain cancer disease details and prior treatments

  Tumor biopsy and/or archival tissue collection

Obtain blood samples for serum chemistry, hematology, coagulation, endocrine function, HBV and HCV serologies

- For HBV serology, hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), and total hepatitis B core antibody (anti-HBc). For subjects where total anti-HBc-positive, HBV DNA by quantitative polymerase chain reaction will be required
- For HCV serology, HCV antibody. For subjects with positive HCV antibody, HCV RNA by quantitative polymerase chain reaction will be required

Obtain urine for urinalysis

Blood pharmacogenomics sample may be collected from enrolled and consented subject before or at Cycle 1, Day 1, predose

CCI [redacted]

Phase 1b Cohort 1 (gastric cancer): HER2 Testing: Prior to randomization, the subject's tumor should have been tested for HER2 status with approved immunohistochemistry (IHC) and in situ hybridization (ISH) kits. HER2 positivity is defined as IHC3+ or IHC2+/ISH+ (ISH positivity is defined as HER2:CEP17 ratio of ≥ 2.0). Results for HER2 status obtained prior to signing informed consent are acceptable if obtained with approved IHC and ISH kits. HER2 status may be determined during screening by testing the tumor at the central laboratory or a local laboratory with approved IHC and ISH kits.

CCI [redacted]

Tumor imaging, unless diagnostic quality tumor imaging is available for exams within 28 days prior to the first dose of study treatment

- Within 14 days prior to the first dose of study treatment:

  Echocardiogram evaluation or MUGA scan

- Within 7 days prior to the first dose of study treatment:

  Full physical examination including vital signs, body weight, and height

  ECOG performance status

  12-lead ECG

- Within 72 hours prior to the first dose of study treatment:

  For women of reproductive potential, a serum pregnancy test will be performed within 72 hours prior to first dose of study treatment. If a serum pregnancy test was performed during screening, but earlier than 72 hours prior to first dose, a urine pregnancy test may be performed prior to first dose. A negative pregnancy test collected within 72 hours prior to first dose must be available prior to the administration of the first dose.

The investigator or qualified designee must obtain documented informed consent from each potential subject prior to participating in the clinical study.

Specimens that may be used for genetic testing include blood and tumor specimens collected during this study.

After a subject signs an informed consent form, the subject will be assigned a unique, sequential subject number. Once a number is assigned, it cannot be reassigned if the original subject is found to be ineligible or withdraws consent.

All subjects will be given an Emergency Medical Support and Subject Card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with an Emergency Medical Support and Subject Card immediately after the subject provides written informed consent.

Subjects who fulfill all of the inclusion criteria and none of the exclusion criteria will be enrolled into the study within 28 days after screening. Subjects who do not meet the inclusion and exclusion criteria will be considered screen fails, and their demographic information and reason for screen failure should be documented.

During the screening period, attention must be given to washout periods for prior treatments and prohibited medications.

Results from assessments performed during the initial screening period are acceptable in lieu of repeating a screening test if performed within the specified period and the results meet the inclusion/exclusion criteria.

From the time of obtaining informed consent through the first administration of investigational medicinal product, record all serious AEs (SAEs), as well as any AEs related to protocol-mandated procedures on the AEs case report form (CRF/eCRF). All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history CRF/eCRF. See Section 7 Adverse Events and Toxicity Management for additional details.

Serum chemistry, hematology, and coagulation and hepatitis serologies performed at screening to assess subject eligibility will be determined by results received from the central lab. If time constraints do not allow for timely processing of tests through central lab, then, eligibility may be determined using local lab results, with documentation of local lab results and sponsor approval.

6.2.2. Re-screening Criteria

Subjects who do not enroll within 28 days of screening will be screen failed.

Re-screening may be allowed. Subjects who are re-screened after 28 days must be re-consented with a new screening number, and the screening assessments must be repeated. For subjects who are re-screened within 28 days, assessments with results that would exclude the subject will need to be repeated.

6.2.3. Medical History and Baseline Assessments

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions; history of HBV, HCV, HIV, and/or human papillomavirus; and any condition diagnosed within the prior 10 years that is considered clinically significant by the Investigator. Medical history will also include an assessment of smoking history.

Baseline symptoms will be assessed for each subject at screening. Baseline symptoms will be graded and recorded according to NCI CTCAE v5.0. Baseline symptoms will be characterized in terms including seriousness, causality to previous treatment, toxicity grading, and action(s) taken if any.

6.2.3.1. Cancer Disease Details and Prior Treatment

Cancer disease history will be recorded separately and not listed as medical history. Current cancer disease details and prior treatment will be obtained for all subjects including:

- Detailed history of the tumor, including histopathological diagnosis, grading, and staging in accordance with the eighth edition of the American Joint Committee on Cancer staging manual (AJCC-8) tumor node metastasis classification at diagnosis
- All therapy used for prior treatment of the tumor (including surgery, radiotherapy, chemotherapy, and immunotherapy)
- Any other conditions treated with chemotherapy, radiation therapy, or immunotherapy
- Current cancer signs and symptoms, and side effects from current and/or previous anticancer treatments
- Current cancer disease status
- Relevant somatic or germ line mutations detected
- Smoking history

- Chronic viral infection status, if available
- Tumor markers, if indicated

6.2.4. Vital Signs, Weight, and Height

The investigator or qualified designee will take vital signs at screening, prior to and following the administration of each dose of study treatment, and through the Follow-up period as specified in the Study Procedures Table (Appendix 2). Vital signs will only be measured while subject is in seated or semi-recumbent position. Vital signs include temperature, pulse, respiratory rate, and blood pressure. Weight should be assessed as specified in Appendix 2 prior to dosing, at the beginning of each cycle, and through the follow-up period. Height will be measured at screening only.

6.2.5. Physical Examination

6.2.5.1. Full Physical Examination

The investigator or qualified designee will perform a complete physical examination during the screening period and at the End-of-Treatment Visit as specified in the Study Procedures Table (Appendix 2). Clinically significant abnormal findings should be recorded as medical history. After consent, new clinically significant abnormal findings should be recorded as AEs as per Section 7.3.

6.2.5.2. Focused Physical Examination

For cycles that do not require a full physical examination as specified in the Study Procedures Table (Appendix 2), the investigator or qualified designee will perform a directed physical examination as clinically indicated prior to study treatment administration. New clinically significant abnormal findings should be recorded as AEs.

6.2.5.3. Eastern Cooperative Oncology Group Performance Status

ECOG performance status will be assessed at screening, prior to the administration of each dose of study treatment and during the Follow-up period as specified in Appendix 2.

6.2.6. Electrocardiogram

A standard 12-lead ECG will be performed using local standard procedures at screening and as specified in Appendix 2. For subjects in Cohorts 5 through 10, a triplicate ECG will be performed at Cycle 1, Day 1 predose, at end of infusion, at 24 hours postdose (Day 2), and 168 hours postdose (Day 8). Clinically significant abnormal findings at screening should be recorded as medical history.

6.2.7. Echocardiogram or MUGA Scan

A full standard echocardiogram evaluation will be performed using local standard procedures at screening to establish a baseline and on Day 1 of every odd cycle, starting at Cycle 3. A MUGA scan is also allowed. Clinically significant abnormal findings at screening should be recorded as medical history and discussed with the medical monitor.

6.2.8. Prior and Concomitant Medications

Prior medication taken by the subject within 30 days prior to screening visit will be recorded. In addition, record all treatments for a prior cancer other than current cancer even if taken greater than 30 days prior to screening. Prior treatments for the current cancer will be recorded separately and not listed as a prior medication.

Concomitant medications, if any, taken by the subject during the study from the date of consent through the 30-Day Follow-up Visit should be recorded. After the 30-Day Follow-up Visit, all medications related to reportable SAEs will be recorded as defined in Section 7.3.

6.2.9. Clinical Laboratory Assessments

The central laboratory will be responsible for chemistry, hematology, coagulation, urinalysis, HBV and HCV serology, and serum pregnancy testing (Table 6-1) as well as processing and/or storage of other study samples. Specific instructions for processing, labeling, and shipping samples will be provided in a central laboratory manual. The date and time of sample collection will be reported to the central laboratory.

If central laboratory results are not available, local laboratories may be used for dosing decisions. Local laboratory assessments resulting in a dose change or as part of an AE assessment, which is not supported by central laboratory results, will be reported on the eCRF. Gilead's standard reference ranges will be used.

Urine pregnancy test will be performed locally at the site.

Laboratory tests for screening should be performed within 28 days prior to the first dose of study treatment. After Cycle 1, predose laboratory procedures can be conducted up to 72 hours prior to dosing.

Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of study treatment. The report of the results must be retained as a part of the subject's medical record or source documents. Blood samples for study-related tests will be collected at time points specified in Appendix 2.

Table 6-1. Analytes

Chemistry	Urinalysis	Hematology	Other
Albumin Alkaline phosphatase ALT AST Bicarbonate BUN/total urea Calcium Chloride Serum Creatinine[a] CRP GGT Glucose LDH Lipase Cholesterol Tryglycerides Amylase Magnesium Phosphorus/phosphates Potassium Sodium Total bilirubin[b] Direct bilirubin Total protein Uric acid	Color and appearance Specific gravity pH Occult blood Protein Glucose Bilirubin Leukocyte esterase Nitrite Urobilinogen Ketones Microscopic[b]	WBC and differential absolute count Eosinophils Lymphocytes Monocytes ANC Hemoglobin Hematocrit Platelet count MCV RBC **Coagulation** Prothrombin time (INR) aPTT	Serum β hCG or urine pregnancy test[c] Endocrine Function Tests (TSH and freeT4[d]) Basal cortisol Hepatitis Serology[b]

β hCG beta human chorionic gonadotropin; ALT alanine aminotransferase; ANC total absolute neutrophil count; aPTT activated partial thromboplastin time; AST aspartate aminotransferase; BUN blood urea nitrogen; CRP C reactive protein; Free T4 free thyroxine; GGT gamma glutamyltransferase; INR international normalized ratio; LDH lactate dehydrogenase; MCH mean corpuscular hemoglobin; MCHC mean corpuscular hemoglobin concentration; MCV mean corpuscular volume; RBC red blood cell; PT prothrombin time; TSH thyroid stimulating hormone; WBC white blood cell

a Estimated creatinine clearance (CL_{cr})/glomerular filtration rate will be calculated based on the Cockcroft Gault formula using actual body weight: CL_{cr} (mL/min) (140 age [years])* weight (kg) / (serum creatinine [mg/dL]*72). If the subject is female, multiply the quantity by 0.85.

b Reflex testing based on other abnormalities

c Females of childbearing potential only. Serum pregnancy will be conducted at screening within 72 hours of first treatment dose (if performed earlier in screening period then a urine pregnancy test may be performed prior to first dose); urine pregnancy test at all other indicated visits.

d TSH and free T4 will be tested by the central laboratory. T4 will be tested reflexively based on abnormal TSH results.

6.3. Randomization

No randomization procedures will be applied to treatment assignment for the study.

6.4. Treatment Assessments

Subject should continue to receive all assessments as defined in the Treatment Phase (Cycle 1 Day 1 [C1D1] until End of Treatment) of the Study Procedures Table (Appendix 2) while they are actively receiving treatment.

6.5. Unscheduled Visits

Unscheduled visits may occur at any time while the subject is enrolled on study. Data generated during an unscheduled visit will be collected in subject source documents and captured in the eCRFs.

6.6. Pharmacokinetic CCI [redacted]

6.6.1. Pharmacokinetic Assessments

6.6.1.1. Pharmacokinetic Parameters

GS-1423 concentrations will be determined by a validated method. The PK parameters to be estimated and reported may include, but may not be limited to, maximum observed drug concentration (C_{max}), area under the concentration versus time curve over the dosing interval (AUC_{tau}), observed drug concentration at the trough (C_{trough}), time to maximum observed concentration (T_{max}), systemic clearance (CL), and V_d as applicable. Unresolved missing data may be imputed when analysis integrity is affected. The conservative principle will be used for data imputation. Noncompartmental techniques will be used to analyze the PK. Compartmental modeling (eg, population PK) analysis may be conducted.

6.6.1.2. PK Sample Collection

Blood sample collection for GS-1423 PK characterization will be conducted throughout the study. The time for collection of PK blood draws should always be referenced from the start of the infusion. It is important to record all infusion start dates/times, infusion end dates/times, infusion interruption(s) start and end dates/times, infusion flush end dates/times, and blood sample dates/times completely and accurately (and to the nearest minute).

Blood will be collected predose [within 0.5 hours predose] at specified time points (Table 6-2, Table 6-3 and Table 6-4) throughout the study. Additionally, blood will be collected at the 30-Day Follow-up Visit (approximately 30 days after last dose) and at the first Posttreatment Follow-up Visit (approximately 3 months after last dose).

6.6.1.2.1. PK Sample Collection for Phase 1a Cohorts

6.6.1.2.1.1. PK Sample Collection for QW Dosing Schedule in Phase 1a Cohorts

At Cycles 1 and 6, blood will be collected predose [within 0.5 hours predose], and at end of infusion [+ 10 minutes], 2 hours [± 15 minutes], 6 hours [± 0.5 hours], Day 2 (24 hours) [± 2 hours], Day 3 (48 hours) [± 4 hours], and Day 5 (96 hours) [± 4 hours] post start of infusion. At Cycle 6, blood will also be collected at Day 8 (168 hours) [± 4 hours] post start of infusion.

Table 6-2. Schedule of Pharmacokinetic Assessments for QW Dosing Schedule in Phase 1a Cohorts

	Day 1	Day 2 (24 h)	Day 3 (48 h)	Day 5 (96 h)	Day 8 (168 h)
Cycle 1	Predose, end of infusion, 2 and 6 h post start of infusion	X	X	X	
Cycle 2	Predose				
Cycle 3	Predose				
Cycle 6	Predose, end of infusion, 2 and 6 h post start of infusion	X	X	X	X [b]
Subsequent every 4 cycles up to 1 year	Predose (and 2 h[a] post start of infusion for last even cycle only)				
30-Day Follow-up Visit (30 days after last dose)	X				
Posttreatment Follow-up Visit (3 months after last dose)	X				

QW every week
a PK collection at 2 hours post start of infusion will only be conducted at the last even cycle visit.
b Blood will be drawn at Cycle 6, Day 8 (± 4 hours) even if the subject discontinues treatment at Cycle 7.

6.6.1.2.1.2. PK Sample Collection for Q2W Dosing Schedule in Phase 1a Cohorts

At Cycles 1 and 4, blood will be collected predose [within 0.5 hours predose], and at end of infusion [+ 10 minutes], 2 hours [± 15 minutes], 6 hours [± 0.5 hours], Day 2 (24 hours) [± 2 hours], Day 3 (48 hours) [± 4 hours], Day 5 (96 hours) [± 4 hours], and Day 8 (168 hours) [± 4 hours] post start of infusion. At Cycle 4, blood will also be collected at Day 15 (336 hours) [± 1 day] post start of infusion.

Table 6-3. Schedule of Pharmacokinetic Assessments for Q2W Dosing Schedule in Phase 1a Cohorts

	Day 1	Day 2 (24 h)	Day 3 (48 h)	Day 5 (96 h)	Day 8 (168 h)	Day 15 (336 h)
Cycle 1	Predose, end of infusion, 2 and 6 h post start of infusion	X	X	X	X	
Cycle 2	Predose					
Cycle 3	Predose					
Cycle 4	Predose, end of infusion, 2 and 6 h post start of infusion	X	X	X	X	X[b]
Subsequent even cycles up to 1 year	Predose (and 2 h[a] post start of infusion for last even cycle only)					
30-Day Follow-up Visit (30 days after last dose)	X					
Posttreatment Follow-up Visit (3 months after last dose)	X					

Q2W every 2 weeks
a PK collection at 2 hours post start of infusion will only be conducted at the last even cycle visit.
b Blood will be drawn at Cycle 4, Day 15 (± 1 day) even if the subject discontinues treatment at Cycle 5.

6.6.1.2.1.3. Pharmacokinetic Sample Collection for Q3W Dosing Schedule in Phase 1a Cohorts

At Cycle 1 and Cycle 3, blood will be collected predose [within 0.5 hours predose], and at end of infusion [+ 10 minutes], 2 hours [± 15 minutes], 6 hours [± 0.50 hours], Day 2 (24 hours) [± 2 hours], Day 3 (48 hours) [± 4 hours], Day 5 (96 hours) [± 4 hours], Day 8 (168 hours) [± 4 hours], and Day 15 (336 hours) [± 1 day] post start of infusion. At Cycle 3, blood will also be collected at Day 22 (504 hours) [± 1 day] post start of infusion.

Table 6-4. Schedule of Pharmacokinetic Assessments for Q3W Dosing Schedule in Phase 1a Cohorts

	Day 1	Day 2 (24 h)	Day 3 (48 h)	Day 5 (96 h)	Day 8 (168 h)	Day 15 (336 h)	Day 22 (504 h)
Cycle 1	Predose, end of infusion, 2 and 6 h post start of infusion	X	X	X	X	X	
Cycle 2	Predose						
Cycle 3	Predose, end of infusion, 2 and 6 h post start of infusion	X	X	X	X	X	X[b]
Subsequent even cycles up to 1 year	Predose (and 2 h[a] post start of infusion for last even cycle only)						
30-Day Follow-up Visit (30 days after last dose)	X						
Posttreatment Follow-up Visit (3 months after last dose)	X						

Q3W every 3 weeks

a PK collection at 2 hours post start of infusion will only be conducted at the last even cycle visit.

b Blood will be drawn at Cycle 3, Day 22 (± 1 day) even if the subject discontinues treatment at Cycle 4.

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CCI [redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]				
[redacted]	[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]				
[redacted]	[redacted]				
[redacted]	[redacted]				
[redacted]	[redacted]				
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]						
[redacted]	[redacted]						
[redacted]	[redacted]						
[redacted]	[redacted]						
[redacted]	[redacted]						

[redacted]

6.6.2. Immunogenicity Assessment

The immunogenicity assessment will be conducted to detect and measure anti-drug antibody against GS-1423 (ADA). Subjects will have ADA assessed at the designated time points as described below.

6.6.2.1. Immunogenicity Assessment in Phase 1a Cohorts

Table 6-8. Schedule of ADA Assessments for QW

Cycle 1 Day 1	Predose
Cycle 3 Day 1	Predose
Cycle 4 Day 1	Predose
Cycle 6 Day 1	Predose
Cycle 6 Day 8	168 h postdose
At Cycle 8 Day 1 and subsequent every 12 cycles	Predose
30-Day Follow-up Visit (30 days after last dose)	X
Posttreatment Follow-up Visit (3 months after last dose)	X

ADA anti drug antibody against GS 1423; h hour(s); QW every week
Note: Blood will be drawn at Cycle 6, Day 8 (± 4 hours) even if the subject discontinues treatment at Cycle7.

Table 6-9. Schedule of ADA Assessments for Q2W

Cycle 1 Day 1	Predose
Cycle 2 Day 1	Predose
Cycle 3 Day 1	Predose
Cycle 4 Day 1	Predose
Cycle 4 Day 15	336 h postdose
At Cycle 6 Day 1 and subsequent every 6 cycles	Predose
30-Day Follow-up Visit (30 days after last dose)	X
Posttreatment Follow-up Visit (3 months after last dose)	X

ADA anti drug antibody against GS 1423; Q2W every 2 weeks
Note: Blood will be drawn at Cycle 4, Day 15 (± 1 day) even if the subject discontinues treatment at Cycle 5.

Table 6-10. Schedule of ADA Assessments for Q3W

Cycle 1 Day 1	Predose
Cycle 2 Day 1	Predose
Cycle 3 Day 1	Predose
Cycle 3 Day 22	504 h postdose
Cycle 6 Day 1	Predose
At Cycle 8 Day 1 and subsequent every 4 cycles	Predose
30-Day Follow-up Visit (30 days after last dose)	X
Posttreatment Follow-up Visit (3 months after last dose)	X

ADA anti drug antibody against GS 1423; Q3W every 3 weeks
Note: Blood will be drawn at Cycle 3, Day 22 (± 1 day) even if the subject discontinues treatment at Cycle 4.

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CCI [redacted]

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CCI [redacted]

[redacted]

6.7. End of Study

End of study will be defined as when the last subject reaches the last scheduled follow-up time point (including posttreatment or survival), or lost to follow-up, withdraws from the study, dies, or the time at which Gilead closes the study.

6.8. Posttreatment Assessments

6.8.1. End-of-Treatment Phase Visits

End-of-Treatment requirements are outlined in Appendix 2. There is an End-of-Treatment Visit within 7 days of last dose of study treatment and a 30-Day Follow-up Visit which occurs 30 days (±7 days) after last dose of study treatment.

6.8.1.1. End-of-Treatment Visit

The End-of-Treatment Visit should occur at the time all study drug is permanently discontinued for any reason. If the End-of-Treatment Visit occurs 30 days from the last dose of study treatment, at the time of the mandatory 30-Day Follow-up Visit, procedures do not need to be repeated. Procedures at the time of discontinuation are detailed in 30-Day Follow-up Visit, Section 6.8.1.2. Subjects who discontinue from the study treatment for reasons other than PD will continue to have imaging/computed tomography (CT) scans at the predefined schedule until documented PD or initiation of a new anticancer treatment.

6.8.1.2. 30-Day Follow-up Visit

The mandatory 30-Day Follow-up Visit should be conducted for all subjects approximately 30 days after the last dose of study treatment or before the initiation of a new anticancer treatment, whichever comes first. Subjects with an AE of Grade > 1 will be further followed until the resolution of the AE to Grade 0 or 1 or until initiation of a new anticancer therapy, whichever occurs first.

6.8.2. Posttreatment Follow-up Phase Visits

All subjects who discontinue study treatment will have at least 1 posttreatment visit at 3 months (± 7 days) from last dose of study treatment. Subjects who discontinue all study treatment for any reason other than PD and/or start of new anticancer therapy will have imaging/CT scans at the predefined schedule until documented PD or initiation of a new anticancer treatment. Subjects who discontinue study drug treatment due to PD and/or start of a new anticancer therapy will not require imaging/CT scans and will move into Survival Follow-up thereafter.

Subjects who have discontinued all study drug treatment due to reasons other than PD and/or start of a new line of therapy should be followed with Posttreatment Follow-up Visits for up to 12 months from last study treatment dose or until PD and/or start of a new line of therapy. Every effort should be made to collect subject information on the start of new anticancer therapy, PD, and death.

6.8.3. Survival Follow-up

After the first Posttreatment Follow-up visit, subjects who present(ed) with PD and/or start(ed) a new anticancer therapy will move into Survival Follow-up. Subjects should be contacted by telephone to assess for survival status every 3 months for up to 12 months. No imaging assessment is required for Survival Follow-up. Information about deaths solicited during the Survival Follow-up Period should be reported, but will not be considered or reported as SAEs. Investigators should abide by the reporting obligations as stated in Section 7.

6.9. Assessments for Early Discontinuation from Study

If a subject discontinues study dosing (for example, as a result of an AE), every attempt should be made to keep the subject in the study and continue to perform the required study-related follow-up and procedures (see Section 6.10.1, Criteria for Discontinuation of Study Treatment). If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

6.10. Criteria for Discontinuation from Treatment or Study

6.10.1. Criteria for Discontinuation from Treatment

Discontinuation of treatment does not represent withdrawal from the study.

As certain data on clinical events beyond treatment discontinuation may be important to the study, they must be collected through the subject's last scheduled follow-up (including 30-Day Follow-up or Posttreatment visits), even if the subject has discontinued treatment. Subjects may discontinue treatment at any time for any reason or be dropped from treatment at the discretion of the investigator should any untoward effect occur. In addition, a subject may be discontinued from treatment by the Investigator or by Gilead if treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

Specific details regarding procedures to be performed at treatment discontinuation are provided in the Study Procedures Tables (Appendix 2). A subject must be discontinued from treatment but continue to be monitored in the trial for any of the following reasons:

- The subject or subject's legally acceptable representative requests to discontinue treatment for any reason.
- Occurrence of an event that would have been considered an exclusion criterion prior to enrollment, that is clinically relevant and affects the subject's safety, and if discontinuation is considered necessary by the investigator and/or Gilead.
- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree.
- Investigator's decision to discontinue the subject
- Initial PD, defined by RECIST 1.1 (Section 6.11.1), unless the subject is considered to derive clinical benefit from the treatment by the investigator, is clinically stable, and there is agreement with Gilead (Section 5.5.7).
- Therapeutic failure (i.e. clinical disease progression)
- Recurrence of previously treated malignancy or any occurrence of another malignancy that requires active treatment
- Pregnancy during the study
- Noncompliance with trial treatment or procedure requirements (Section 5.5.6.1)
- Use of a non-permitted concomitant drug, as defined in Section 5.6.2, for which the predefined consequence is withdrawal from study drug (Gilead may be contacted to discuss whether study treatment must be discontinued).
- Any requirement for > 10 mg of prednisone per day or equivalent for more than 6 weeks
- Dose delay of GS-1423 which results in no GS-1423 dosing for more than 4 weeks (QW or Q2W) or 6 weeks (Q3W)
- Discontinuation of the study at the request of Gilead, a regulatory agency, or an IRB/IEC
- Any AE and/or laboratory abnormality in the judgment of the investigator, presents a substantial clinical risk to the subject with continued treatment
- AEs specifically described in Section 5.5.6 must lead to study drug discontinuation.

NOTE: Tumor flare phenomenon, defined as local pain, irritation, or rash localized at sites of known or suspected tumor does not require treatment discontinuation.

6.10.2. Discontinuation from Disease Response Evaluation

Tumor evaluation will be discontinued if any of the following occurs:

- In a subject who does not meet the criteria to continue study drug treatment beyond initial RECIST 1.1-defined PD (Section 5.5.7).
- In a clinically stable subject (defined in Section 5.5.7), at the time of PD is assessed in a second, consecutive assessment (using the same imaging modality) no less than 4 weeks from previous imaging assessment.
- Initiation of new anticancer therapy

6.10.3. Criteria for Discontinuation from Study

Subjects should be discontinued from the study for 1 or more of the following:

- Withdrawal of consent
- Lost to follow-up
- Death
- Subject noncompliance (Section 5.5.6.1)
- Administrative study closure

6.11. Efficacy Assessments

6.11.1. Response Assessment

Response assessment will be performed according to RECIST 1.1 {Eisenhauer 2009}.

For all subjects, tumor response assessment will be performed by CT or magnetic resonance imaging (MRI) of the chest/abdomen/pelvis (plus other regions as required for specific tumor types) and other established assessments of tumor burden if CT/MRI imaging is insufficient for the individual subject. All scans performed at baseline and other imaging performed as clinically required (other supportive imaging) will be repeated at subsequent visits. In general, lesions detected at baseline should be followed using the same imaging methodology and preferably the same imaging equipment at subsequent tumor evaluation visits.

For each subject, the investigator will designate 1 or more of the following measures of tumor status to follow for determining response: CT or MRI images of primary and/or metastatic tumor masses, physical examination findings, and results of other assessments. All available images collected during the study period will be considered. The most appropriate measures to evaluate a subject's tumor status should be used. Measure(s) chosen for sequential evaluation during the

study must correspond to measures used to document progressive tumor status that qualifies the subject for enrollment.

Subjects who experience initial radiologic PD and are doing well clinically are considered to have initial RECIST 1.1-defined PD and will be permitted, with Gilead's approval, to continue with study drug treatment (see Section 6.11.2). These subjects will be reevaluated using the same imaging modality no less than 4 weeks later to assess whether study drug treatment will be continued. If initial progression is based on occurrence of a new lesion in an area not scanned at baseline, an on-study scan no less than 4 weeks from initial observation of new lesion should be considered before performing the End-of-Treatment Visit.

Tumor responses to treatment will be assigned based on evaluation of response of target, non-target, and new lesions according to RECIST 1.1 (all measurements should be recorded in metric notation; see {Eisenhauer 2009}). To assess objective response, tumor burden at baseline will be estimated and used for comparison with subsequent measurements. At baseline, tumor lesions will be categorized in target and non-target lesions as described in {Eisenhauer 2009}.

Results for these evaluations will be recorded with as much specificity as possible so that pretreatment and posttreatment results will provide the best opportunity for evaluating tumor response.

Any complete response (CR) or partial response (PR) should be confirmed by CT or MRI scan as described in {Eisenhauer 2009} no less than 28 days after initial assessment.

The investigator may perform scans in addition to a scheduled study scan for medical reasons or if PD is suspected.

6.11.2. Tumor Assessments

Tumor samples from archival tissues or biopsies will be collected. Subjects must have available tissue samples to enter the study. Alternatively, subjects must agree to have a biopsy taken prior to entering the study to provide adequate tissue. CCI [redacted]

6.11.2.1. Tissue Collection

Tumor tissue CCI [redacted] will be collected at the time of screening from a biopsy obtained preferably either at the time of or after the diagnosis of advanced disease has been made, and from a site not previously irradiated.

If a tumor biopsy was obtained from a target lesion during eligibility assessment, it is preferred that a new baseline scan be obtained.

CCI [redacted]

CCI [redacted]

In Cohort 2 in Phase 1b, pretreatment and C3D1 biopsies are mandatory.

For additional details and instructions regarding tissue requirements, collection, storage and shipment, refer to the study Laboratory Manual.

6.11.2.2. Tumor Imaging

Investigator-assessed imaging will be done at defined time points. The initial tumor imaging to establish baseline disease will be performed ≤ 28 days prior to first dose. Scans performed as part of routine clinical management are acceptable for use as screening scan if they are of diagnostic quality and ≤ 28 days prior to first dose. On-study imaging as listed on Table 6-18 will be performed as specified below and in Appendix 2.

Table 6-18. Postbaseline Imaging Schedule

Cohort	Postbaseline Imaging Schedule	Duration of Tumor Imaging Assessments
Phase 1a (all cohorts), Phase 1b Cohort 2	Week 6, 12, 18, and 24 (± 7 days) from the first treatment dose; then every 12 weeks thereafter	Until PD is assessed by investigator, new line of therapy, or 1 year after first treatment dose, whichever occurs first
Phase 1b Cohort 1	Week 6, 12, 18, and 24 (± 7 days) from the first treatment dose; then every 12 weeks thereafter	Until PD is assessed by investigator, new line of therapy, or 2 years after first treatment dose, whichever occurs first

PD progressive disease

Note: For subjects who permanently discontinued all study drug(s) in the absence of PD (eg, experienced unexpected toxicity), CT or MRI imaging should continue to be performed until PD or initiation of a new anticancer therapy other than the study treatment, whichever occurs first (see Section 6.8.2).

The timing of on-study treatment imaging should follow calendar days and should not be adjusted for delays in treatment administration or for visits. Additional imaging at the End-of-Treatment Visit and 30-Day Follow-up Visit is not required provided imaging assessments have been performed per schedule and last imaging must be performed within less than 30 days. Subjects that discontinue from the study for any reason other than PD will continue to have imaging/CT scans at the predefined schedule until documented PD or initiation of a new anticancer treatment.

The same imaging technique should be used in a subject throughout the study. In general, lesions detected at baseline should be followed using the same imaging methodology and preferably the same imaging equipment at subsequent tumor evaluation visits. The Investigator may perform scans in addition to a scheduled study scan for medical reasons or if PD is suspected.

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7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study subject administered an investigational product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. Adverse events may also include pretreatment or posttreatment complications that occur as a result of protocol-specified procedures or special situations (Section 7.7). Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs. Adverse events should be reported as described in Section 7.3.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and must be reported.
- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (ie, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (Section 7.7.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the informed consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be preexisting and should be documented as medical history.

7.1.2. Serious Adverse Events

An SAE is defined as an event that, at any dose, results in the following:

- Death (**Note:** In the case of death, the primary cause of death or the event leading to death should be recorded and reported as an SAE. “Fatal” will be recorded as the outcome of this respective event; death will not be recorded as separate event. Only if no cause of death can be reported (eg, sudden death, unexplained death), might the death per se be reported as an SAE. Please refer to Section 7.1.2.3 for exceptions.)

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

- In-patient hospitalization or prolongation of existing hospitalization

- Persistent or significant disability/incapacity

- A congenital anomaly/birth defect

- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse.

7.1.2.1. Protocol-Specific Adverse Event Instructions

Given the intended mechanism of action, particular attention should be given to AEs that may result from enhanced T-cell activation, such as dermatitis, colitis, hepatitis, uveitis, or other immune-related reactions. When clinically indicated, ophthalmologic examinations should be considered for signs or symptoms of uveitis.

An irAE may be defined as an AE of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes prior to labeling an AE as immune related. Immunological, serological, and histological (biopsy) data should be used to support the diagnosis of an immune-related toxicity.

Complete, accurate, and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the eCRF. Any serious irAEs should be reported in accordance to Section 7.3.

It is important that each AE report include a description of the event, its duration (onset and resolution dates and times to be completed when it is important to assess time of AE onset relative to recorded treatment administration time), its severity, causal relationship with study treatment, any other potential causal factors, any treatment administered, or other action taken (including dose modification or discontinuation of the study drug), and outcome. In addition, serious cases should be identified, and the appropriate seriousness criteria documented.

Specific guidance can be found in the eCRF Completion and Monitoring Conventions.

7.1.2.2. Events of Clinical Interest

Events of clinical interest, regardless of seriousness, are to be reported within 24 hours to Gilead either by electronic media or paper. Gilead contact information can be found in the Investigator Study File Binder (or equivalent).

Events of clinical interest for this study include:

- An elevated AST or ALT lab value ≥ 3 × ULN and an elevated total bilirubin lab value ≥ 2 × ULN and, at the same time, an alkaline phosphatase lab value < 2 × ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.

  Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

7.1.2.3. Disease Progression

In order to maintain the integrity of the study, the following events that are assessed as unrelated to study drugs will not be considered SAEs:

- Disease progression of malignancy being studied
- Death due to disease progression of malignancy being studied

Disease progression and death due to disease progression of malignancy being studied should be reported as an SAE by the investigator only if it is assessed as related to study drug.

7.2. Assessment of Adverse Events and Serious Adverse Events

The Investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship to study drug using clinical judgment and the following considerations:

- **No**: Evidence exists that the AE has an etiology other than the study drug. For SAEs, an alternative causality must be provided (ie, preexisting condition, underlying disease, intercurrent illness, or concomitant medication).
- **Yes**: There is reasonable possibility that the event may have been caused by the study drug.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

The relationship to study procedures (ie, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the AE has an etiology other than the study procedure.
- **Yes:** The AE occurred as a result of protocol procedures (ie, venipuncture).

7.2.2. Assessment of Severity

Adverse events will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE v5.0. A general grading (severity/intensity) scale is provided at the beginning of the referenced document, and specific event Grades are also provided. If a particular AE severity/intensity is not specifically graded by the guidance document, the investigator is to revert to the general definitions of Grade 1 through Grade 5 and use his/her best medical judgment.

The 5 general Grades of AE severity are:

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe
- Grade 4: Life-threatening or disabling
- Grade 5: Death related to AE

7.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Gilead

Requirements for collection prior to study drug initiation:

After informed consent, but prior to initiation of study medication, the following types of events must be reported on the applicable eCRFs: all SAEs and AEs related to protocol-mandated procedures.

7.3.1. Adverse Events

Following initiation of study medication, collect all AEs, regardless of cause or relationship, until the study's End-of-Treatment Safety Visit, 30 days after last administration of study drug and they must be reported on the eCRFs as instructed.

All AEs should be followed up until resolution or until the AE is stable, if possible. Gilead may request that certain AEs be followed beyond the protocol-defined follow-up period.

7.3.2. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occurs after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, up to 30-Day Follow-up Visit, must be reported on the applicable eCRFs and to Gilead PVE as instructed below in this section. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Any SAEs and deaths that occur after the End-of-Treatment Visit but within 30 days of the last dose of study drug, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol-defined follow-up period; however, if the investigator learns of any SAEs that occur after the protocol-defined follow-up period has concluded and the event is deemed relevant to the use of study drug, the investigator should promptly document and report the event to Gilead PVE.

- All AEs and SAEs will be recorded in the eCRF database within 24 hours.

Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead PVE within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.

- If for any reason it is not possible to record the SAE information electronically (ie, the eCRF database is not functioning), record the SAE on the paper SAE reporting form and submit within 24 hours to:

  Gilead PVE: Fax: PPD
  E-mail: PPD

- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF database according to instructions in the eCRF completion guidelines.

- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.

- Additional information may be requested to ensure the timely completion of accurate safety reports.

- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's CRF/eCRF and the event description section of the SAE reporting form.

7.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US Food and Drug Administration Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions, or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the investigator's brochure or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study drug. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.5. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (ie, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (ie, ECG, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (ie, anemia), not the laboratory result (ie, decreased hemoglobin).

7.6. Toxicity Management

Severity should be recorded and graded according to NCI CTCAE v5.0 (Appendix 4).

7.7. Special Situations Reports

7.7.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of AEs associated with product complaints, and pregnancy reports regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.

Misuse is defined as any intentional and inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labeling. In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

- For monitoring purposes, any case of overdose, whether or not associated with an AE (serious or non-serious), must be reported to Gilead's or designated CRO's global drug safety department in an expedited manner using the Special Situations Report (SSR) form.
- There is no data on GS-1423 overdose to date.
- The investigator should use his/her clinical judgment when treating an overdose of GS-1423.

Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

7.7.2. Instructions for Reporting Special Situations

7.7.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study medication and throughout the study, including the Posttreatment Follow-up Period, to Gilead PVE using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

Refer to Section 7.3 and the eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination of pregnancy (ie, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 7.3.2. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead PVE.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead PVE using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE via:

Gilead PVE: Fax: PPD
E-mail: PPD

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to Gilead PVE using the pregnancy report and pregnancy outcome report forms within 24 hours. Monitoring of the subject should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE.

Refer to Appendix 5 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.7.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the SSR form and forwarded to Gilead PVE within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study drug and/or Gilead concomitant medications but do not apply to non-Gilead concomitant medications.

Special situations involving non-Gilead concomitant medications does not need to be reported on the SSR form; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be reported on the AE form.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse" but may be more appropriately documented as a protocol deviation.

Refer to Section 7.3 and the eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE CRF/eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The objectives of this study are described in Sections 2.1 and 2.2.

8.1.2. Primary Endpoints

Phase 1a Part A, Phase 1b Cohort 1 Safety Run-in

The primary endpoint is the occurrence of DLTs in subjects (ie, percentage of subjects who had DLTs) in dose escalation during the first 28 days of treatment.

Phase 1b Cohort 1 Post Safety Run-in

The primary endpoint is the confirmed ORR per RECIST 1.1, as determined by investigator and defined as the proportion of subjects who achieve best confirmed overall response of CR or PR as assessed by RECIST 1.1.

Phase 1a Part B, Phase 1b Cohort 2

The primary endpoints are:

- Percentage of subjects with treatment-emergent AEs
- Percentage of subjects with treatment-emergent Grade 3 or 4 laboratory abnormalities
- Percentage of subjects with clinically significant abnormal 12-lead ECG

8.1.3. Secondary Endpoints

The secondary endpoints of this study are:

Phase 1a Part A

- Percentage of subjects with treatment-emergent AEs
- Percentage of subjects with treatment-emergent Grade 3 or 4 laboratory abnormalities
- Percentage of subjects with clinically significant abnormal 12-lead ECG
- GS-1423 PK parameters (AUC_{tau})
- Percentage of subjects who developed ADA

Phase 1a Part B

- GS-1423 PK parameters (AUC_{tau})
- Percentage of subjects who developed ADA

Phase 1b Cohort 1

- Percentage of subjects with treatment-emergent AEs
- Percentage of subjects with treatment-emergent Grade 3 or 4 laboratory abnormalities
- Percentage of subjects with clinically significant abnormal 12-lead ECG

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8.2. Planned Analyses

8.2.1. Interim Analysis

8.2.1.1. Dose Escalation Analysis

For the purpose of making the decision to escalate to the next dose level/cohort, interim analyses of relevant safety and PK (if available) data will be conducted by Gilead after all subjects in each cohort have completed dosing and the follow-up period as defined in Section 3.2.3. Safety assessments (ie, AEs, ECG, and laboratory results) will be displayed by dose level/cohort to facilitate the decision to dose escalate.

8.2.1.2. Planned Internal Analysis

For Phase 1b Cohort 1 post safety run-in, one futility interim analysis may be performed after approximately 35 (ie, 50% of the planned sample size for this part of study) subjects have been enrolled and are able to complete study treatment for at least 6 months. The futility stopping boundary at the interim analysis will be determined by assessing predictive power. Details for the futility interim analysis will be specified in the statistical analysis plan. The enrollment for **Phase** 1b Cohort 1 will not be paused.

8.2.2. Final Analysis

The final analysis will be performed after all subjects have completed or discontinued from the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

8.3. Analysis Conventions

8.3.1. Analysis Sets

8.3.1.1. All Enrolled Analysis Set

The All Enrolled Analysis Set includes all subjects who received a study subject identification number in the study after screening. This will be the primary analysis set for by-subject listings.

8.3.1.2. DLT-Evaluable Analysis Set

The DLT-Evaluable Analysis Set includes all subjects who were enrolled for dose escalation, received the protocol-specified treatment, and completed safety procedures through Day 28 (inclusive) or experienced a DLT prior to Day 28. For Phase 1a Part A and Phase 1b Cohort 1 safety run-in, determination of the DLT and/or MTD or RP2D will be based on the DLT-Evaluable Analysis Set.

8.3.1.3. Safety Analysis Set

The Safety Analysis Set includes all subjects who received at least 1 dose of study drug. This will be the primary analysis set for safety analyses.

8.3.1.4. Full Analysis Set

The Full Analysis Set includes all enrolled subjects who received at least 1 dose of study drug. This will be the primary analysis set for efficacy analyses.

8.3.1.5. Pharmacokinetics Analysis Set

The PK Analysis Set includes all enrolled subjects who received at least 1 dose of study drug and have at least 1 non-missing postdose concentration value reported by the PK laboratory. This will be the primary analysis set for all PK analyses.

8.3.1.6. Immunogenicity Analysis Set

The Immunogenicity Analysis Set includes all enrolled subjects who received at least 1 dose of study drug and had at least 1 ADA test. This will be the primary analysis set for immunogenicity data analyses.

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8.4. Data Handling Conventions

By-subject listings will be created for important variables from each eCRF module. Summary tables for continuous variables will contain the following statistics: N (number in population), n (number with data), mean, standard deviation, 90% confidence intervals (CIs) on the mean, median, minimum, and maximum. Summary tables for categorical variables will include: N, n, percentage, and 90% CIs on the percentage. Unless otherwise indicated, 90% CIs for binary variables will be calculated using the binomial distribution (exact method) and will be 2-sided. Data will be described and summarized by dose level/cohort, analysis set, and time point. As appropriate, changes from baseline to each subsequent time point will be described and summarized. Similarly, as appropriate, the best change from baseline during the study will also be described and summarized. Graphical techniques (ie, waterfall plots, Kaplan-Meier [KM] curves, line plots) may be used when such methods are appropriate and informative.

The baseline value used in each analysis will be the last (most recent) pretreatment value. Data from all sites will be pooled for all analyses. Analyses will be based upon the observed data unless methods for handling missing data are specified. If there is a significant degree of non-normality, analyses may be performed on log-transformed data or nonparametric tests may be applied, as appropriate.

8.5. Demographic and Baseline Characteristics

Demographic and baseline measurements will be summarized using standard descriptive methods.

Demographic summaries will include sex, race/ethnicity, and age.

Baseline data will include a summary of body weight, height, and body mass index.

8.6. Efficacy Analysis

8.6.1. Categorical Endpoints

Categorical endpoints, such as ORR and DCR will be summarized. The corresponding 90% exact CIs may be present if appropriate. The response at each scheduled tumor assessment will be listed for each subject.

8.6.2. Time-to-Event Endpoints

Time-to-event endpoints, such as PFS, OS, and DOR, will be analyzed using KM methods.

The KM estimate of the survival function will be computed, and the results will be presented using KM curves. The median will be provided along with the corresponding 90% CI.

8.7. Safety Analysis

All safety data collected on or after the start of treatment up to 30 days after the last dose of study drug will be summarized by dose level/cohort for subjects in the Safety Analysis Set. Data for the pretreatment and posttreatment follow-up period will be included in data listings.

For categorical safety data including incidence of AEs and categorizations of laboratory data, count and percent of subjects will be summarized. For continuous safety data including laboratory data, sample size, mean, standard deviation, minimum, quartiles, median, and maximum will be summarized.

8.7.1. Extent of Exposure

A subject's extent of exposure to GS-1423 data will be generated from the GS-1423 administration data. Exposure data will be summarized by dose level/cohort.

8.7.2. Adverse Events

Clinical and laboratory AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System organ class, high-level group term, high-level term, preferred term, and lower-level term will be attached to the clinical database.

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent AE will be defined as any AE that begins on or after the date of first dose of study drug up to the last dose of study drug plus 30 days.

Summaries (number and percentage of subjects) of treatment-emergent AEs (by system organ class and preferred term) will be provided by treatment group.

8.7.3. Laboratory Evaluations

Selected laboratory data (using conventional units) will be summarized using only observed data. Data and change from baseline at all scheduled time points will be summarized.

Graded laboratory abnormalities will be defined using the NCI CTCAE v5.0.

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline at any time point postbaseline will be summarized by dose level/cohort. If baseline data are missing, then any graded abnormality (ie, at least a Grade 1) will be considered treatment emergent.

Laboratory abnormalities that occur before the first dose of study drug or after the subject has been discontinued from treatment for at least 30 days will be included in a data listing.

8.7.4. Other Safety Evaluations

Similar general approaches to the AE and clinical laboratory data will be utilized to summarize other safety measures.

8.8. Pharmacokinetic Analysis

Plasma concentrations for GS-1423 will be summarized by nominal sampling time using descriptive statistics (ie, sample size, arithmetic mean, geometric mean, % coefficient of variation, standard deviation, median, minimum, and maximum) by dose level/cohort. Plasma concentrations of GS-1423 over time may be plotted in semi-logarithmic and linear formats as mean ± standard deviation by dose level/cohort.

Pharmacokinetic parameters (AUC_{tau}, C_{max}, C_{trough}, T_{max}, CL, V_d, etc, as appropriate) will be listed and summarized using descriptive statistics by dose level/cohort.

8.9. Immunogenicity Analysis

Immunogenicity to GS-1423 will be evaluated based upon the incidence of ADA formation. Number and percentage of positive or negative ADA results at each specified time point will be summarized by dose level/cohort using the Immunogenicity Analysis Set. Supporting data including treatment, nominal sampling day, actual date and time of sampling, and ADA results, will be included in a listing.

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8.11. Sample Size

Phase 1a Part A

Assuming that up to 7 planned dose levels for escalation will be tested with up to 6 subjects per dose level (42 subjects for escalation) and 10% of subjects are not evaluable, and 6 additional subjects may be enrolled at a dose level at or below MTD to obtain additional safety, PK, and CCI information, up to 53 subjects will be enrolled.

Phase 1a Part B

Assuming 10% of subjects are not evaluable for PK and CCI assessments in the first 28 days on and after the first dosing of GS-1423, up to 40 subjects may be enrolled to obtain 12 evaluable subjects per cohort for up to 3 planned cohorts.

Phase 1b Cohort 1 Safety Run-in

Assuming that up to 2 planned dose levels for escalation will be tested with up to 6 subjects per dose level (12 subjects for escalation) and 10% of subjects are not evaluable, and 6 additional subjects may be enrolled at a dose level at or below MTD to obtain additional safety, CCI and CCI information, up to 20 subjects will be enrolled.

Phase 1b Cohort 1 Post Safety Run-in

In a randomized Phase 3 study, the ORR of mFOLFOX6 as first-line treatment in subjects with advanced gastric or gastroesophageal junction adenocarcinoma was approximately 40% {Lee 2010}. Phase 1b Cohort 1 post safety run-in will be a single-arm study. The null hypothesis of a 35% confirmed ORR will be tested against the alternative hypothesis of a 50% confirmed ORR with GS-1423 in combination with mFOLFOX6. A sample size of 70 subjects will provide at least 85% power at a 1-sided significance level of 0.1 using a binomial test.

Phase 1b Cohort 2

This cohort will enroll subjects until evaluable paired biopsies from at least 15 subjects are available, with at least 5 of which NSCLC subjects and 5 CRC or pancreatic cancer subjects.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with ICH E6(R2) addendum to its guidelines for GCP and applicable laws and regulations.

9.1.2. Financial Disclosure

The Investigator and subinvestigators will provide prompt and accurate documentation of their financial interest or arrangements with Gilead or proprietary interests in the investigational drug during the course of a clinical study. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

9.1.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Review and Approval

The Investigator (or Gilead as appropriate according to local regulations) will submit this protocol, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The Investigator will not begin any study subject activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the Investigator will submit to and receive documented approval from the IRB/IEC any modifications made to the protocol or any accompanying material to be provided to the subject after initial approval, with the exception of those necessary to reduce immediate risk to study subjects.

9.1.4. Informed Consent

The Investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study before undertaking any study-related procedures. The investigator must use the most current IRB/IEC approved informed consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB/IEC local requirements. The informed consent form will inform subjects about pharmacogenomic testing

and sample retention, and their right to receive clinically relevant pharmacogenomic analysis results.

9.1.5. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code and any other unique identifier(s) as allowed by local law (such as year of birth) will be recorded on any form or biological sample submitted to Gilead, IRB/IEC, or laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions. NOTE: The investigator must keep a screening log with details for all subjects screened and enrolled in the study, in accordance with the site procedures and regulations. Subject data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the investigator's brochure, this protocol, CRF/eCRF, the study drug, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.6. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories: (1) investigator's study file and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, paper or electronic completed subject CRFs, IRB/IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each subject:

- Subject identification
- Documentation that subject meets eligibility criteria, ie, medical history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria)
- Documentation of the reason(s) a consented subject is not enrolled

- Participation in study (including study number)
- Study discussed and date of informed consent
- Dates of all visits
- Documentation that protocol-specific procedures were performed
- Results of efficacy parameters, as required by the protocol
- Start and end date (including dose regimen) of study drug, including dates of dispensing and return
- Record of all AEs and other safety parameters (start and end date, causality and severity) and documentation that adequate medical care has been provided for any AE
- Concomitant medication (including start and end date, dose if relevant, dose changes)
- Date of study completion and reason for early discontinuation, if it occurs

All clinical study documents must be retained by the investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, US, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

9.1.7. Case Report Forms

For each subject consented, an eCRF casebook will be completed by an authorized study staff member whose training for this function is completed in the EDC system. The eCRF will only capture the data required per the protocol schedule of events and procedures. The inclusion/exclusion criteria and enrollment eCRFs should be completed only after all data related to eligibility have been received. Data entry should be performed in accordance with the eCRF Completion Guidelines provided by Gilead. Subsequent to data entry, a study monitor will

perform source data verification within the EDC system. System-generated or manual queries will be issued in the EDC system as data discrepancies are identified by the monitor or Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site investigator or site coordinator or other designee is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry and providing the reason for the update (eg, data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. At a minimum, prior to any interim time points or database lock (as instructed by Gilead), the investigator will use his/her log in credentials to confirm that the forms have been reviewed and that the entries accurately reflect the information in the source documents. At the conclusion of the study, Gilead will provide the site investigator with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.6.

9.1.8. Investigator Inspections

The investigator will make available all source documents and other records for this study to Gilead's appointed study monitors, to IRB/IECs, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB/IEC in accordance with local requirements and receive documented IRB/IEC approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency(ies). Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years.
- The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.
- No such communication, presentation, or publication will include Gilead's confidential information (see Section 9.1.5).
- The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol (ie, attendance at investigator meetings). If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to federal and state agencies any expenses paid or reimbursed for such services, including any clinical study payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

The monitor is responsible for routine review of the CRF/eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries in the CRF/eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both Gilead and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the subjects, appropriate regulatory authority, IRBs, and ECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404

STUDY ACKNOWLEDGMENT

A Phase 1a/1b Study of GS-1423, an Anti-CD73-TGFβ-Trap Bifunctional Antibody, as Monotherapy or in Combination with a Chemotherapy Regimen in Subjects with Advanced Solid Tumors

GS-US-505-5452, Protocol Amendment 2, 29 April 2020

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPD

Name (Printed)
Author

PPD

Signature

01 May 2020

Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Study Procedures Tables

Study Procedures Table for QW Dosing Schedule

	Screening	Treatment Phase (For QW Dosing Schedule)					End-of-Treatment		Posttreatment Follow-up[a]			Survival Follow-up
		Cycle 1		Cycle 2 and 3	Cycle 4 and every cycle until EOT	Cycle 4 and every 3 cycles until EOT	End-of-Treatment Visit	30-Day Follow-up	Visit 1	Visit 2	Visits 3 and 4	
Visits Schedule (days)		**1**	**2**	**1**	**1**	**1**	**At End-of-Treatment**	**30 d from last dose**	**3 m from last dose**	**6 m from last dose**	**3 m from last visit**	**3 m from last visit**
Schedule Window (days)[b]		**+ 2**		**+ 2**	**± 2**	**± 2**	**≤ 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**
Administrative Procedures	**< -28 days**											
Informed consent	X											
Review of inclusion/exclusion criteria	X	X										
Issue Emergency Medical Support and Subject Card	X											
Review of medical history and demographics	X											
Review of baseline symptoms	X	X										
Review of prior and concomitant medications	X	X	X	X	X		X	X				
Cancer disease details and prior treatment	X											
Subsequent anticancer therapy status							X	X	X	X	X	
Clinical Procedures/Assessments	**< -7 days**											
Review AEs[c]	X	X	X	X	X		X	X				
Full Physical Examination	X						X					
Focused Physical Examination		X[d]		X	X			X	X	X	X	
Vital Signs, Weight and Height[e]	X	X	X	X	X		X	X	X	X	X	
12 lead ECG[f]	X	X[f]	X[f]	X[f]		X	X	X				
Echocardiogram or MUGA[g]	X[g]					Every 6 cycles						
ECOG Performance Status[d]	X	X[d]	X	X	X		X	X	X	X	X	

	Screening	Treatment Phase (For QW Dosing Schedule)					End-of-Treatment		Posttreatment Follow-up[a]			Survival Follow-up
		Cycle 1		Cycle 2 and 3	Cycle 4 and every cycle until EOT	Cycle 4 and every 3 cycles until EOT	End-of-Treatment Visit	30-Day Follow-up	Visit 1	Visit 2	Visits 3 and 4	
Visits Schedule (days)		1	2	1	1	1	At End-of-Treatment	30 d from last dose	3 m from last dose	6 m from last dose	3 m from last visit	3 m from last visit
Schedule Window (days)[b]		+ 2		+ 2	± 2	± 2	≤ 7	± 7	± 7	± 7	± 7	± 7
Imaging Assessments[h]	< -28 days											
Tumor Imaging[h]	X	Every 6 weeks (± 7 days) the first 4 assessments then see footnote.										
Laboratory Procedures/Assessments[i]	< -28 days											
Blood for PK Assays[j]		X						X	X			
Blood for ADA Assays[k]		X						X	X			
CCI												
Blood for pharmacogenomics	X[m]											
CCI												
CCI												
CCI												
Serum chemistry[q]	X	X[d]		X	X		X	X	X			
Hematology tests[q]	X	X[d]		X	X		X	X	X			
Coagulation tests[q]	X			X		X	X	X	X			
Endocrine function tests[q]	X			X		Every 6 cycles	X	X	X			
Hepatitis Serology[q]	X											
Urinalysis[q]	X			X		Every 6 cycles	X	X	X			
Serum pregnancy test	X[r]											
Urine pregnancy test[s]		X[r]				Every 6 cycles	X	X	X			

	Screening	Treatment Phase (For QW Dosing Schedule)					End-of-Treatment		Posttreatment Follow-up[a]			Survival Follow-up
		Cycle 1		Cycle 2 and 3	Cycle 4 and every cycle until EOT	Cycle 4 and every 3 cycles until EOT	End-of-Treatment Visit	30-Day Follow-up	Visit 1	Visit 2	Visits 3 and 4	
Visits Schedule (days)		**1**	**2**	**1**	**1**	**1**	**At End-of-Treatment**	**30 d from last dose**	**3 m from last dose**	**6 m from last dose**	**3 m from last visit**	**3 m from last visit**
Schedule Window (days)[b]		**+ 2**		**+ 2**	**± 2**	**± 2**	**≤ 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**
Study drug administration												
GS 1423[t]		X		X	X							
Overall Survival[u]												X[u]

ADA anti drug antibody against GS 1423; AEs adverse events; CRF case report form; ECG electrocardiogram; eCRF electronic case report form; ECOG Eastern Cooperative Oncology Group; MUGA multigated acquisition; PBMC peripheral blood mononuclear cell; PD progressive disease; PK pharmacokinetics; QW every week; SAE serious adverse event

Note: Where applicable, assessments are to be performed prior to treatment unless otherwise indicated.

a All subjects who discontinue treatment will have at least one 30 Day Follow up Visit 30 days (± 7 days) from last treatment dose. Subjects who discontinue due to PD and/or start of a new line of therapy will then enter the Survival Follow up Period for up to 12 months for survival status. Subjects who have discontinued treatment due to reasons other than PD and/or start of a new line of therapy will be in Posttreatment Follow up for up to approximately 12 months from last treatment dose or until PD and/or start of a new line of therapy. Every effort should be made to collect subject information on the start of new anticancer therapy, PD, and death.

b Treatment administration and associated procedures for that visit may be delayed for treatment related AEs beyond the window and subsequent schedule adjusted accordingly.

c After informed consent, but prior to initiation of study medication, the following types of events should be reported on the case report form (CRF/eCRF): all SAEs and AEs related to protocol mandated procedures.

d 72 hour window for C1D1 physical examination, safety labs, and ECOG performance status collection.

e Vital signs will only be measured while subject is in seated or semi recumbent position. Height only collected at screening. Vital signs are to be measured prior to each infusion commencing, at the end of each infusion, and for the first 2 cycles, 1 hour (± 15 minutes) after the end of the GS 1423 infusion. Thereafter, the final vital signs can be taken 30 minutes (10/+20 minutes) after the end of each GS 1423 infusion. Subjects will remain in the clinic under close supervision for the duration of this monitoring period.

f 12 lead ECG on Cycle 1 Day 1, before and 2 hours (10/+20 minutes) after GS 1423 administration; on subsequent cycles, 12 lead ECG will be collected every 3 cycles on Day 1, at end of GS 1423 infusion (10/+20 minutes), or as indicated. For subjects in Cohort 9, a triplicate ECG will be performed at C1D1 (predose and at end of infusion), at C1D2 (24 hours postdose) and C2D1 (predose).

g Complete echocardiogram assessment will be conducted at screening to determine baseline (may be done within 14 days prior to the first dose of study treatment). For QW, echocardiogram assessment will be conducted every 6 cycles, on Day 1, starting at Cycle 4 (±3 days). A MUGA scan is allowed.

h The initial tumor imaging will be performed within 28 days prior to first dose. Scans performed as part of routine clinical management are acceptable for use as screening scan if they are of diagnostic quality and < 28 days prior to first dose. On study imaging will be performed at 6, 12, 18, and 24 weeks (± 7 days) from first treatment dose and then every 12 weeks thereafter. Imaging assessments will continue until PD as assessed by the investigator, unexpected toxicity occurs, or a new line of therapy is initiated for up to 1 year. The timing of on study treatment imaging should follow calendar days and should not be adjusted for delays in treatment administration or for visits. The same imaging technique should be used in a subject throughout the study. In general, lesions detected at baseline should be followed using the same imaging methodology and preferably the same imaging equipment at subsequent tumor evaluation visits.

i Unless otherwise specified, samples should be collected before treatment administration. Refer to the Laboratory Manual for instructions and additional information.
j PK Assays: Refer to Section 6; Table 6 2 and Table 6 6 in the body of the protocol.
k ADA Assays: Refer to Section 6; Table 6 8 in the body of the protocol.
[redacted]
m Blood pharmacogenomics sample collected from enrolled subject before or at C1D1, predose. If the sample is missed, it can be taken later on in the study.
[redacted]
q Laboratory tests for screening should be performed within 28 days prior to the first dose of study treatment. After Cycle 1, predose laboratory procedures can be conducted up to 72 hours prior to dosing.
r Serum β human chorionic gonadotropin (β HCG) pregnancy test for women of childbearing potential at screening within 72 hours of first treatment dose (if performed earlier in screening period, then a urine pregnancy test may be performed prior to first dose); urine pregnancy test at all other indicated visits; results must be available prior to dosing.
s Urine pregnancy results to be obtained on site.
t GS 1423 should be administered intravenously within 60 minutes (10/+20 minutes). Subjects must be observed for 1 hour postinfusion for infusion related reaction for the first 2 cycles and thereafter, 30 minutes after the end of the GS 1423 infusion. If administration of GS 1423 is delayed due to an AE, treatment visits may be delayed beyond the window of 3 days and schedules for subsequent visits should be adjusted accordingly.
u After the 1 posttreatment follow up visit, subjects who present(ed) with PD and/or start(ed) a new anticancer therapy will move into Survival Follow up. Subjects should be contacted by telephone to assess for survival status every 3 months for up to 12 months. No imaging assessment is required for Survival Follow up.

Study Procedures Table for Q2W/Q3W Dosing Schedule

	Screening	Treatment Phase (For Q2W and Q3W Dosing Schedules)								End-of-Treatment		Posttreatment Follow-up[a]			Survival Follow-up
		Cycle 1			Cycle 2			Every Subsequent Odd Cycle	Every Subsequent Even Cycle	End-of-Treatment Visit	30-Day Follow-up	Visit 1	Visit 2	Visits 3 and 4	
Visits Schedule (days)		**1**	**2**	**8**	**1**	**2**	**8**	**1**	**1**	**At End-of-Treatment**	**30d from last dose**	**3 m from last dose**	**6 m from last dose**	**3 m from last visit**	**3 m from last visit**
Schedule Window (days)[b]		**+ 2**			**+ 2**			**+ 2[aa]**	**+ 2[aa]**	**≤ 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**
Administrative Procedures	**< -28 days**														
Informed consent	X														
Review of inclusion/exclusion criteria	X	X													
Issue Emergency Medical Support and Subject Card	X														
Review of medical history and demographics	X														
Review of baseline symptoms	X	X													
Review of prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X				
Cancer disease details and prior treatment	X														
Subsequent anticancer therapy status										X	X	X	X	X	
Clinical Procedures/Assessments	**< -7 days**														
Review AEs[c]	X	X	X	X	X	X	X	X	X	X	X				
Full Physical Examination	X									X					
Focused Physical Examination		X[d]			X			X	X		X	X	X	X	
Vital Signs, Weight and Height[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12 lead ECG[f]	X	X[f]	X[f]	X[f]				X		X	X				
Echocardiogram or MUGA[g]	X[g]							X							
ECOG Performance Status[d]	X	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	

	Screening	Treatment Phase (For Q2W and Q3W Dosing Schedules)								End-of-Treatment		Posttreatment Follow-up[a]			Survival Follow-up
		Cycle 1			Cycle 2			Every Subsequent Odd Cycle	Every Subsequent Even Cycle	End-of-Treatment Visit	30-Day Follow-up	Visit 1	Visit 2	Visits 3 and 4	
Visits Schedule (days)		1	2	8	1	2	8	1	1	At End-of-Treatment	30d from last dose	3 m from last dose	6 m from last dose	3 m from last visit	3 m from last visit
Schedule Window (days)[b]		+ 2			+ 2			+ 2[aa]	+ 2[aa]	≤ 7	± 7	± 7	± 7	± 7	± 7
Imaging Assessments[h]	**< -28 days**														
Tumor Imaging[h]	X	Every 6 weeks (± 7 days) the first 4 assessments then see footnote.													
Laboratory Procedures/Assessments[i]	**< -28 days**														
Blood for PK Assays[j]		X									X	X			
Blood for ADA Assays[k]		X									X	X			
CCI															
Blood for pharmacogenomics	X[p]														
CCI															
Collection of required pretreatment biopsy (Phase 1b Cohort 2)[z]	X														
CCI															
Collection of required on treatment biopsy (Phase 1b Cohort 2)[y]								X							
CCI															
Serum chemistry[t]	X	X[d]		X	X		X		X	X	X	X			
Hematology tests[t]	X	X[d]		X	X		X	X	X	X	X	X			
Coagulation tests[t]	X				X		X	X		X	X	X			
Endocrine function tests[t]	X				X		X	X		X	X	X			
Hepatitis Serology	X														
Urinalysis[t]	X			X	X		X	X		X	X	X			

	Screening	Treatment Phase (For Q2W and Q3W Dosing Schedules)								End-of-Treatment		Posttreatment Follow-up[a]			Survival Follow-up
		Cycle 1			Cycle 2			Every Subsequent Odd Cycle	Every Subsequent Even Cycle	End-of-Treatment Visit	30-Day Follow-up	Visit 1	Visit 2	Visits 3 and 4	
Visits Schedule (days)		**1**	**2**	**8**	**1**	**2**	**8**	**1**	**1**	**At End-of-Treatment**	**30d from last dose**	**3 m from last dose**	**6 m from last dose**	**3 m from last visit**	**3 m from last visit**
Schedule Window (days)[b]		**+ 2**			**+ 2**			**+ 2[aa]**	**+ 2[aa]**	**≤ 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**
Serum pregnancy test	X[u]														
Urine pregnancy test[v,bb]		X[u]						X		X	X	X	X[bb]		
HER2 Testing[cc]	X														
Study drug administration															
GS 1423 (All cohorts)[w]		X			X			X	X						
mFOLFOX6 (Phase 1b Cohort 1)[x]		X			X			X	X						
Overall Survival [dd]															X [dd]

5 FU 5 fluorouracil; ADA anti drug antibody against GS 1423; AEs adverse events; CRF case report form; ECG electrocardiogram; eCRF electronic case report form; ECOG Eastern Cooperative Oncology Group; HER2 human epidermal growth factor receptor 2; IHC immunohistochemistry; ISH in situ hybridization; MUGA multigated acquisition; PBMC peripheral blood mononuclear cell; PD progressive disease; PK pharmacokinetics; Q2W every 2 weeks; Q3W every 3 weeks; SAE serious adverse event

Note: Where applicable, assessments are to be performed prior to treatment unless otherwise indicated.

a All subjects who discontinue treatment will have at least one 30 Day Follow up Visit 30 days (± 7 days) from last treatment dose. Subjects who discontinue due to PD and/or start of a new line of therapy will then enter the Survival Follow up Period for up to 12 months for survival status. Subjects who have discontinued treatment due to reasons other than PD and/or start of a new line of therapy will be in Posttreatment Follow up for up to approximately 12 months from last treatment dose or until PD and/or start of a new line of therapy. Every effort should be made to collect subject information on the start of new anticancer therapy, PD, and death.

b Treatment administration and associated procedures for that visit may be delayed for treatment related AEs beyond the window and subsequent schedule adjusted accordingly.

c After informed consent, but prior to initiation of study medication, the following types of events should be reported on the case report form (CRF/eCRF): all SAEs and AEs related to protocol mandated procedures.

d 72 hour window for C1D1 physical examination, safety labs, and ECOG performance status collection.

e Vital signs will only be measured while subject is in seated or semi recumbent position. Height only collected at screening. Phase 1a and Phase 1b (Cohort 2): Vital signs are to be measured prior to each infusion commencing, at the end of each infusion, and for the first 2 cycles, 1 hour (± 15 minutes) after the end of the GS 1423 infusion. Thereafter, the final vital signs can be taken 30 minutes (10/+20 minutes) after the end of each GS 1423 infusion. Subjects will remain in the clinic under close supervision for the duration of this monitoring period. Phase 1b (Cohort 1): Additional vital signs for subjects being administered the mFOLFOX6 regimen will be measured as per standard institutional guidelines.

f 12 lead ECG on Cycle 1 Day 1, before and 2 hours (10/+20 minutes) after GS 1423 administration; on subsequent cycles, 12 lead ECG will be collected every odd cycle, on Day 1, at end of GS 1423 infusion(10/+20 minutes), or as indicated. For subjects in Cohorts 5 through 8 and Cohort 10, a triplicate ECG will be performed at Cycle 1, Day 1 predose, at end of infusion, at 24 hours postdose (Day 2), and 168 hours postdose (Day 8).

g Complete echocardiogram assessment will be conducted at screening to determine baseline (may be done within 14 days prior to the first dose of study treatment); and at every odd cycle, on Day 1, starting at Cycle 3 (±3 days). A MUGA scan is allowed.

h The initial tumor imaging will be performed within 28 days prior to first dose. Scans performed as part of routine clinical management are acceptable for use as screening scan if they are of diagnostic quality and < 28 days prior to first dose. On study imaging will be performed at 6, 12, 18, and 24 weeks (± 7 days) from first treatment dose and then every 12 weeks thereafter. Imaging assessments will continue until PD as assessed by the investigator, unexpected toxicity occurs, or a new line of therapy is initiated for up to 1 year (Phase 1a and Phase 1b Cohort 2) or 2 years (Phase 1b Cohort 1. The timing of on study treatment imaging should follow calendar days and should not be adjusted for delays in treatment administration or for visits. The same imaging technique should be used in a subject throughout the study. In general, lesions detected at baseline should be followed using the same imaging methodology and preferably the same imaging equipment at subsequent tumor evaluation visits.

i Unless otherwise specified, samples should be collected before treatment administration. Refer to the Laboratory Manual for instructions and additional information.

j PK Assays: Refer to Section 6; Table 6 3, Table 6 4, Table 6 5 and Table 6 7 in the body of the protocol.

k ADA Assays: Refer to Section 6; Table 6 9 and Table 6 10 in the body of the protocol.

l Not applicable (This footnote is obsolete with Amendment 1.)

m Not applicable (This footnote is obsolete with Amendment 1.)

n Not applicable (This footnote is obsolete with Amendment 1.)

[redacted]

p Blood pharmacogenomics sample collected from enrolled subject before or at C1D1, predose. If the sample is missed, it can be taken later on in the study.

[redacted]

t Laboratory tests for screening should be performed within 28 days prior to the first dose of study treatment. After Cycle 1, predose laboratory procedures can be conducted up to 72 hours prior to dosing.

u Serum β human chorionic gonadotropin (β HCG) pregnancy test for women of childbearing potential at screening within 72 hours of first treatment dose (if performed earlier in screening period, then a urine pregnancy test may be performed prior to first dose); urine pregnancy test at all other indicated visits; results must be available prior to dosing.

v Urine pregnancy results to be obtained on site.

w GS 1423 should be administered intravenously within 60 minutes (10/+20 minutes). Subjects must be observed for 1 hour postinfusion for infusion related reaction for the first 2 cycles and thereafter, 30 minutes after the end of the GS 1423 infusion. If administration of GS 1423 is delayed due to an AE, treatment visits may be delayed beyond the window of 3 days and schedules for subsequent visits should be adjusted accordingly.

x The mFOLFOX6 regimen consists of *l* leucovorin/*dl* leucovorin 200/400 mg/m^2 and oxaliplatin 85 mg/m^2 followed by bolus 5 FU 400 mg/m^2 and a 46 hour infusion of 5 FU 2400 mg/m^2. Administration of mFOLFOX6 will follow administration of GS 1423 on Day 1 of each cycle. The chemotherapy regimen mFOLFOX6 will be administered Q2W for up to 12 cycles (6 months). After 12 cycles, subjects may continue to receive 5 FU and leucovorin at the investigator's discretion until the subject meets study treatment discontinuation criteria.

y Required on treatment biopsy should be collected at C3D1 or up to 1 week prior on Q2W treatment cycle.

z Required pretreatment biopsy must be obtained prior to C1D1 on a tumor from which 2 biopsies can be obtained (1 pretreatment and 1 on treatment).

aa Treatment Phase visit window starting at Cycle 4 until End of Treatment is ± 2 days.
bb This will only be performed for subjects receiving mFOLFOX6. Urine pregnancy tests will be performed at 4 months and 6 months after the last dose of mFOLFOX6.
cc For subjects in Phase 1b Cohort 1 (gastric cohort) tumor tissue will be tested for HER2 status, if unknown, with an approved IHC and ISH kit.
dd After the 1 posttreatment follow up visit, subjects who present(ed) with PD and/or start(ed) a new anticancer therapy will move into Survival Follow up. Subjects should be contacted by telephone to assess for survival status every 3 months for up to 12 months. No imaging assessment is required for Survival Follow up.

Appendix 3. Response Evaluation Criteria in Solid Tumors (RECISTVersion 1.1)

Measurability of tumor at baseline

Definitions: At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

10 mm by CT scan (CT scan slice thickness no greater than 5 mm).

10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).

20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be P15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

Non- measurable: All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

Bone lesions:

Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are non-measurable.

Cystic lesions:

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same subjects, these are preferred for selection as target lesions.

Lesions with prior local treatment:

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Baseline documentation of 'target' and 'non-target' lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where subjects have only one or 2 organ sites involved a maximum of 2 and 4 lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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, and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Tumor response evaluation

Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of non-target lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Appendix Table 1. Time point response: patients with target (+/- non-target) disease

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not 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	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR complete response, PR partial response, SD stable disease, PD progressive disease, and NE not evaluable.

Appendix Table 2. Time point response: patients with non-target disease only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

a 'Non CR/non PD' is preferred over 'stable disease' for non target disease since SD is increasingly used as endpoint for assessment of efficacy in some studies so to assign this category when no lesions can be measured is not advised.

Appendix 4. NCI CTCAE v5.0 Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

Appendix 5. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a female-born subject is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming postmenopausal, unless permanently sterile or with medically documented ovarian failure.

Women are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause. In addition, women of any age with amenorrhea of ≥ 12 months may also be considered postmenopausal if their follicle stimulating hormone level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age.

b. Definition of Male Fertility

For the purposes of this study, a male born subject is considered of fertile after the initiation of puberty unless permanently sterile by bilateral orchidectomy or medical documentation.

2) Contraception Requirements for Female Subjects

a. Study Drug Effects on Pregnancy and Hormonal Contraception

GS-1423 is contraindicated in pregnancy as the potential to cause malformations is unknown. A clinically relevant interaction between GS-1423 and contraceptive steroids is not expected because of their distinct metabolic pathways and therefore, hormonal contraception may be used as part of the birth control methods.

Please refer to the latest version of the investigator's brochure for additional information.

Please refer to the regional prescribing information for information on the potential risks of treatment with mFOLFOX6.

3) Contraceptive Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of highly effective contraceptive measures from the screening/randomization visit throughout the study period and throughout the protocol-defined follow-up period. They must have a negative serum pregnancy test at screening and a negative pregnancy test on the Cycle 1, Day 1 visit prior to enrollment. Pregnancy tests will be performed at regular intervals thereafter (as described in the protocol).

Female subjects must agree to one of the following from screening until 90 days following last dose of GS-1423 or for 4 months after the last dose of oxaliplatin or 6 months after the last dose of 5-FU, whichever occurs later.

- Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the subject's preferred and usual lifestyle.
- Female subjects who wish to use a hormonally based method must use it in conjunction with a barrier method, preferably a male condom. Female subjects who utilize a hormonal contraceptive as one of their birth control methods must have consistently used the same method for at least 3 months prior to study dosing. Hormonally based contraceptives and barrier methods permitted for use in this protocol are as follows:
- **Barrier methods (each method must be used with a hormonal method)**

  Male condom (with or without spermicide)

  Female condom (with or without spermicide)

  Diaphragm with spermicide

  Cervical cap with spermicide

  Sponge with spermicide

- **Hormonal methods (each method must be used with a barrier method, preferably male condom)**

  Oral contraceptives (either combined or progesterone only)

  Injectable progesterone

  Implants of levonorgestrel

  Transdermal contraceptive patch

  Contraceptive vaginal ring

Female subjects must also refrain from egg donation, egg harvesting for the purpose of fertilization, and in vitro fertilization during treatment and until at least 90 days after the last dose of GS-1423 or for 4 months after the last dose of oxaliplatin or 6 months following the last dose of 5-FU, whichever occurs later.

4) Contraception Requirements for Male Subjects

It is theoretically possible that a relevant systemic concentration may be achieved in a female partner from exposure of the male subject's seminal fluid. Therefore, male subjects with female partners of childbearing potential must use condoms from the screening visit until 90 days after the administration of the last dose of GS-1423 or for 6 months after the last dose of oxaliplatin or 6 months after the last dose of 5-FU, whichever occurs later.

Male subjects must also refrain from sperm donation during treatment and until at least 90 days after last administration of GS-1423 and for 6 months after the last dose of oxaliplatin or 6 months after the last dose of 5-FU, whichever occurs later.

5) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (ie, calendar, ovulation, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method. Female condom and male condom should not be used together.

6) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study or if they become pregnant within 90 days of last study drug dose (GS-1423) and within 4 months (or 6 months for the partner of male subjects) of the last dose of oxaliplatin, or 6 months after last dose of 5-FU, whichever occurs later. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects she is pregnant during the study must report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.7.2.1.

Appendix 6. Dose Modification Tables for mFOLFOX6

Appendix Table 3. Recommended Dose Modifications for Oxaliplatin, 5-Fluorouracil, and Leucovorin[a]

NCI CTCAE v5.0 System Organ Class[b]	Adverse Event	Dose Level for Subsequent Cycles Based on Interval Adverse Events	At Time of Retreatment
All Adverse Events < 1		Maintain dose level	Maintain dose level
Blood and lymphatic system disorders:	Hemolytic uremic syndrome[c] > Grade 3	Discontinue oxaliplatin	Discontinue oxaliplatin
Investigations:	Neutrophil count decreased ANC < LLN 1500/mm^3 ANC < 1500 1000/mm^3 ANC < 1000 500/mm^3 ANC < 500/mm^3	 Maintain dose level Maintain dose level Omit bolus 5 FU and decrease 1 oxaliplatin dose level Omit bolus 5 FU and decrease both infusion 5 FU and oxaliplatin 1 dose level	If ANC < 1500/mm^3 at start of cycle, hold and check weekly then treat based on interval adverse event. If ANC < 1500/mm^3 after 4 weeks, discontinue therapy.
	Platelet count decreased PLT < LLN 75,000/mm^3 PLT < 75,000 50,000/mm^3 PLT < 50,000 25,000/mm^3 PLT < 25,000/mm^3	 Maintain dose level Maintain dose level Omit bolus 5 FU and decrease 1 oxaliplatin dose level Omit bolus 5 FU and decrease 2 oxaliplatin dose levels	If PLT < 75,000/mm^3 at start of cycle, hold and check weekly then treat based on interval adverse event. If PLT < 75,000/mm^3 after 4 weeks, discontinue therapy.
Gastrointestinal disorders:	Diarrhea Grade 1, 2 Grade 3 Grade 4	 Maintain dose level Decrease one 5 FU dose level Decrease both 5 FU and oxaliplatin 1 dose level	If Grade ≥ 2 at start of cycle, hold and check weekly then treat based on interval adverse event. If Grade ≥ 2 after 4 weeks, discontinue therapy.
	Mucositis oral Grade 1, 2 Grade 3 Grade 4	 Maintain dose level Decrease one 5 FU dose level Decrease one 5 FU dose level	
	Vomiting Grades 1, 2 Grade 3 Grade 4	 Maintain dose level Decrease oxaliplatin 1 dose level Decrease both 5 FU and oxaliplatin 1 dose level	

NCI CTCAE v5.0 System Organ Class[b]	Adverse Event	Dose Level for Subsequent Cycles Based on Interval Adverse Events	At Time of Retreatment
Metabolism and nutrition disorders:	Hypomagnesemia	**Note:** Dose reduction is not required for hypomagnesemia unless symptoms are present. If Grade ≥ 2 after 4 weeks, discontinue therapy.	
Neurology:	Do not use CTCAE.	See Appendix Table 4 for adverse event scale and oxaliplatin dose modifications.	
Respiratory, thoracic, and mediastinal disorders:	Cough ≥ Grade 3 Dyspnea ≥ Grade 3 Hypoxia ≥ Grade 3 Pneumonitis ≥ Grade 3	Hold oxaliplatin until interstitial lung disease is ruled out. If interstitial lung disease, oxaliplatin should be permanently discontinued.	
Other non-hematologic adverse events[d,e]:	Grades 1, 2 Grades 3, 4	Maintain dose level Decrease offending agent 1 dose level	

5 FU 5 fluorouracil; ANC absolute neutrophil count; FDP fibrin degradation products; LLN lower limit of normal; NCI CTCAE National Cancer Institute Common Terminology Criteria for Adverse Events; PLT platelet

a The dose of leucovorin will not be adjusted due to adverse event. It should remain at 400 mg/m^2 of *dl* leucovorin or 200 mg/m^2 of leucovorin for all courses. Leucovorin will be given immediately prior to each 5 FU dose; thus, if 5 FU is delayed, leucovorin will be delayed. Leucovorin doses may be adjusted per institutional guidelines in the event of a supply shortage.

b For ≤ NCI CTCAE v5.0 Grade 2 toxicity not described above, maintain dose level of agent.

c Recommended evaluation of suspected hemolytic uremic syndrome: Evaluation should include complete blood count differential, platelets, prothrombin time, partial thromboplastin time, fibrinogen, FDP, Anti thrombin III, Von Willebrand factor, anti nuclear antibody, rheumatoid factor, Compliment Cascade C3, C4, and CH50, anti platelet antibodies, platelet associated immunoglobulin G, and circulating immune complexes. Renal evaluation should include creatinine, blood urea nitrogen, and urinalysis with microscopic examination. Other laboratory and hematologic evaluations as appropriate should also be obtained, including peripheral blood smear and free hemoglobin.

d Exceptions: Fatigue, anorexia, nausea/vomiting if can be controlled by antiemetics, and viral infections.

e Dose modifications for other non hematologic adverse events at the start of subsequent courses of therapy, and at time of retreatment are also based on NCI CTCAE v5.0 criteria.

Appendix Table 4. Oxaliplatin[a] Dose Modifications for Non-CTCAE Neurologic Adverse Events

Adverse Events	Duration of Adverse Event		Persistent[b] Between Cycles
	1-7 Days	> 7 Days	
Paresthesias/Dysesthesias			
Paresthesias/dysesthesias[c] of short duration that resolve and do not interfere with function (Grade 1)	No change	No change	No change
Paresthesias/dysesthesias[c] interfering with function, but not activities of daily living (ADL) (Grade 2)	No change	No change	Decrease 1 oxaliplatin dose level
Paresthesias/dysesthesias[c] with pain or with functional impairment that also interfere with ADL (Grade 3)	First time: Decrease 1 oxaliplatin dose level Second time: Decrease 1 oxaliplatin dose level	First time: Decrease 1 oxaliplatin dose level Second time: Decrease 1 oxaliplatin dose level	Discontinue
Persistent paresthesias/dysesthesias that are disabling or life-threatening (Grade 4)	Discontinue	Discontinue	Discontinue
Laryngeal Dysesthesias (investigator's discretion used for grading):			
Grade 0 = none; Grade 1 = mild	No change	Increase duration of infusion to 6 hours	Increase duration of infusion to 6 hours
Grade 2 = moderate (Also recommended is administration of benzodiazepine and patient education. Management of patient if ≥ Grade 2 laryngeal dysesthesias occurs while treatment is being administered.)	Stop oxaliplatin infusion. Administer benzodiazepine and give patient reassurance. At the discretion of the investigator, the infusion can be restarted at 1/3 the original rate of infusion.		
Grade 3 = severe			

ADL activities of daily living; CTCAE Common Terminology Criteria for Adverse Events

a If oxaliplatin is discontinued, continue other study agents unless adverse events preclude their continuation.
b Not resolved by the beginning of the next cycle.
c May be cold induced.