CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1b/2 Dose Escalation/Expansion Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of GS-4224 in Subjects with Advanced Solid Tumors
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number:	143047
EudraCT Number:	2019-004605-27
Clinical Trials.gov Identifier:	NCT04049617
Indication:	Advanced Solid Tumors
Protocol ID:	GS-US-494-5484
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Original: 10 May 2019 Amendment 1: 07 June 2019 Amendment 2: 12 August 2019 Amendment 3: 04 May 2020 Amendment 4: 07 August 2020 Amendment 5: 02 October 2020

This study will be conducted under United States Food and Drug Administration investigational new drug (IND) regulations (21 Code of Federal Regulations Part 312); however, sites located in the European Economic Area and Switzerland are not included under the IND and are considered non-IND sites.

TABLE OF CONTENTS

TABLE OF CONTENTS 2
LIST OF IN-TEXT TABLES 5
LIST OF IN-TEXT FIGURES 5
PROTOCOL SYNOPSIS 6
GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS 24
1. INTRODUCTION 29
1.1. Background 29
1.2. GS-4224 29
1.2.1. General Information 29
1.2.2. Preclinical Pharmacology and Toxicology 29
1.2.3. Clinical Trials of GS-4224 31
1.3. Rationale for this Study 31
1.4. Rationale for the Dose Selection 31
1.5. Risk/Benefit Assessment for the Study 33
1.6. Compliance 33
2. OBJECTIVES 34
3. STUDY DESIGN 35
3.1. Endpoints 35
3.2. Study Design 36
3.2.1. Dose Escalation (Phase 1b) 36
3.2.2. Dose Expansion (Phase 2) 40
3.2.3. Safety Review Team 40
3.3. Study Treatments 40
3.4. Duration of Treatment 41
3.5. Study Discontinuation Criteria 41
3.6. Poststudy Care 41
3.7. Source Data 41
CCI [redacted]
4. SUBJECT POPULATION 44
4.1. Number of Subjects and Subject Selection 44
4.1.1. Target Population 44
4.1.2. Subject Replacement 44
4.2. Inclusion Criteria 45
4.3. Exclusion Criteria 46
5. INVESTIGATIONAL MEDICINAL PRODUCTS 49
5.1. Randomization, Blinding and Treatment Codes 49
5.2. Description and Handling of GS-4224 49
5.2.1. Formulation 49
5.2.2. Packaging and Labeling 49
5.2.3. Storage and Handling 50

5.3. Dosage and Administration of GS-4224 50
5.4. Dose Modifications and Treatment Interruption of GS-4224 50
5.4.1. Dose Modifications 50
5.4.2. Treatment Interruption for GS-4224 51
5.4.3. Management of Immune-Related Adverse Events 51
5.4.4. Dermatological irAEs 52
5.4.5. Gastrointestinal (GI) irAEs 52
5.4.6. Pulmonary irAEs 53
5.4.7. Hepatic irAEs 54
5.4.8. Endocrine irAEs 55
5.4.9. Renal irAEs 56
5.4.10. Neurological irAEs 57
5.5. Prior and Concomitant Medications 58
5.5.1. Concomitant Medications 58
5.5.2. Rescue Medications and Supportive Care 60
5.5.3. Prohibited and/or Restricted Treatments 61
5.5.4. Other Restrictions and Precautions 62
5.6. Accountability 62
5.7. Investigational Medicinal Product (IMP) Return or Disposal 62

6. STUDY PROCEDURES 63

6.1. Subject Enrollment and Treatment Assignment 63
6.2. Pretreatment Assessments 63
6.2.1. Screening Visit 63
6.2.2. Re-screening Criteria 65
6.2.3. Baseline Assessments and Medical History 65
6.2.4. Physical Examination Including Height and Weight 66
6.2.5. Vital Signs 66
6.2.6. Eastern Cooperative Oncology Group Performance (ECOG) 66
6.2.7. Electrocardiogram 66
6.2.8. Prior and Concomitant Medications 67
6.2.9. Clinical Laboratory Assessments 67
6.3. Treatment Assessments 68
6.4. Unscheduled Visits 68
6.5. Pharmacokinetic, Pharmacodynamic, Genetic, and Other Assessments 69
6.5.1. Pharmacokinetic Assessments 69
CCI [redacted]
6.6. Disease Assessments 71
6.6.1. CT with Contrast or MRI Scan 71
6.6.2. PET-CT 72
6.6.3. Response Assessment 72
6.7. End of Study 73
6.8. Posttreatment Assessments 73
6.8.1. End of Treatment Visits 73
6.9. Assessments for Premature Discontinuation from Study 74
6.10. Criteria for Discontinuation from Treatment or Study 74
6.10.1. Criteria for Discontinuation from Treatment 74
6.10.2. Discontinuation from Disease Response Evaluation 75
6.10.3. Criteria for Discontinuation from Study 75

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT 76

7.1. Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events 76
7.1.1. Adverse Events 76
7.1.2. Serious Adverse Events 76

7.1.3. Study Drugs and Gilead Concomitant Therapy Special Situations Reports 77
7.2. Assessment of Adverse Events and Serious Adverse Events 78
7.2.1. Assessment of Causality for Study Drugs and Procedures 78
7.2.2. Assessment of Severity 79
7.3. Investigator Reporting Requirements and Instructions 79
7.3.1. Requirements for Collection Prior to Study Drug Initiation 79
7.3.2. Adverse Events 79
7.3.3. Serious Adverse Events 80
7.3.4. Study Drug Special Situations Reports 80
7.3.5. Concomitant Therapy Reports 80
7.4. Reporting Process for Serious Adverse Events and Special Situation Reports 81
7.4.1. Serious Adverse Event Reporting Process 81
7.4.2. Special Situations Reporting Process 82
7.5. Gilead Reporting Requirements 83
7.5.1. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events 84
7.6. Toxicity Management 84

8. STATISTICAL CONSIDERATIONS 85

8.1. Analysis Objectives and Endpoints 85
8.1.1. Analysis Objectives 85
8.1.2. Primary Endpoint 85
8.1.3. Secondary Endpoint 86
CCI
CC1 [redacted]
8.2. Planned Analyses 87
8.2.1. Interim Analysis 87
8.2.2. Final Analysis 87
8.3. Analysis Conventions 87
8.3.1. Analysis Sets 87
8.4. Data Handling Conventions 88
8.5. Demographic Data and Baseline Characteristics 89
8.6. Efficacy Analysis 89
8.7. Safety Analysis 89
8.7.1. Extent of Exposure 90
8.7.2. Adverse Events 90
8.7.3. Laboratory Evaluations 91
CCI [redacted]
8.10. Sample Size 92

9. RESPONSIBILITIES 93

9.1. Investigator Responsibilities 93
9.1.1. Good Clinical Practice 93
9.1.2. Financial Disclosure 93
9.1.3. Institutional Review Board/Independent Ethics Committee Review and Approval 93
9.1.4. Informed Consent 93
9.1.5. Confidentiality 94
9.1.6. Study Files and Retention of Records 94
9.1.7. Case Report Forms 95
9.1.8. Investigational Medicinal Product Accountability and Return 96
9.1.9. Inspections 96
9.1.10. Protocol Compliance 96

9.2. Sponsor Responsibilities 96
9.2.1. Protocol Modifications 96
9.2.2. Study Report and Publications 97
9.3. Joint Investigator/Sponsor Responsibilities 97
9.3.1. Payment Reporting 97
9.3.2. Access to Information for Monitoring 97
9.3.3. Access to Information for Auditing or Inspections 98
9.3.4. Study Discontinuation 98
10. REFERENCES 99
11. APPENDICES 100

Appendix 1. Investigator Signature Page 101
Appendix 2. Study Procedures Table 102
Appendix 3. Tumor Specific Inclusion/Exclusion Criteria 106
Appendix 4. NCI-CTCAE Grading Scale for Severity of Adverse Events and Laboratory Abnormalities 110
Appendix 5. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements 111
Appendix 6. Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1) 114
Appendix 7. Response Assessment for Classic Hodgkin Lymphoma (Lugano Classification) 118
Appendix 8. Pandemic Risk Assessment and Mitigation Plan 122

LIST OF IN-TEXT TABLES

Table 1-1. IND Nonclinical Safety Package 30
Table 3-1. Dose Escalation (Phase 1b) Dose Levels 37
Table 5-1. Dermatological irAE Management Algorithm 52
Table 5-2. Gastrointestinal (GI) irAE Management Algorithm 53
Table 5-3. Pulmonary irAE Management Algorithm 54
Table 5-4. Hepatic irAE Management Algorithm 55
Table 5-5. Endocrine irAE Management Algorithm 56
Table 5-6. Renal irAE Management Algorithm 57
Table 5-7. Neurological irAE Management Algorithm 58
Table 5-8. List of Agents Disallowed with GS-4224 59
Table 6-1. Analytes 68

LIST OF IN-TEXT FIGURES

Figure 3-1. Phase 1b Study Design Schema 36

PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Study Title:	A Phase 1b/2 Dose Escalation/Expansion Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of GS-4224 in Subjects with Advanced Solid Tumors
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	143047 2019-004605-27 NCT04049617
Study Centers Planned:	Approximately 35 centers in United States (US), Europe, and rest of world (ROW)
Objectives:	The primary objectives of this study are as follows: <u>Phase 1b Dose Escalation</u> • Characterize the safety and tolerability of GS-4224 in subjects with advanced solid tumors • Determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of GS-4224 in subjects with advanced solid tumors The secondary objectives of this study are as follows: <u>Phase 1b Dose Escalation</u> • Evaluate the pharmacokinetics (PK) of GS-4224 in subjects with advanced solid tumors <u>Phase 2 Dose Expansion</u> • Evaluate the safety and tolerability of GS-4224 in subjects with advanced solid tumors

CCI

Study Design:

This is an open-label, multicenter, sequential dose-escalation and dose expansion study to evaluate the safety, tolerability, PK, and efficacy of GS-4224 in subjects with advanced solid tumors. The study will consist of 2 parts: the dose escalation portion, followed by dose expansion in subjects with tumors for which programmed cell death protein 1 (PD-1)/ligand 1 of programmed cell death protein 1 (PD-L1) treatments are approved or are known to be active.

Dose Escalation (Phase 1b)

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 oral GS-4224 as monotherapy once daily (400-1500 mg QD cohorts) and as monotherapy at 1000 mg twice daily (1000 mg BID cohort).

Dose escalation will proceed using a standard 3+3 design. The starting dose is 400 mg QD, with subsequent doses of 700 mg QD, 1000 mg QD, 1500 mg QD, and 1000 mg BID. Dose level increases will be 3-fold or less.

Dose Level Schema

GS-4224 (mg)	Fold Increase
400 QD	-
700 QD	≤ 3×
1000 QD	≤ 3×
1500 QD	≤ 3×
1000 BID	≤ 3×

In the 1000 mg BID dose cohort, at least 6 subjects (as part of the initial 3+3 design) and up to an additional 14 subjects (for a total of 20 subjects) with locally advanced, inoperable or metastatic cancer expressing PD-L1 (tumor proportion score [TPS] ≥ 10% or combined positive score [CPS] ≥ 10) and who have not previously been treated with anti-PD-1/L1 antibodies will be enrolled. The additional 14 subjects will not be enrolled at the 1000 mg BID dose level if the subject incidence of dose-limiting toxicity (DLTs) is > 1 in the first 6 subjects. If the subject incidence of DLTs is > 1 in the first 6 subjects at 1000 mg BID, then 20 additional subjects with locally advanced, inoperable or metastatic cancer expressing PD-L1 [TPS ≥ 10% or CPS ≥ 10] and who have not previously been treated with anti-PD-1/L1 antibodies will enroll at the MTD. Tumor types of interest include non-small cell lung cancer (NSCLC), melanoma, renal cell carcinoma (RCC), urothelial, esophageal, hepatocellular carcinoma (HCC), cutaneous squamous cell, Merkel cell, microsatellite instability-high (MSI-H) cancers, and classical Hodgkin lymphoma (cHL). See Appendix 3 for the PD-L1 expression requirement for specific tumor types.

For the 1000 mg BID dose cohort, subjects must have available sufficient and adequate formalin-fixed tumor tissue sample 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. Subjects with melanoma, Merkel cell, MSI-H cancers, and cHL are not required to have archival or fresh biopsy tissue.

The safety and tolerability of each dose level will be assessed by a safety review team (SRT) after up to 6 subjects enrolled in the dose level have been followed for at least 21 days after the first dose of GS-4224 or 2 DLTs have been observed, whichever is earlier. The SRT will consist of at least 1 investigator and the following Gilead study team members: the medical monitor, representatives from Global Patient Safety (GLPS), Clinical Operations, and Biostatistics. Others may be invited to participate as members of the SRT if additional expertise is desired. The SRT will review safety data and relevant clinical data and make the dose escalation/stay/de-escalation decision based on the 3+3 design dose escalation rules as follows.

The initial block of each dose consists of 3 subjects. Dose escalation may occur if no subjects experience DLT during the first 21 days of study drug dosing. If 1 subject within the initial cohort of 3 subjects experiences a DLT during the first 21 days of study drug dosing, an

additional 3 subjects will be enrolled at the same dose level. If no DLTs are observed in the additional 3 subjects, dose escalation will occur. If 2 or more subjects of the 6 subjects experience DLTs within the first 21 days, dose de-escalation to an intermediate dose will occur. The MTD is the highest dose level with a subject incidence of DLTs during the first 21 days of study drug dosing of 0 or 1 out of 6. 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 21 days for a reason other than a DLT will be replaced.

If 2 or more delayed DLT-type adverse events (AEs) are noted after the first 21-day observation period within a dose escalation cohort, further accrual at all sites will be held pending safety analysis of the event, and will be restarted only with investigator and sponsor approval.

DLT Definition

A DLT is any toxicity defined below excluding toxicities clearly related to disease progression or disease-related processes occurring during the DLT assessment window (Day 1 through Day 21):

- Grade ≥ 4 neutropenia (absolute neutrophil count [ANC] < 500/mm^3)
- Grade ≥ 3 neutropenia (ANC < 1000/mm^3) with fever (a single temperature of > 38.3°C or a sustained temperature of ≥ 38°C for more than 1 hour)
- Grade ≥ 3 thrombocytopenia
- Grade ≥ 2 bleeding (eg, gastrointestinal [GI], respiratory, epistaxis, or purpura)
- Grade ≥ 3 anemia
- Grade ≥ 3 or higher non-hematologic toxicity, except:

  Grade 3 nausea or emesis with maximum duration of 48 hours on adequate medical therapy

  Grade 3 diarrhea which persists for < 72 hours in the absence of maximal medical therapy.
- Grade ≥ 2 non-hematologic treatment-emergent adverse event (TEAE) that in the opinion of the investigator is of potential clinical significance such that further dose escalation would expose subjects to unacceptable risk

- Continuous treatment interruption of ≥ 7 days due to unresolved toxicity
- Any toxicity event that precludes further administration of GS-4224
- Any Grade 3 or Grade 4 elevation in aspartate aminotransferase (AST) or alanine transaminase (ALT) associated with a Grade 2 elevation in bilirubin lasting ≥ 7 days
- An immune-related adverse event (irAE, defined as AEs of unknown etiology that were consistent with an immune phenomenon primarily involving the GI tract and the skin, and were considered causally related to drug exposure by investigators) for which immunotherapy should be permanently discontinued (eg, any grade encephalitis, Grade 3 myocarditis, reoccurrence of the same Grade 3 adverse reaction).

For certain toxicities, such as laboratory assessments without a clear clinical correlate, a discussion between the investigator and medical monitor may take place to determine if this AE should be assessed as a DLT.

Excluded from this definition:

- Grade 3 AEs of tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumor)
- Grade 3 rash without systemic signs or symptoms
- Grade 3 irAE that resolves to a Grade 1 or less within 21 days except as described above.

The RP2D will be determined by Gileadin discussion with SRT based on all relevant clinical data from all subjects treated in the escalation phase. The RP2D will not exceed the MTD and will consider toxicities through 90 days of dosing.

CCI [redacted]

CCI
CCI

[redacted]

Dose Expansion (Phase 2)

Dose expansion may begin when the RP2D has been determined. The dose expansion part includes the following cohort:

Cohort B1 (Basket Cohort expressing PD-L1 [TPS ≥ 1% or CPS ≥ 1 or ≥ 10] or MSI-H cancers, single arm, open label study of GS-4224)

To further characterize the safety and preliminary efficacy of GS-4224, a cohort of ~40 subjects with locally advanced, inoperable or metastatic cancer expressing PD-L1 [TPS ≥ 1% or CPS ≥ 1] will be enrolled at the RP2D level. Tumor types of interest include NSCLC, melanoma, RCC, urothelial, gastric, squamous cell head and neck, HCC, MSI-H cancers, Merkel cell, cutaneous squamous cell, esophageal cancers, and cHL. PD-L1 expression will not be required for Merkel cell, melanoma, MSI-H cancers, and cHL. See Appendix 3 for the PD-L1 expression requirement for specific tumor types.

For this cohort, subjects must have available sufficient and adequate formalin-fixed tumor tissue sample 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. Subjects with biopsy accessible tumors may also undergo optional posttreatment tumor biopsies at Cycle 3 and at end of treatment (EOT). Subjects

	must agree to and give a separate, specific written consent to provide baseline, on-treatment, and/or EOT biopsies. Biopsies at Cycle 3 should be collected after radiographic tumor scans scheduled for that cycle have been completed.
Number of Subjects Planned:	Up to 120 subjects will be enrolled. • Phase 1b (Dose Escalation): Up to 44 subjects [redacted] • Phase 2 (Dose Expansion): Cohort B1 (Basket): ~40 subjects
Target Population:	Phase 1b: Adult subjects with a histologically or cytologically confirmed advanced malignant solid tumor that is refractory to or intolerant of standard therapy or for which no standard therapy is available. For the 1000 mg BID dose cohort, histologically or cytologically confirmed advanced tumor expressing PD-L1 (TPS ≥ 10% or CPS ≥ 10) or MSI-H cancers. Tumor types of interest include NSCLC, melanoma, RCC, urothelial, esophageal, HCC, cutaneous squamous cell, Merkel cell, MSI-H cancers, and cHL. PD-L1 expression will not be required for Merkel cell, melanoma, MSI-H cancers, and cHL. See Appendix 3 for the PD-L1 expression requirement for specific tumor types. Phase 2: • Cohort B1 (Basket): Histologically or cytologically confirmed advanced tumor expressing PD-L1 (TPS ≥ 1% or CPS ≥ 1 or ≥ 10) or MSI-H cancers. Tumor types of interest include NSCLC, melanoma, RCC, urothelial, gastric, squamous cell head and neck, HCC, MSI-H cancers, Merkel cell, cutaneous squamous cell, esophageal cancers, and cHL. PD-L1 expression will not be required for Merkel cell, melanoma, MSI-H cancers, and cHL. See Appendix 3 for the PD-L1 expression requirement for specific tumor types.
Duration of Treatment:	GS-4224 will be administered until disease progression, unacceptable toxicity, substantial noncompliance with study procedures or study drug, study discontinuation, or withdrawal from study.

Diagnosis and Main Eligibility Criteria:

Inclusion Criteria:

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study. Additional indication-specific inclusion criteria for 1000 mg BID Dose Escalation Cohort and Phase 2 are provided in Appendix 3.

1. Male or female ≥ 18 years of age.
2. Dose Escalation Cohorts: Histologically or cytologically confirmed advanced malignant solid tumor that is refractory to or intolerant of all standard therapy or for which no standard therapy is available.
3. Dose Expansion and 1000 mg BID Dose Escalation Cohorts: Subjects must have available sufficient and adequate formalin-fixed tumor sample 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. For the 1000 mg BID dose escalation cohort, subjects with melanoma, Merkel cell, MSI-H cancers, and cHL are not required to have archival or fresh biopsy tissue.
4. Dose Escalation Biopsy Substudy and 1000 mg BID Dose Escalation Cohorts: Documented PD-L1 expression in the tumor (TPS ≥ 10% or CPS ≥ 10). See Appendix 3 for the PD-L1 expression requirement for specific tumor types.
    a) In the 1000 mg BID Cohort, PD-L1 expression will not be required for Merkel cell, melanoma, MSI-H cancers, and cHL.
5. All persisting toxic effects of any prior antitumor therapy resolved to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 Grade ≤ 1 or baseline before the first dose of study drug (with the exception of alopecia [Grade 1 or 2 permitted] and neurotoxicity [Grade 1 or 2 permitted]).
6. Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 2
7. Life expectancy of ≥ 3 months, in the opinion of the investigator

8. Adequate organ function defined as follows:
   a) Hematologic: Platelets $\geq 100 \times 10^9$/L ($\geq 60 \times 10^9$/L in subjects with HCC); Hemoglobin ≥ 9.0 g/dL; ANC $\geq 1.5 \times 10^9$/L (without blood transfusion, platelet transfusion, or growth factors within previous 7 days of the hematologic laboratory values obtained at screening visit)
   b) Hepatic: AST/ALT $\leq 2.5 \times$ upper limit of normal (ULN) (if liver metastases are present, $\leq 5 \times$ ULN); Total or conjugated bilirubin $\leq 1.5 \times$ ULN
   c) Renal: Creatinine clearance (CL_{cr}) ≥ 45 mL/min as calculated by the Cockcroft-Gault method
9. Coagulation: Subjects on full-dose oral anticoagulation, except warfarin, which is an excluded medication, must be on a stable dose (minimum duration 14 days). Subjects on low molecular weight heparin will be allowed.
10. Negative serum pregnancy test for female subjects
11. Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception as described in Appendix 5.
12. Females who are nursing must agree to discontinue nursing before the first dose of GS-4224.
13. Able and willing to provide written informed consent to participate in the study
14. Patients with history of human immunodeficiency virus (HIV) infection should have a CD4+ T-cell count ≥ 350 cells/µL at screening.
15. Patients with serological evidence of chronic hepatitis B virus infection (HBV) should have HBV viral load below the limit of quantification at screening.
16. Patients with serological evidence of hepatitis C virus infection (HCV) should have completed curative antiviral treatment and have HCV viral load below the limit of quantification at screening.

Exclusion Criteria:

Subjects who meet any of the following exclusion criteria are not to be enrolled in this study. Additional indication-specific exclusion criteria for 1000 mg BID Dose Escalation Cohort and Phase 2 are provided in Appendix 3.

1) History or evidence of clinically significant disorder, condition, or disease that, in the opinion of the investigator or medical monitor would pose a risk to subject safety or interfere with the study evaluations, procedures, or completion.
2) Dose Escalation Cohorts: History of ≥ Grade 3 AEs during prior treatment with an immune checkpoint inhibitor, or history of discontinuation of treatment with an immune checkpoint inhibitor due to AEs.
3) Dose Escalation 1000 mg BID and Dose Expansion Cohorts: Prior treatment with an immune checkpoint inhibitor (anti-PD-1, anti-PD-L1, or anti-ligand 2 of programmed cell death protein 1 [PD-L2] antibodies).
4) History of autoimmune disease (for example, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis).
5) Positive serum pregnancy test (Appendix 5)
6) Patient has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are clinically stable for at least 4 weeks prior to study entry, have no evidence of new or enlarging brain metastases and if taking corticosteroids, are on stable or decreasing doses for at least 7 days from first dose of study drug.
7) Uncontrolled intercurrent illness including, but not limited to, active uncontrolled infection, active or chronic bleeding event within 28 days prior to first dose of study drug, or psychiatric illness/social situation that would limit compliance with study requirements as judged by treating physician.
8) Myocardial infarction, symptomatic congestive heart failure (New York Heart Association Classification > Class II), unstable angina, or serious uncontrolled cardiac arrhythmia within the last 6 months of first dose of study drug.

9) Major surgery, defined as any surgical procedure that involves general anesthesia and a significant incision (ie, larger than what is required for placement of central venous access, percutaneous feeding tube, or biopsy) within 28 days of the first dose of study drug.
10) Impairment of GI function or GI disease that may significantly alter the absorption of GS-4224, including any unresolved nausea, vomiting, or diarrhea that is Common Terminology Criteria for Adverse Events (CTCAE) Grade > 1.
11) Symptomatic ascites or pleural effusion. A patient who is clinically stable following treatment for these conditions (including thora- or para-centesis) is eligible.
12) Minor surgical procedure(s) within 7 days of enrollment, or not yet recovered from prior surgery (placement of central venous access device, fine needle aspiration, or endoscopic biliary stent ≥ 1 day before enrollment is acceptable).
13) Prior systemic radiation therapy completed within 4 weeks of the first dose of study drug, prior local radiation therapy completed within 2 weeks of Cycle 1 Day 1 (C1D1), or radiopharmaceuticals (strontium, samarium) within 8 weeks of C1D1.
14) Antitumor therapy (chemotherapy, antibody therapy, molecular targeted therapy) within 21 days or 5 half-lives, whichever is longer, of study drug dosing (6 weeks for nitrosoureas, mitomycin C, or molecular agents with $t_{1/2}$ > 10 days); concurrent use of hormone therapy for prostate cancer is permitted.
15) History of long QT syndrome or additional risk factors for Torsades de Pointes or whose corrected QT interval (QTc) measured (Fridericia method) at screening is prolonged (> 480 ms).
16) Use of concomitant medications that prolong QT/QTc interval at screening
17) Clinically significant bleeding within 28 days of the first dose of study drug
18) Known hypersensitivity to study drug, the metabolites, or formulation excipients
19) Use of any prohibited concomitant medications as described in Section 5.5 and any investigational agent within 2 weeks of study treatment initiation

20) Breastfeeding female

21) Received live virus vaccination within 30 days of first dose of study treatment. Seasonal flu vaccines that do not contain live virus are permitted.

22) History of hematologic stem cell transplant or solid organ transplant

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. For Phase 1b, dose escalation, subjects in screening will be assigned to an applicable cohort. Screening procedures will include the following: medical history review; physical exam; vital signs; 12-lead electrocardiogram (ECG); ECOG Performance Status; prior/concomitant medication review; blood collection for pregnancy test (females of child bearing potential); chemistry, hematology, and coagulation; AE assessment; archival or recent biopsy formalin-fixed paraffin-embedded (FFPE) tissue block collection; and computed tomography (CT) or magnetic resonance imaging (MRI) and positron emission tomography-computed tomography (PET-CT) in subjects with cHL (scans that meet protocol requirements that are obtained as part of standard medical practice up to 6 weeks prior to C1D1 are acceptable). For Phase 2, PD-L1 expression in the tumor will be determined by an immunohistochemistry (IHC) test. Baseline tumor lesions will be measured and characterized prior to C1D1 to assess the subject disease status prior to beginning treatment.

Treatment:

Subjects who meet eligibility criteria will receive GS-4224 orally once daily in the 400 1500 mg QD cohorts and 1000 mg twice daily in the 1000 mg BID cohort (separated by approximately 12 hours). Each cycle will consist of 21 days. Safety and efficacy assessments will occur on an outpatient basis including assessment of tumor response, physical exam, vitals, ECG, collection of blood samples (for routine safety labs, GS-4224 PK, pharmacodynamic markers, and other biomarkers at applicable visits), urine pregnancy test (every 3 weeks while receiving GS-4224 in females of childbearing potential), and assessment of AEs. In addition, subjects will undergo postbaseline CT/MRI and PET-CT (for cHL) scans for tumor response assessment. A subject who does not show evidence of disease progression by clinical assessment or by CT/MRI or applicable scan may continue receiving study treatment until disease progression (clinical or radiographic), unacceptable toxicity, withdrawal of consent, or other reasons specified in Section 3.5.

After discontinuation of all study treatment, subjects will be followed for safety for 30 days.

Pharmacokinetic Assessment:

Intensive PK will be collected in all subjects in Phase 1b dose cohorts between 400 mg and 1500 mg QD. In the 1000 mg BID dose escalation cohort, intensive PK will be collected at select sites and in at least 6 subjects. CCI

CC1

Intensive PK samples will be collected predose on Cycle 1 Days 1 and 15, followed by 0.5, 1, 1.5, 2.5, 4, 6, 12 (1000 mg BID dose cohort) and 0.5, 1, 1.5, 2.5, 4, 6, and 24 (400 1500 mg QD dose cohorts) hours postdose relative to the AM dose. For the 1000 mg BID cohort, the 12 hours postdose samples will be collected prior to the PM dose. Every effort should be made to collect Intensive PK samples at the indicated time; actual sample collection time should be recorded.

CCI

CCI

CCI

[redacted]

CCI

[redacted]

Tumor Assessment:

CT/MRI will be performed approximately every 6 weeks for the first 2 postbaseline scans and then every 9 weeks. The same method of assessment and the same technique (eg, scan type, scanner, subject position, dose of contrast, injection/scan interval) should be used to characterize each identified and reported lesion at baseline and during study treatment and follow up.

For subjects with cHL, in addition to CT or MRI scan, a baseline PET-CT is required at screening (or within 6 weeks before C1D1 if the scan was performed as part of standard medical practice), at Cycle 3 Day 1, and Cycle 5 Day 1. Per Lugano 2014 criteria, PET-CT is required to confirm radiographic complete response (CR). If radiographic CR has not been confirmed by PET-CT at Cycle 3 or 5, additional PET-CT will be required within 4 weeks of the CT/MRI scan that assessed radiographic CR.

For solid tumors, responses will be evaluated using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) with modifications. For subjects with cHL, Lugano 2014 response criteria will be used. Because of the potential for pseudo-progression, subjects whose scans show radiographic progression in the absence of clinical deterioration including worsening performance status as assessed by the investigator may remain on study treatments and an additional scan should be obtained no less than 4 weeks later as outlined in Section 6.6. If this subsequent scan shows disease progression, the subject will be discontinued from study treatments.

Response to disease (CR or partial response [PR]) will be confirmed by the same imaging technique no less than 4 weeks after the criteria for response are first met.

All relevant clinical and radiographic information required to make each assessment must be made available for source verification and submission to an independent review committee (IRC). Scans will be transferred to a central reader for collection and future analysis. Disease progression will be determined by the investigator or qualified designee for patient management in real time.

Test Product, Dose, and Mode of Administration:	GS-4224 tablets will be self-administered orally once daily in the 400 1500 mg QD cohorts and 1000 mg twice daily in the 1000 mg BID cohort, from their first dose and thereafter at approximately the same time each day until EOT. GS-4224 is supplied as 100 mg, 200 mg, and 500 mg tablets. On the intensive PK sampling days for subjects in Phase 1b, GS-4224 will be administered in the clinic under fasted conditions.
Reference Therapy, Dose, and Mode of Administration:	Not Applicable
Criteria for Evaluation:	
Safety:	Safety will be evaluated by assessment of clinical laboratory tests, physical examination, 12-lead ECG, vital signs measurements, and the documentation of AEs. AEs will be graded using NCI-CTCAE version 5.0.
Efficacy:	Efficacy will be evaluated by overall response rate (ORR) (CR + PR), assessed as per RECIST v 1.1 with modifications, or per Lugano 2014 response criteria for cHL, and progression-free survival (PFS), defined as the interval from the first dosing date of study drug to the earlier of the first documentation of definitive disease progression or death from any cause.
Pharmacokinetics:	The following PK parameters for GS-4224 will be calculated as applicable: T_{last}, T_{max}, C_{max}, C_{trough}, AUC_{last}, AUC_{tau}, and $t_{1/2}$. Dose proportionality and time-dependency in drug exposure may be evaluated as applicable.
CCI [redacted]	[redacted]

Statistical Methods:

The study primary analysis will be conducted when all enrolled subjects have discontinued the study or have been on treatment of GS-4224 for at least 48 weeks and completed response assessment of Week 48.

Analysis Data Set

The All Enrolled Analysis Set includes all subjects who received a study subject identification number in the study after screening.

The Full Analysis Set (FAS) includes all subjects who took at least 1 dose of study treatment. It will be used in the analyses of efficacy endpoints.

The Safety Analysis Set will include data from all subjects who receive at least 1 dose of study treatment, with treatment assignments designated according to the actual treatment received. This analysis set will be used in the analyses of safety variables as well as study treatment administration.

The DLT-Evaluable Analysis Set includes all subjects in the Safety Analysis Set who enroll to the dose escalation cohorts (up to the first 6 subjects in the 1000 mg BID dose escalation cohort; excluding the Dose Escalation Biopsy Substudy), complete ≥ 75% of the prescribed study treatment and have safety assessments through the protocol-specified DLT assessment window (first 21 days of study dosing, inclusive) or have experienced a DLT prior to the completion of first 21 days of study dosing. Safety assessment relevant to the DLT-Evaluable Analysis Set definition will include laboratory serum chemistry tests and hematology tests as specified in the protocol. Determination of the MTD will be based on the DLT-Evaluable Analysis Set.

The PK Analysis Set will include data from subjects in the Safety Analysis Set who have received the study drug and have at least 1 sample with detectable drug concentration.

An IRC may review radiographic data in order to provide independent evaluation of tumor status. Tumor response status and progression will be assessed by the IRC using RECIST v1.1 with modifications or Lugano 2014 response criteria for cHL.

Efficacy Analysis

In efficacy analysis, ORR will be evaluated by tumor type and treatment in FAS. Tumor types with less than 5 subjects enrolled will be pooled for ORR summary. Subjects who do not have sufficient baseline or on-study tumor assessment to characterize response will be counted as nonresponders. Estimates and the corresponding 95% CIs based on the Clopper-Pearson exact method will be provided.

Median, first quartile (Q1), third quartile (Q3) of the PFS distribution, and the proportion of subjects who are progression-free at Week 12, 24, and 48 from the first dosing date will be estimated by tumor type using the Kaplan-Meier (KM) method along with the corresponding 95% CIs. KM curves will be provided.

The ORR and PFS analyses will be conducted using the investigator assessments and IRC assessments if available.

Safety Analysis

Safety will be assessed via AEs, clinical laboratory tests, and concomitant medications in the Safety Analysis Set by cohort, indication and treatment. Information regarding study drug administration, study drug compliance, and other safety variables will also be summarized.

Pharmacokinetic (PK) Analysis

GS-4224 plasma concentrations and PK parameters will be described and summarized. Plasma concentrations of GS-4224 metabolite(s) may also be determined and explored.

Sample Size

The sample size of the study will be determined based on the number of dose levels evaluated and the emerging GS-4224-related toxicities and efficacy. The study is planned to enroll approximately 120 subjects.

Approximately 44 subjects will be enrolled in the dose escalation phase (Phase 1b)[redacted] Approximately 40 subjects will be enrolled into the Dose Expansion Cohort B1.

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
λz	terminal disposition rate constant, estimated by linear regression of the terminal elimination phase of the log concentration of drug versus time curve of the drug
3D	three-dimensional
ADA	anti-drug antibody
ADL	activities of daily living
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AJCC-8	American Joint Committee on Cancer staging manual
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AR	accumulation ratio
ARA	acid-reducing agent
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{last}	area under the drug concentration-time curve from time zero to last time point with measurable concentration
AUC_{tau}	area under the concentration-time curve from time zero to the end of the dosing interval
aVR	augmented Vector Right
BCRP	breast cancer resistance protein
BOR	best overall response
BUN	blood urea nitrogen
C1D1	Cycle 1 Day 1
CD80	cluster determinant 80
CFR	Code of Federal Regulations
CHB	chronic hepatitis B
cHL	classical Hodgkin Lymphoma
CI	confidence interval
CL	systemic clearance
C_{max}	maximum observed drug concentration
C_{trough}	observed concentration at the end of the dosing interval
CNS	central nervous system
CPS	combined positive score
CR	complete response
CL_{cr}	creatinine clearance

CRF	case report form
CRO	Contract Research Organization
CRP	C-reactive protein
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CYP	cytochrome P450 enzyme
DCR	disease control rate
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
EC	effective concentration
EC_{50}	Half-maximal effective concentration
EC_{90}	90% effective concentration
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EF	ejection fraction
EOT	end of treatment
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose (18F)
FFPE	formalin-fixed paraffin-embedded
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GGT	gamma-glutamyltransferase
GI	gastrointestinal
GLP	Good Laboratory Practices
GLPS	Global Patient Safety
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma

HCV	hepatitis C virus
HED	human equivalent dose
hERG	human ether-à-go-go-related gene
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HNSCC	head and neck squamous cell cancer
HuMC38	Human PD-L1-expressing MC38
IB	investigator's brochure
IC_{50}	half-maximal inhibitory concentration
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
ICF	informed consent form
IEC	independent ethics committee
IgG1	immunoglobulin G1
IHC	immunohistochemistry
ILD	interstitial lung disease
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
irAE	immune-related adverse event
IRB	institutional review board
IRC	independent review committee
ITP	immune thrombocytopenia purpura
ITT	intent-to-treat
IV	intravenous(ly)
IXRS	interactive voice/web response system
KM	Kaplan-Meier
mAb	monoclonal antibody
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
MABEL	minimally anticipated biologic effect level
MRI	magnetic resonance imaging
MRSD	maximum recommended starting dose
MSI-H	microsatellite instability-high
NCA	noncompartmental analysis
NCI	National Cancer Institute

NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NHP	non-human primate
NK	natural killer
NOAEL	no observed adverse effect level
NSAID	nonsteroidal anti-inflammatory drugs
NSCLC	non-small cell lung cancer
OATP	organic anion transporting polypeptide
ORR	overall response rate
OS	overall survival
OTC	over-the-counter (drug)
PBMC	peripheral blood mononuclear cell
PET-CT	positron emission tomography-computed tomography
PT	Preferred Term
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	ligand 1 of programmed cell death protein 1
PD-L1 high	tumor cells expressing high levels of PD-L1
PD-L1 low	peripheral immune cells expressing basal levels of PD-L1
PD-L2	ligand 2 of programmed cell death protein 1
PD PBMC	pharmacodynamic peripheral blood mononuclear cell
PFS	progression-free survival
P-gp	P-glycoprotein
PHI	protected health information
PI	Principal Investigator
PMBCL	primary mediastinal B-cell lymphoma
PK	pharmacokinetic(s)
PR	partial response
Q1, Q3	first quartile, third quartile
QT, QTc	QT interval corrected for heart rate
Q-TBNK	Quantitative T, B, and natural killer
RANKL	receptor activator of nuclear factor kappa-B ligand
RBC	red blood cell
RCC	renal cell carcinoma
RECIST v1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
RNA	ribonucleic acid
ROW	rest of world
RP2D	recommended Phase 2 dose
TPS	tumor proportion score
SADR	serious adverse drug reaction
SAE	serious adverse event

SAP	Statistical Analysis Plan
SD	stable disease
SDV	source data verification
SJS	Stevens-Johnson Syndrome
SOC	system organ class
SOP	standard operating procedure
SRT	safety review team
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal elimination half-life
T4	thyroxine
TBL	total bilirubin
TCR	T-cell receptor
TEAE	treatment-emergent adverse event
TEN	toxic epidermal necrolysis
T_{last}	time of last observable plasma concentration
T_{max}	time to maximum observed concentration
TNM	tumor node metastasis
TSH	thyroid-stimulating hormone
UGT1A1	uridine diphosphate glucuronosyltransferase 1A1
ULN	upper limit of normal
US	United States
Vd	volume of distribution

1. INTRODUCTION

1.1. Background

GS-4224 is a potent, selective, and orally bioavailable small molecule inhibitor that binds specifically to ligand 1 of programmed cell death protein 1 (PD-L1) and promotes dimerization, leading to inhibition of programmed cell death protein 1 (PD-1) receptor binding.
The mechanism of action of GS-4224 translated to potent and rapid PD-L1 occupancy on tumor cells expressing high levels of PD-L1 (PD-L1 high), versus on peripheral immune cells expressing basal levels of PD-L1 (PD-L1 low). This unique feature may translate to an improved therapeutic index in patients with PD-L1 high tumors, as compared with existing antibodies that saturate PD-L1 (or PD-1) irrespective of cellular expression level.

GS-4224 exhibits an on-target selectivity profile comparable with PD-L1 antibodies. GS-4224 selectively blocks PD-1/PD-L1 and PD-L1/cluster determinant 80 (CD80) interactions and does not inhibit PD-1/programmed cell death protein 1 ligand 2 (PD-L2) or cytotoxic T lymphocyte associated-4 (CTLA-4)/CD80 receptor-ligand interactions.

GS-4224 restored responses and effector functions of T cells inhibited by PD-L1 in a variety of T-cell activation assays and demonstrated potent antitumor activity in mouse tumor models. Furthermore, GS-4224 enhanced both cytolytic and noncytolytic functions of hepatitis B virus (HBV)-specific T cells present in human peripheral blood mononuclear cells (PBMCs) isolated from chronic hepatitis B (CHB) patients.

Taken together, these data support the development of GS-4224 as a potent, selective, and orally bioavailable PD-L1 small molecule inhibitor for the treatment of solid tumors, as well as CHB.

1.2. GS-4224

1.2.1. General Information

For further information on GS-4224, refer to the current investigator's brochure (IB) for GS-4224.

1.2.2. Preclinical Pharmacology and Toxicology

GS-4224 exhibits an on-target-selectivity profile comparable with PD-L1 antibodies, as it selectively blocks PD-1/PD-L1 and PD-L1/CD80 interactions (half-maximal inhibitory concentration [IC_{50}] < 1 nM) and does not inhibit PD-1/ PD-L2 or CTLA-4/CD80 receptor-ligand interactions (IC_{50} > 10,000 nM).

GS-4224 restored the responses and effector functions of T cells inhibited by PD-L1 in a variety of T-cell activation assays, including a three-dimensional (3D) spheroid co-culture assay that measured T-cell mediated tumor lysis in response to GS-4224. Half-maximal effective concentration (EC_{50}) values in these assays ranged between 12 nM and 94 nM. Furthermore, in a human whole blood stimulation assay, GS-4224 promoted interferon-gamma (IFN-γ) secretion with an average 90% effective concentration (EC_{90}) of 338 nM.

GS-4224 demonstrated potent antitumor activity in mouse tumor models. The first model is a human PD-L1-expressing MC38 (HuMC38) colorectal tumor model where only tumor cells express human PD-L1 while mouse immune cells retain expression of mouse PD-1 and PD-L1. The second model is the implantation of HuMC38 tumor cells into a genetically engineered human PD-L1 knock-in (KI) mouse. In this model, both tumor and immune cells express human PD-L1. For both models, GS-4224 achieved > 90% target occupancy in tumor cells for at least 24 hours at all doses administered: HuMC38 tumor model (10 mg/kg once daily, 25 mg/kg twice daily, and 50 mg/kg once daily) and HuMC38 tumor model in human PD-L1 KI mouse (30 mg/kg twice daily).

The nonclinical safety profile of GS-4224 has been well characterized through the conduct of safety pharmacology, repeat dose toxicity, genetic toxicology, and impurity qualification studies. Data from the investigational new drug (IND) nonclinical safety package (Table 1-1) and 13-week interim analysis from the 26-week rat and 39-week monkey studies can be found in the GS-4224 IB.

Table 1-1. IND Nonclinical Safety Package

Study Type	Study Title[a]
Safety Pharmacology	Effect of GS 4224 01[b] on Cloned hERG Potassium Channels Expressed in Human Embryonic Kidney Cells
	Cardiovascular Assessment Following Single Oral Gavage Administration of GS 4224 01 to Conscious Radiotelemetry Instrumented Cynomolgus Monkeys
	Central Nervous System (CNS) Assessment (Modified Irwin Test) of GS 4224 01 Following Single Dose Oral Gavage Administration in Male Wistar Han Rats
	Respiratory Assessment Following Single Dose Oral Gavage Administration of GS 4224 01 to Plethysmograph Restrained Male Wistar Han Rats
General Toxicology	A 4 Week Oral Gavage Toxicity and Toxicokinetics Study of GS 4224 01 in Wistar Han Rats with a Bone Marrow Micronucleus Assay
	A 4 Week Oral Gavage Toxicity and Toxicokinetic Study of GS 4224 01 in Cynomolgus Monkeys
	A 7 Day Oral Gavage Dose Range Finding Toxicity and Toxicokinetic Study of GS 954418 in Wistar Han Rats (Non GLP)
	A 7 Day Oral Gavage Dose Range Finding Toxicity and Toxicokinetic Study of GS 954418 in Male Cynomolgus Monkeys (Non GLP)
Genetic Toxicology	GS 4224 01 Salmonella E. Coli/Mammalian Microsome Reverse Mutation Assay
	GS 4224 01 In Vitro Chromosome Aberration Test in Cultured Human Peripheral Blood Lymphocytes
	A 4 Week Oral Gavage Toxicity and Toxicokinetics Study of GS 4224 01 in Wistar Han Rats with a Bone Marrow Micronucleus Assay
	Rat Alkaline Comet Assay Following Oral Gavage Administration of GS 4224 01
Other Studies	A 4 Week Oral (Gavage) Impurity Qualification Toxicity and Toxicokinetic Study of GS 4224 03 in Wistar Han Rats

CNS central nervous system; GLP Good Laboratory Practices; HCl hydrochloride; hERG human ether à go go related gene; IND investigational new drug
a Studies are GLP except where indicated
b GS 4224 01 bis HCl salt of GS 4224

1.2.3. Clinical Trials of GS-4224

Study GS-US-439-4660 is an ongoing Phase 1 study to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of GS-4224 for the first time in humans. This study consists of 2 parts (A and B). Part A (Cohorts 1-5, 8-10) entails administration of GS-4224 to healthy volunteers with the objective of better understanding the safety and clinical pharmacology profile of GS-4224. Part B (Cohorts 11-16) will be a multicenter, randomized, blinded, placebo-controlled study of GS-4224 in subjects with CHB. At this time, Cohorts 1-5 in Part A have been completed and used to support the study design outlined in this protocol. Full details on the study design and safety data from the completed portion can be found in the IB.

1.3. Rationale for this Study

Therapeutic antibodies that block the PD-1/PD-L1 interaction have emerged as a class of foundational cancer therapies. Six antibodies targeting the PD-1/PD-L1 pathway have been approved by the United States (US) Food and Drug Administration (FDA) in over 20 different tumor indications, with at least 50 additional antibodies targeting this axis in clinical development as monotherapy or in combination with other agents. By contrast, only one oral small molecule inhibitor of the PD-1/PD-L1 interaction has entered development (Phase 1 study, NCT03762447, initiated Dec 2018 for INCB086550). The current study will determine the safety and preliminary efficacy of GS-4224, an oral small molecule inhibitor of PD-1/PD-L1 interaction, which may provide an alternative treatment option to patients with tumor types that have shown activity with antibodies that target the same pathway.

1.4. Rationale for the Dose Selection

In Phase 1b of this study, starting dose of GS-4224 400 mg once daily will be administered to subjects with advanced solid tumors. This starting dose is supported by preclinical PK and toxicology studies as well as available safety, tolerability, and PK data in healthy volunteers (GS-US-439-4660).

The proposed starting dose of GS-4224 400 mg once daily is expected to be well tolerated for administration to subjects with advanced solid tumors. Based on available clinical PK data in healthy volunteers from Study GS-US-439-4660, the mean steady-state exposure (AUC_{tau}) of once daily 400 mg GS-4224 is expected to be approximately 10,100 h*ng/mL, which is 5.1-fold lower exposure than that observed at the no observed adverse effect level (NOAEL) in the nonclinical multiple dose Good Laboratory Practices (GLP) 28-day toxicology study (the most sensitive species was rat; an AUC_{tau} of 51,400 h*ng/mL was observed after 100 mg/kg/day GS-4224 administration, Section 1.2.2) and 1.6-fold that of the exposure observed at the NOAEL in the nonclinical multiple dose chronic toxicology study (the most sensitive species was rat; an AUC_{tau} of 16,100 h*ng/mL was observed after 30 mg/kg/day GS-4224 administration, Section 1.2.2). These safety margins provide adequate coverage for the starting dose as well as the escalation strategy (escalation will proceed from the 400 mg QD starting dose to 700 mg QD, 1000 mg QD, 1500 mg QD, then to the maximum dose of 1000 mg BID).

The proposed starting dose is also supported by the ongoing healthy volunteer study, GS-US-439-4660. This study is a Phase 1 study to evaluate the safety, tolerability, PK, and pharmacodynamics of GS-4224 (see GS-4224 IB). This study consists of 2 parts (A and B). Part A entails administration of GS-4224 to healthy volunteers for the first time with the objective of evaluating in a step-wise fashion the safety, tolerability, PK, and pharmacodynamics of single and multiple escalating doses of GS-4224. As of 8 July 2019, the 20, 60, 180, 540, and 1000 mg single and multiple dosing cohorts have completed with no significant safety concerns. PK and preliminary pharmacodynamic data for single-/multiple-dose 20 to 1000 mg and 20 to 540 mg, respectively, are currently available (see GS-4224 IB).

Given this study includes subjects with advanced solid tumors, selection of a pharmacodynamically active dose is important. Daily administration of 400 mg GS-4224 is expected to provide pharmacodynamically active GS-4224 exposure. Average steady-state GS-4224 exposures at this dose approximate the protein adjusted EC_{90} for in vitro whole blood T-cell stimulation (see GS-4224 IB). Furthermore, available preliminary pharmacodynamic data in healthy volunteers (see GS-4224 IB) indicates that multiple daily doses of 400 mg GS-4224 is expected to provide similar or greater PD-L1 target occupancy in the PBMCs of subjects with solid tumors than that which was observed in healthy volunteers (17% and 36% PD-L1 target occupancy after multiple dose administration of 180 mg and 540 mg GS-4224, respectively). Based on in vitro data, it is expected that target occupancy will be higher at the site-of-action if PD-L1 is over-expressed on the tumor (see GS-4224 IB).

Considering expected exposure to provide a pharmacological response, the supportive safety data from the ongoing clinical study and toxicology data, a starting dose of 400 mg once daily is considered appropriate for initial evaluation in this study.

A maximum GS-4224 dose of 2000 mg daily administered as 1000 mg twice daily will be evaluated in Phase 1b and dose escalation from the 400 mg once daily starting dose to the maximum dose will proceed via a standard 3+3 study design (as described in Section 3.2). The mean daily steady-state exposure ($AUC_{0\ 24}$) of GS-4224 1000 mg twice daily is expected to be approximately 45,700 h*ng/mL, assuming dose proportionality. This is 1.1- and 0.4-fold relative to the exposures observed at the NOAELs of the most sensitive species tested (rat) in the nonclinical multiple dose GLP 28-day and chronic toxicology studies, respectively (see GS-4224 IB). The NOAEL determining adverse effect observed in rats after chronic dosing (> 28 days) is readily monitorable in the clinic (see GS-4224 IB). In the dose escalation phase and healthy volunteer study (GS-US-439-4660), no clinically meaningful safety or tolerability findings have been observed at doses up to 1000 mg. Based on these data, a maximum daily dose of 2000 mg (1000 mg twice daily) is expected to maintain a favorable safety profile in subjects with solid tumors.

The recommended Phase 2 dose (RP2D) to be evaluated in Phase 2 will be selected based on all relevant clinical data from all subjects treated in Phase 1b dose escalation, will consider toxicities through 90 days of dosing, and will not exceed the maximum tolerated dose (MTD).

1.5. Risk/Benefit Assessment for the Study

Potential risks of a participant's study involvement include immune-related adverse events (irAEs) (defined as adverse events [AEs] of unknown etiology that were consistent with an immune phenomenon primarily involving the gastrointestinal [GI] tract and the skin, and were considered causally related to drug exposure by investigators) described with other anti-PD-1/PD-L1 agents, unknown AEs, general risks associated with frequent clinic visits and laboratory blood draws, and the associated pain and discomfort of phlebotomy. Strategies to mitigate these risks include close monitoring of lab values as well as AEs. Parameters for discontinuation of the study drug are defined in Section 6.10.1.

There may be no direct benefit to subjects participating in this study; however, data from this study will support the development of GS-4224 for the treatment in subjects with advanced solid tumors. Potential benefits may include the participant's contribution to understanding the safety, tolerability, efficacy, pharmacodynamics, and PK of multiple and escalating doses of GS-4224.

Based on available information, the benefit/risk balance for this study is considered positive.

During a pandemic, additional potential risks to subjects may include adequate study drug availability, interruptions to the study visit schedule, and adherence to protocol-specified safety monitoring or laboratory assessments. Refer to Appendix 8 for further details on the risks and risk mitigation strategy.

1.6. Compliance

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

2. OBJECTIVES

The primary objectives of this study are as follows:

Phase 1b Dose Escalation

- Characterize the safety and tolerability of GS-4224 in subjects with advanced solid tumors
- Determine the MTD and RP2D of GS-4224 in subjects with advanced solid tumors

The secondary objectives of this study are as follows:

Phase 1b Dose Escalation

- Evaluate the PK of GS-4224 in subjects with advanced solid tumors

Phase 2 Dose Expansion

- Evaluate the safety and tolerability of GS-4224 in subjects with advanced solid tumors

CCI

3. STUDY DESIGN

3.1. Endpoints

The primary endpoint of this study is as follows:

Phase 1b Dose Escalation

- Incidence of dose-limiting toxicity (DLT) as defined in Section 3.2.

The secondary endpoints are as follows:

Phase 1b Dose Escalation

- PK parameters (T_{last}, T_{max}, C_{max}, C_{trough}, AUC_{last}, AUC_{tau} and $t_{1/2}$, as applicable) for GS-4224 in subjects with advanced solid tumors.

Phase 2 Dose Expansion

- Incidence of Grade ≥ 3 treatment-emergent adverse events (TEAEs) in Cohort B1 subjects with advanced solid tumors
- Incidence of Grade ≥ 3 treatment-emergent laboratory abnormalities in Cohort B1 subjects with advanced solid tumors

CCI

[redacted]

CCI

[redacted]

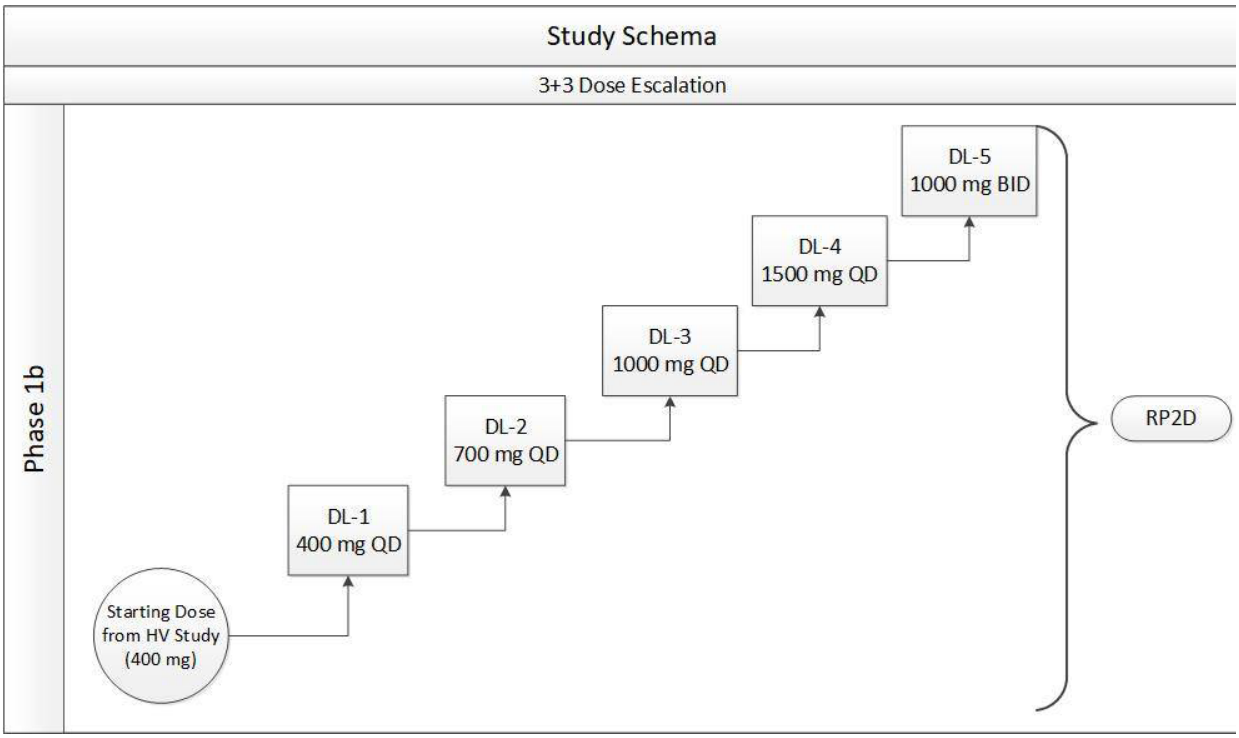
3.2. Study Design

This is an open-label, multicenter, sequential dose escalation and dose expansion study to evaluate the safety, tolerability, PK, and efficacy of GS-4224 in subjects with advanced solid tumors. The study will consist of 2 parts: the dose escalation portion (Phase 1b), followed by dose expansion (Phase 2) in subjects with tumors for which PD-1/PD-L1 treatments are approved or are known to be active.

3.2.1. Dose Escalation (Phase 1b)

The overall Phase 1b study design is presented graphically in Figure 3-1.

Figure 3-1. Phase 1b Study Design Schema



DL dose level; HV healthy volunteers; QD once a day; BID twice a day; RP2D recommended Phase 2 dose

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 oral GS-4224 as monotherapy once daily (400 1500 mg QD cohorts) and as monotherapy at 1000 mg twice daily (1000 mg BID cohort).

Dose escalation will proceed using a standard 3+3 design. The starting dose is 400 mg QD, with subsequent doses of 700 mg QD, 1000 mg QD, 1500 mg QD, and 1000 mg BID. Dose level increases will be 3-fold or less.

Table 3-1. Dose Escalation (Phase 1b) Dose Levels

Dose Level Schema	
GS-4224 (mg)	**Fold Increase**
400 QD	-
700 QD	≤ 3×
1000 QD	≤ 3×
1500 QD	≤ 3×
1000 BID	≤ 3×

In the 1000 mg BID dose cohort, at least 6 (as part of the initial 3+3 design) and up to an additional 14 subjects (for a total of 20 subjects) with locally advanced, inoperable or metastatic cancer expressing PD-L1 (tumor proportion score [TPS] ≥ 10% or combined positive score [CPS] ≥ 10) and who have not previously been treated with anti-PD-1/L1 antibodies will be enrolled. The additional 14 subjects will not be enrolled at the 1000 mg BID dose level if the subject incidence of DLTs is > 1 in the first 6 subjects. If the subject incidence of DLTs is > 1 in the first 6 subjects at 1000 mg BID, then 20 additional subjects with locally advanced, inoperable or metastatic cancer expressing PD-L1 [TPS ≥ 10% or CPS ≥ 10] and who have not previously been treated with anti-PD-1/L1 antibodies will enroll at the MTD. Tumor types of interest include non-small cell lung cancer (NSCLC), melanoma, renal cell carcinoma (RCC), urothelial, esophageal, hepatocellular carcinoma (HCC), cutaneous squamous cell, Merkel cell, MSI-H cancers, and cHL. See Appendix 3 for the PD-L1 expression requirement for specific tumor types.

For the 1000 mg BID dose cohort, subjects must have available sufficient and adequate formalin-fixed tumor tissue sample 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. Subjects with melanoma, Merkel cell, MSI-H cancers, and cHL are not required to have archival or fresh biopsy tissue.

The safety and tolerability of each dose level will be assessed by a safety review team (SRT) after up to 6 subjects enrolled in the dose level have been followed for at least 21 days after the first dose of GS-4224 or 2 DLTs have been observed, whichever is earlier. See Section 3.2.3 for more information about the SRT.

The initial block of each dose consists of 3 subjects. Dose escalation may occur if no subjects experience DLTs during the first 21 days of study drug dosing. If 1 subject within the initial cohort of 3 subjects experiences a DLT during the first 21 days of study drug dosing, an additional 3 subjects will be enrolled at the same dose level. If no DLTs are observed in the additional 3 subjects, dose escalation will occur. If 2 or more of the 6 subjects experience DLTs within the first 21 days, dose de-escalation to an intermediate dose will occur. The MTD is the

highest dose level with a subject incidence of DLTs during the first 21 days of study drug dosing of 0 or 1 out of 6. 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 21 days for a reason other than a DLT will be replaced.

If 2 or more delayed DLT-type AEs are noted after the first 21-day observation period within a dose escalation cohort, further accrual at all sites will be held pending safety analysis of the event, and will be restarted only with investigator and sponsor approval.

The SRT will review safety and relevant clinical data and make the dose escalation/stay/de-escalation decision. Source Data Verification (SDV) is not required to be performed prior to SRT meetings, as there will be alternative quality control checks implemented. These checks will be described in the SRT Charter.

3.2.1.1. DLT Definition

A DLT is any toxicity defined below excluding toxicities clearly related to disease progression or disease-related processes occurring during the DLT assessment window (Day 1 through Day 21):

- Grade ≥ 4 neutropenia (absolute neutrophil count [ANC] < 500/mm^3)
- Grade ≥ 3 neutropenia (ANC < 1000/mm^3) with fever (a single temperature of > 38.3°C or a sustained temperature of ≥ 38°C for more than 1 hour)
- Grade ≥ 3 thrombocytopenia
- Grade ≥ 2 bleeding (eg, GI, respiratory, epistaxis, or purpura)
- Grade ≥ 3 anemia
- Grade ≥ 3 or higher non-hematologic toxicity, except:

  Grade 3 nausea or emesis with maximum duration of 48 hours on adequate medical therapy

  Grade 3 diarrhea which persists for < 72 hours in the absence of maximal medical therapy.

- Grade ≥ 2 non-hematologic TEAE that in the opinion of the investigator is of potential clinical significance such that further dose escalation would expose subjects to unacceptable risk
- Continuous treatment interruption of ≥ 7 days due to unresolved toxicity
- Any toxicity event that precludes further administration of GS-4224

- Any Grade 3 or Grade 4 elevation in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) associated with a Grade 2 elevation in bilirubin lasting ≥ 7 days

- An irAE for which immunotherapy should be permanently discontinued (eg, any grade encephalitis, Grade 3 myocarditis, reoccurrence of the same Grade 3 adverse reaction).

For certain toxicities, such as laboratory assessments without a clear clinical correlate, a discussion between the investigator and medical monitor may take place to determine if this AE should be assessed as a DLT.

Excluded from this definition:

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

- Grade 3 rash without systemic signs or symptoms

- Grade 3 irAE that resolves to a Grade 1 or less within 21 days, except as described above.

3.2.1.2. Recommended Phase 2 Dose Determination

The RP2D will be determined by Gilead in discussion with the SRT based on all relevant clinical data from all subjects treated in the escalation phase. The RP2D will not exceed the MTD and will consider toxicities through 90 days of dosing.

CCI [redacted]

3.2.2. Dose Expansion (Phase 2)

Dose expansion may begin when the RP2D has been determined.

The dose expansion phase includes the following cohort:

Cohort B1 (Basket Cohort expressing PD-L1 [TPS ≥ 1% or CPS ≥ 1 or ≥ 10] or MSI-H cancers, single arm, open-label study of GS-4224)

To further characterize the safety and preliminary efficacy of GS-4224, a cohort of ~40 subjects with locally advanced, inoperable or metastatic cancer expressing PD-L1 [TPS ≥ 1% or CPS ≥ 1] will be enrolled at the RP2D level. Tumor types of interest include NSCLC, melanoma, RCC, urothelial, gastric, squamous cell head and neck, HCC, MSI-H cancers, Merkel cell, cutaneous squamous cell, esophageal cancers, and cHL. See Appendix 3 for the PD-L1 expression requirement for specific tumor types.

3.2.3. Safety Review Team

An SRT will be established to assess safety, make decisions on dose escalation, define the MTD, and propose RP2D for dose expansion consideration.

The SRT will consist of at least 1 investigator and the following Gilead study team members: the medical monitor, representatives from Global Patient Safety (GLPS) (formerly Gilead Pharmacovigilance and Epidemiology), Clinical Operations, and Biostatistics. Others may be invited to participate as members of the SRT if additional expertise is desired. The medical monitor serves as the chair of the SRT.

An SRT Charter (or similar document) will be agreed by all SRT members prior to the first SRT meeting. The SRT Charter will describe the dose escalation process, including the following:

- Data required for review before initiating the next specified dose
- Data quality required
- Stopping rules for individual and for the study
- Minimum quorum of study and sponsor personnel required to make decisions
- Who makes the final dose escalation decision and documentation of the decision

3.3. Study Treatments

The study drug is GS-4224. Subjects will be given GS-4224 tablets once daily in the 400-1500 mg QD cohorts and twice daily in the 1000 mg BID cohort.

Formulation, packaging, and dosing regimens are further described in Section 5.

3.4. Duration of Treatment

GS-4224 will be administered until disease progression, unacceptable toxicity, substantial noncompliance with study procedures or study drug, study discontinuation or withdrawal from study.

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-4224
- Sponsor's decision
- Poor enrollment of subjects, making completion of the study within an acceptable timeframe unlikely
- Discontinuation of development of GS-4224

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

The entire study may be terminated or suspended upon request of health authorities.

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. Poststudy Care

Upon withdrawal from study treatment, subjects may receive the care upon which they and their physicians agree.

3.7. Source Data

The subject identification numbers captured by the interactive voice/web response system (IXRS) are considered source data.

CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Up to 120 subjects will be enrolled at approximately 35 centers in the US, Europe, and rest of world (ROW).

Phase 1b (Dose Escalation): Up to 44 subjects

CCI [redacted]

Phase 2 (Dose Expansion):

- Cohort B1 (Basket): Approximately 40 subjects

4.1.1. Target Population

Phase 1b: Adult subjects with a histologically or cytologically confirmed advanced malignant solid tumor that is refractory to or intolerant of standard therapy or for which no standard therapy is available. For the 1000 mg BID cohort, histologically or cytologically confirmed advanced tumor expressing PD-L1 (TPS ≥ 10% or CPS ≥ 10) or MSI-H cancers. Tumor types of interest include NSCLC, melanoma, RCC, urothelial, esophageal, HCC, cutaneous squamous cell, Merkel cell, MSI-H cancers, and cHL. PD-L1 expression will not be required for Merkel cell, melanoma, MSI-H cancers, and cHL. See Appendix 3 for the PD-L1 expression requirement for specific tumor types.

Phase 2 (See Appendix 3):

- Cohort B1 (Basket): Histologically or cytologically confirmed advanced tumor expressing PD-L1 (TPS ≥ 1% or CPS ≥ 1 or ≥ 10) or MSI-H cancers. Tumor types of interest include NSCLC, melanoma, RCC, urothelial, gastric, squamous cell head and neck, HCC, MSI-H cancers, Merkel cell, cutaneous squamous cell, esophageal cancers, and cHL. See Appendix 3 for the PD-L1 expression requirement for specific tumor types.

4.1.2. Subject Replacement

A subject who is withdrawn from the study before the completion of the first 21 days for a reason other than a DLT or who receives less than 16 of 21 doses of GS-4224 in the first 21 days will be replaced.

4.2. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study. Additional indication-specific inclusion criteria for 1000 mg BID Dose Escalation Cohort and Phase 2 are provided in Appendix 3.

1) Male or female ≥ 18 years of age

2) Dose Escalation Cohorts: Histologically or cytologically confirmed advanced malignant solid tumor that is refractory to or intolerant of all standard therapy or for which no standard therapy is available.

3) Dose Expansion and 1000 mg BID Dose Escalation Cohorts: Subjects must have available sufficient and adequate formalin-fixed tumor sample 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. For the 1000 mg BID dose escalation cohort, subjects with melanoma, Merkel cell, MSI-H cancers, and cHL are not required to have archival or fresh biopsy tissue.

CCI [redacted]

5) All persisting toxic effects of any prior antitumor therapy resolved to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 Grade ≤ 1 or baseline before the first dose of study drug (with the exception of alopecia [Grade 1 or 2 permitted] and neurotoxicity [Grade 1 or 2 permitted]).

6) Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 2

7) Life expectancy of ≥ 3 months, in the opinion of the investigator

8) Adequate organ function defined as follows:

   a) Hematologic: Platelets ≥ 100×10^9/L (≥ 60×10^9/L in subjects with HCC); Hemoglobin ≥ 9.0 g/dL; ANC ≥ 1.5×10^9/L (without blood transfusion, platelet transfusion, or growth factors within previous 7 days of the hematologic laboratory values obtained at screening visit)

   b) Hepatic: AST/ALT ≤ 2.5 × upper limit of normal (ULN) (if liver metastases are present, ≤ 5 × ULN); total or conjugated bilirubin ≤ 1.5 × ULN

   c) Renal: Creatinine clearance (CL_{cr}) ≥ 45 mL/min as calculated by the Cockcroft-Gault method

9) Coagulation: Subjects on full-dose oral anticoagulation, except warfarin, which is an excluded medication, must be on a stable dose (minimum duration 14 days). Subjects on low molecular weight heparin will be allowed.

10) Negative serum pregnancy test for female subjects

11) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception as described in Appendix 5.

12) Females who are nursing must agree to discontinue nursing before the first dose of GS-4224.

13) Able and willing to provide written informed consent to participate in the study

14) Patients with history of human immunodeficiency virus (HIV) infection should have a CD4+ T-cell count ≥ 350 cells/μL at screening.

15) Patients with serological evidence of chronic HBV should have HBV viral load below the limit of quantification at screening.

16) Patients with serological evidence of hepatitis C virus infection (HCV) should have completed curative antiviral treatment and have HCV viral load below the limit of quantification at screening.

4.3. Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study. Additional indication-specific exclusion criteria for 1000 mg BID Dose Escalation Cohort and Phase 2 are provided in Appendix 3.

1) History or evidence of clinically significant disorder, condition, or disease that, in the opinion of the investigator or medical monitor would pose a risk to subject safety or interfere with the study evaluations, procedures, or completion.

2) Dose Escalation Cohorts: History of ≥ Grade 3 AEs during prior treatment with an immune checkpoint inhibitor, or history of discontinuation of treatment with an immune checkpoint inhibitor due to AEs.

3) Dose Escalation 1000 mg BID and Dose Expansion Cohorts: Prior treatment with an immune checkpoint inhibitor (anti-PD-1, anti-PD-L1, or anti-PD-L2 antibodies).

4) History of autoimmune disease (for example, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis).

5) Positive serum pregnancy test (Appendix 5)

6) Patient has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are clinically stable for at least 4 weeks prior to study entry, have no evidence of new or enlarging brain metastases and if taking corticosteroids, are on stable or decreasing doses for at least 7 days from first dose of study drug.

7) Uncontrolled intercurrent illness including, but not limited to, active uncontrolled infection, active or chronic bleeding event within 28 days prior to first dose of study drug, or psychiatric illness/social situation that would limit compliance with study requirements as judged by treating physician.

8) Myocardial infarction, symptomatic congestive heart failure (New York Heart Association Classification > Class II), unstable angina, or serious uncontrolled cardiac arrhythmia within the last 6 months of first dose of study drug.

9) Major surgery, defined as any surgical procedure that involves general anesthesia and a significant incision (ie, larger than what is required for placement of central venous access, percutaneous feeding tube, or biopsy) within 28 days of the first dose of study drug.

10) Impairment of GI function or GI disease that may significantly alter the absorption of GS-4224, including any unresolved nausea, vomiting, or diarrhea that is Common Terminology Criteria for Adverse Events (CTCAE) Grade > 1.

11) Symptomatic ascites or pleural effusion. A patient who is clinically stable following treatment for these conditions (including thora- or para-centesis) is eligible.

12) Minor surgical procedure(s) within 7 days of enrollment, or not yet recovered from prior surgery (placement of central venous access device, fine needle aspiration, or endoscopic biliary stent ≥ 1 day before enrollment is acceptable).

13) Prior systemic radiation therapy completed within 4 weeks of the first dose of study drug, prior local radiation therapy completed within 2 weeks of Cycle 1 Day 1 (C1D1), or radiopharmaceuticals (strontium, samarium) within 8 weeks of C1D1.

14) Antitumor therapy (chemotherapy, antibody therapy, molecular targeted therapy) within 21 days or 5 half-lives, whichever is longer, of study drug dosing (6 weeks for nitrosoureas, mitomycin C, or molecular agents with $t_{1/2}$ > 10 days); concurrent use of hormone therapy for prostate cancer is permitted.

15) History of long QT syndrome or additional risk factors for Torsades de Pointes or whose corrected QT interval (QTc) measured (Fridericia method) at screening is prolonged (> 480 ms).

16) Use of concomitant medications that prolong QT/QTc interval at screening

17) Clinically significant bleeding within 28 days of the first dose of study drug

18) Known hypersensitivity to study drug, the metabolites, or formulation excipients

19) Use of any prohibited concomitant medications as described in Section 5.5 and any investigational agent within 2 weeks of study treatment initiation

20) Breastfeeding female

21) Received live virus vaccination within 30 days of first dose of study treatment. Seasonal flu vaccines that do not contain live virus are permitted.

22) History of hematologic stem cell transplant or solid organ transplant

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding and Treatment Codes

An IXRS will be employed to manage the conduct of the study. In Phase 1b and/or Phase 2, the IXRS will be used to maintain a central log documenting enrollment, to manage dose modifications, to assess current inventories of study drug, to initiate any necessary resupply of study drug, and to document discontinuation of study drug and study participation.

This is an open-label study in both the dose escalation (Phase 1b) and the dose expansion (Phase 2) portions of the study.

5.2. Description and Handling of GS-4224

5.2.1. Formulation

GS-4224 tablets are prepared using GS-4224-03 (bis-fumarate salt). Orange, film-coated tablets are available at a strength of 100 mg (free base equivalent) and are supplied as orange, capsule-shaped, plain-faced, film-coated tablets. In addition to the active ingredient, each orange, film-coated tablet contains the following inactive ingredients: mannitol, microcrystalline cellulose, crospovidone, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide yellow, iron oxide red, and ferrosoferric oxide.

Green, film-coated tablets are also prepared using GS-4224-03 (bis-fumarate salt) and are available in strengths of 100 mg, 200 mg, and 500 mg (free base equivalent). The 100-mg-strength tablets are supplied as green, round, film-coated tablets that are debossed with "GSI" on one side of the tablet and "100" on the other side of the tablet. The 200-mg-strength tablets are supplied as green, round, film-coated tablets that are debossed with "GSI" on one side of the tablet and "200" on the other side of the tablet. The 500-mg-strength tablets are supplied as green, capsule-shaped, film-coated tablets that are debossed with "GSI" on one side of the tablet and "500" on the other side of the tablet. In addition to the active ingredient, each green, film-coated tablet contains the following inactive ingredients: microcrystalline cellulose, crospovidone, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide yellow, and ferrosoferric oxide.

5.2.2. Packaging and Labeling

GS-4224 tablets are packaged in white, high density polyethylene bottles. Each bottle contains 30 tablets, silica gel desiccant, and polyester packing material. Each bottle is capped with a child-resistant polypropylene screw cap fitted with an induction sealed, aluminum-faced liner.

Study drug(s) to be distributed to centers in participating countries shall be labeled to meet applicable requirements of the FDA, European Union (EU) Guideline to Good Manufacturing Practice - Annex 13 (IMP), and/or other local regulations.

5.2.3. Storage and Handling

GS-4224 tablets should be stored refrigerated (2-8°C). Storage conditions are specified on the label. Keep bottles tightly closed to protect from moisture and allow them to warm to room temperature prior to opening. When a 100-mg bottle is removed from storage for dosing, keep tightly closed when not in use and store below 30°C for up to 4 weeks (28 days). The 200-mg and 500-mg tablets may be stored below 30°C for up to 12 weeks (84 days). Until dispensed to the subjects, all study drug bottles should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability and proper identification, the drug products should be stored in the containers in which they were supplied.

5.3. Dosage and Administration of GS-4224

The GS-4224 study drug will be supplied as tablets in strengths of 100 mg, 200 mg, and/or 500 mg. GS-4224 will be taken once daily in the morning (400 1500 mg QD cohorts) and 1000 mg twice daily separated by approximately 12 hours (1000 mg BID cohort).

On days with intensive PK (Cycle 1 Days 1 and 15), study drug will be administered at the same time every morning with approximately 240 mL of water and following an overnight fast (no food or drinks, except water, for at least 8 hours). For study treatments including those of more than 5 tablets, up to an additional 120 mL of water can be administered, if necessary. Water will be withheld starting 1 hour before and for 2 hours after dose administration, except for water given with the study drug. Water may be consumed by subjects following the 2-hour blood draw for the remainder of the collection period. A meal (standardized lunch) will be provided to subjects after the 4 hour postdose blood draw. All other fluids will be allowed after the 4 hour postdose blood draw.

For all days that study drug is administered where no intensive PK assessments are required, GS-4224 should be administered without regard to food at approximately the same time every morning. Subjects should administer study drug with a full glass of water.

If vomiting occurs after administration of study drug, the dose should not be repeated.

5.4. Dose Modifications and Treatment Interruption of GS-4224

5.4.1. Dose Modifications

For Dose Escalation 400 1500 mg QD cohorts, after completing 4 cycles of treatment and C5D1 scans, subjects receiving GS-4224 at a dose level below that which has been deemed to be safe by the SRT may, at the investigator's discretion, receive GS-4224 at the highest dose deemed to be safe by the SRT. CCI

5.4.2. Treatment Interruption for GS-4224

The following qualifying AEs must lead to interruption of GS-4224 administration, unless there is another obvious attribution (eg, trauma, PD):

- Dose interruption should occur for Grade ≥ 3 serum creatinine (more than 3× baseline) toxicity;
- Dose interruption should occur in subjects with any Grade 3 or Grade 4 elevation in AST or ALT associated with a Grade 2 elevation in bilirubin;
- Any Grade ≥ 3 non-skin, drug-related AE with the following exceptions:

  Do not interrupt treatment for Grade ≥ 3 fatigue
- Any Grade ≥ 3 drug-related laboratory abnormality with the following exceptions for lymphopenia:

  Grade 3 lymphopenia does not require a dose interruption
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants interrupting the dose of study drug

Subjects receiving GS-4224 who have drug-related toxicities that meet the criteria for dose interruption should have GS-4224 interrupted until criteria to resume treatment are met.

Note: GS-4224 should be discontinued in subjects who experience any Grade ≥ 3 skin drug-related AE with systemic signs or symptoms or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN).

5.4.3. Management of Immune-Related Adverse Events

Immuno-oncology agents such as GS-4224 are associated with irAEs. 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: GI, pulmonary, dermatological, renal, hepatic, neurological, and endocrine, among others.

AEs (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.

5.4.4. Dermatological irAEs

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

Table 5-1. 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-4224 therapy per protocol.	**If persists > 1 to 2 weeks or recurs**: Consider skin biopsy. Delay GS-4224 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-4224 therapy per protocol. **If worsens**: Treat as Grade 3-4.
Grade 3-4 Covering > 30% body surface area; life-threatening consequences	Interrupt or discontinue GS-4224 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-4224 therapy per protocol.

CTCAE Common Terminology Criteria for Adverse Events; irAE immune related adverse event; IV intravenous(ly)

5.4.5. Gastrointestinal (GI) irAEs

Rule out non-inflammatory causes. If 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 5-2. Gastrointestinal (GI) irAE Management Algorithm

Gastrointestinal (GI) irAEs		
CTCAE Grade of Diarrhea/Colitis	**Management**	**Follow Up**
Grade 1 Diarrhea: < 4 stools/day over baseline. Colitis: asymptomatic.	Continue GS-4224 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.	Interrupt GS-4224 therapy per protocol. Symptomatic treatment.	**If improves to Grade 1**: Resume GS-4224 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-4224 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-4224 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(ly)

5.4.6. Pulmonary irAEs

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

Table 5-3. Pulmonary irAE Management Algorithm

Pulmonary irAEs		
CTCAE Grade of Pneumonitis	**Management**	**Follow Up**
Grade 1 Radiographic changes only.	Consider interruption of GS-4224 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	Interrupt GS-4224 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-4224 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-4224 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 h 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(ly)

5.4.7. Hepatic irAEs

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

Table 5-4. 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-4224 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	Interrupt GS-4224 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, discontinue GS-4224 therapy per protocol.	**If returns to baseline**: Resume routine monitoring; resume GS-4224 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-4224 therapy per protocol.
Grade 3-4 AST or ALT > 5 × ULN and/or total bilirubin > 3 × ULN.	Discontinue GS-4224 therapy per protocol Increase frequency of monitoring to every 1-2 days 1-2 mg/kg/day methylprednisolone IV or oral equivalent.* 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.

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

5.4.8. Endocrine irAEs

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

Table 5-5. Endocrine irAE Management Algorithm

Endocrine irAEs		
Endocrine Disorder	**Management**	**Follow Up**
Asymptomatic TSH abnormality	Continue GS-4224 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**: Interrupt GS-4224 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-4224 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)	Interrupt or discontinue GS-4224 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(ly); LLN lower limit of normal; MRI magnetic resonance imaging; TSH thyroid stimulating hormone; ULN upper limit of normal

5.4.9. Renal irAEs

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

Table 5-6. 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-4224 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	Interrupt GS-4224 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-4224 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-4224 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(ly); ULN upper limit of normal

5.4.10. Neurological irAEs

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

Table 5-7. 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-4224 therapy per protocol	Continue to monitor subject **If worsens**: Treat as Grade 2 or Grade 3-4
Grade 2 Moderate symptoms; limiting instrumental ADL.	Interrupt GS-4224 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-4224 therapy per protocol **If worsens**: Treat as Grade 3-4
Grade 3-4 Severe symptoms; limiting self-care ADL; life-threatening	Discontinue GS-4224 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(ly)

5.5. Prior and Concomitant Medications

5.5.1. Concomitant Medications

As of 30 March 2020, limited clinical drug-drug-interaction studies have been conducted with GS-4224.

In vitro data suggest that GS-4224 is a potential inhibitor of P-glycoprotein (P-gp), cytochrome P450 enzyme (CYP)2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A, uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) and organic anion transporting polypeptide (OATP)1B1/3. In the absence of clinical data, administration of sensitive substrates of, or narrow therapeutic index drugs that are metabolized or transported by, these enzymes and transporters is not permitted from 14 days prior to the first dose of GS-4224, during the study period, and through the end of the follow-up visit, unless new data becomes available that would allow concomitant use of drugs described above during the study. Furthermore, in vitro data suggest that GS-4224 may be eliminated by metabolism with contribution by CYP3A and Sulfotransferase Family 2A Member 1 (SULT2A1), and may be a substrate of P-gp and breast cancer resistance protein (BCRP) transporters. In the absence of clinical data, administration of strong or moderate inhibitors or inducers of these enzymes and transporters is not permitted from 14 days prior to the first dose of GS-4224, during the study period, and through the end of the follow-up visit.

Examples of medications which are prohibited 14 days prior to the first dose of study drug, during the study period and through the end of the follow-up visit are listed in Table 5-8. Administration of the listed medications may be permitted only if the study investigator deems it necessary for the treatment of a condition that emerges during the course of the study and with the approval of the medical monitor.

Preliminary data from a study that evaluated the effect of famotidine on the plasma exposures of GS-4224 indicated no clinically meaningful effect of acid-reducing agents on the PK of GS-4224. Based on these results, subjects can be allowed to concomitantly administer acid-reducing agents. It is recommended that subjects do not exceed the standard doses of the acid-reducing agents that are substrates for enzymes that are potentially inhibited by GS-4224 (eg, rabeprazole 20 mg once daily, lansoprazole 30 mg once daily, omeprazole 40 mg once daily, etc.).

Any medications not on the list should be reviewed with the sponsor prior to and during the study treatment period with GS-4224.

Subjects who are currently taking other prescription or non-prescription medications may still be entered into the study if, in the judgment of the sponsor and the investigator, the medication will not interfere with the study procedures or compromise subject safety and/or PK assessments. In instances where an excluded medication is initiated prior to discussion with the sponsor, the investigator must notify Gilead as soon as he/she is aware of the use of the excluded medication. Vitamins, ibuprofen, acetaminophen (preferred over ibuprofen if both are applicable), and hormonal contraceptive medications are allowed during the study period.

Table 5-8. List of Agents Disallowed with GS-4224

Drug Class	Agents Disallowed
Antibiotics	Ciprofloxacin, Clarithromycin, Erythromycin
Anticonvulsants	Carbamazepine, Oxcarbazepine, Phenobarbital, Phenytoin
Antidiabetics	Glimepiride, Glyburide, Repaglinide
Antidepressants	Fluoxetine, Fluvoxamine, Nefazodone
Antifungals	Fluconazole, Itraconazole, Ketoconazole, Posaconazole, Voriconazole
Antimycobacterials	Rifamycins
Antipsychotic	Lurasidone, Pimozide, Quetiapine
Anxiolytics	Buspirone, Diazepam, Triazolam
Cardiac Medications	Amiodarone, Bosentan, Dabigatran Etexilate, Digoxin, Diltiazem, Dronedarone, Eplerenone, Felodipine, Nisoldipine, Propafenone, Quinidine, Ranolazine, Rivaroxaban, Telmisartan, Tolbutamide, Verapamil, Warfarin
Diuretics	Conivaptan
GI Motility Agents	Cisapride
Herbal/Natural Supplements	Chinese herb sho saiko to (or Xiao Shai Hu Tang), Echinaccea. Milk thistle (ie, silymarin), St. John's Wort
Other	Aprepitant, Celecoxib, Colchicine, Cyclosporine, Fexofenadine, HMG CoA Reductase Inhibitors ("Statins"), Modafanil, Sildenafil, Tacrolimus, Tadalafil

GI gastrointestinal; HMG CoA 3 hydroxy 3 methylglutaryl coenzyme A

The potential for GS-4224 to prolong the QT interval has not been evaluated. In the absence of clinical data, administration of any drug that is known to demonstrate QT prolongation should not be permitted from 14 days prior to the first dose of GS-4224, during the study period and through the end of the follow-up visit. Administration of a drug that is known to demonstrate QT prolongation may be permitted only if the study investigator deems it necessary for the treatment of a condition that emerges during the course of the study and with the approval of the medical monitor.

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 include all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. All concomitant medications received within 30 days before the first dose of study treatment through the 30 day follow-up visit should be recorded on the electronic case report form (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 v1.1 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.

5.5.2. 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.

- 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 (Polyethylene Glycol-Coated) G-CSF, or Granulocyte Macrophage Colony-Stimulating Factor (GM CSF) is not allowed in this study. Therapeutic use of G-CSF is allowed in subjects with Grade 3-4 febrile neutropenia. Consider a potential immunologic etiology.

- Thrombocytopenia: Transfusion of platelets may be used if clinically indicated. Immune thrombocytopenia purpura (ITP) 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 Sections 5.4.3 to 5.4.10 for management algorithms guidance).

5.5.3. Prohibited and/or Restricted Treatments

Pre-medications should not be administered routinely prior to dosing of study drugs.

Subjects are prohibited from receiving the following therapies and treatments during the study:

- Immunotherapy not specified in this protocol

- Chemotherapy

- Investigational agents other than GS-4224

- Corticosteroids for any purpose other than to modulate symptoms from an irAE, or for use as a premedication in subjects with a known history of hypersensitivity reactions (ie, IV contrast for imaging)

  Note: Systemic corticosteroid dose of prednisone 10 mg daily or equivalent is permitted while on study

  Note: Use of intraocular, intranasal, inhaled, or topical corticosteroid is permitted

- Bisphosphonates and/or receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor therapies should be initiated if indicated before informed consent has been signed. These therapies may be continued if treatment with an agent from one of these 2 classes was initiated **prior** to signing informed consent.

- Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study.

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

5.5.4. Other Restrictions and Precautions

The following nondrug 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.

5.6. Accountability

The investigator is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study drug (quantity and condition). All used and unused study drug dispensed to subjects must be returned to the site.

Each study site must keep accountability records for GS-4224 that capture:

- The date received and quantity of study drug kits
- The date, subject number, and the study drug kit number dispensed
- The date, quantity of used and unused study drug kit returned, along with the initials of the person recording the information.

5.7. Investigational Medicinal Product (IMP) Return or Disposal

Gilead recommends that used and unused study drug supplies be returned to the shipping facility from which it came for eventual destruction. The study monitor will provide instructions for return. If return is not possible, the study monitor will evaluate each study center's study drug disposal procedures and provide appropriate instruction for destruction of unused stud drug supplies. If the investigator 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 trial master file.

If study drug is destroyed on site, the investigator must maintain accurate records for all study drug destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drug. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be returned to Gilead.

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

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 protocol procedures and notify the sponsor or contract research organization (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. It is the responsibility of the investigator to ensure that subjects are eligible to participate in the study prior to enrollment and continue to remain eligible throughout the study.

6.2. Pretreatment Assessments

6.2.1. Screening Visit

Subjects will be screened within 28 days prior to the first dose of study drug to determine eligibility for participation in the study. The following will be performed and documented at screening:

Within 28 days prior to the first dose of study drug:

- Obtain written informed consent
- Obtain medical and medication history
- Complete physical examination including vital signs, body weight, and height
- Obtain blood samples for serum pregnancy and biomarkers
- Perform 12-lead electrocardiogram (ECG)
- Perform computed tomography (CT) scan with contrast or magnetic resonance imaging (MRI). For subjects with cHL, positron emission tomography-computed tomography (PET-CT) will also be performed. Baseline scans within 6 weeks of Cycle 1 Day 1 are acceptable.
- Assess ECOG performance status
- For the 1000 mg BID dose escalation cohort, CCI [redacted] the Phase 2 Dose Expansion cohort, determine level of tumor PD-L1
- For the Phase 2 Dose Expansion cohort, collect archival tumor sample or, alternatively, consent for an additional pretreatment tumor biopsy.

Within 10 days prior to the first dose of study drug:

- Obtain blood sample for chemistry and hematology

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 28 days after screening into the study.

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

After a subject signs an informed consent form (ICF), 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. Subjects who do not meet any of the inclusion criteria or meet any of the exclusion criteria will be considered screen fails, and their demographic information and reason for screen failure should be documented.

Screening procedures are to be completed within the windows detailed below and prior to the first dose of study treatment:

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 study drug, 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.

Subjects' 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. PD-L1 expression may be performed using a central or local laboratory.

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 reconsented with a new screening number and the screening assessments must be repeated, as applicable. For subjects that are re-screened within 28 days, assessments with results that would exclude the subject will need to be repeated except for CT/MRI and/or PET-CT scans performed within 6 weeks of C1D1 and screening biomarker samples.

6.2.3. Baseline Assessments and Medical History

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 papilloma virus; and any condition diagnosed within the prior 10 years that is considered to be 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 version 5.0. 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 (TNM) 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 disease status
- Relevant somatic or germ line mutations detected
- Chronic viral infection, status if available
- Tumor markers if indicated

6.2.4. Physical Examination Including Height and Weight

The investigator or qualified designee will perform a complete physical exam during the screening period and at the EOT visit as per Schedule of Assessments and Procedures (Appendix 2). Beginning on C1D1, a modified physical exam will be performed to monitor for any changes (eg, lymph nodes, lung, cardiac, abdomen, skin, neurologic, and any systems, as clinically indicated).

For cycles that do not require a full physical exam per the Schedule of Assessments and Procedures (Appendix 2), the investigator or qualified designee will perform a modified physical exam as clinically indicated prior to study treatment administration.

Weight without shoes should be measured at each exam.

Height without shoes should be measured at screening only.

Clinically significant abnormal findings prior to the first dose of study drug should be recorded as medical history. After consent, new clinically significant abnormal findings should be recorded as AEs.

6.2.5. Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of study treatment, and at the EOT visit as specified in the table of assessments in 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.

6.2.6. Eastern Cooperative Oncology Group Performance (ECOG)

ECOG performance status is an investigator assessment of the impact of the disease on the subject's activities of daily living. ECOG assessments will be performed at the time points listed in the Study Procedures Table (Appendix 2).

6.2.7. Electrocardiogram

A standard 12-lead ECG will be performed using local standard procedures at screening and at subsequent visits as specified in Appendix 2. Clinically significant abnormal findings at screening should be recorded as medical history.

Subjects should rest quietly in the supine position for a minimum of 10 minutes prior to each scheduled ECG acquisition and should remain in that position until the recording is complete.

Where time points for ECG collection correspond to blood collection time points, ECGs should be acquired prior to blood collection.

There should be no environmental distractions (eg, TV, radio, conversation, etc.) while the subjects are resting prior to and during the recordings. Electrocardiograms will be recorded using the site's standard 12-lead ECG equipment. All ECGs will be obtained using instruments that analyze data using the same algorithms and produce the same data for interpretation. Electrode placement will be performed according to the method of Wilson, Goldberger, and Einthoven with a check to confirm that the augmented Vector Right (aVR) lead is not inverted.

The investigator or other qualified individuals at the study center will review ECGs to assess for changes in ECG intervals and morphology as compared to pretreatment ECGs.

6.2.8. Prior and Concomitant Medications

Prior medication taken by the subject within 30 days before starting the study 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 Visit 1. 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 safety follow-up visit should be recorded. After the 30-day safety follow-up visit, all medications related to reportable SAEs will be recorded as defined in Section 7.

6.2.9. Clinical Laboratory Assessments

The central laboratory will be responsible for chemistry, hematology, coagulation, urinalysis, and serum pregnancy testing (per 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 lab 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 (Table 6-1) 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 h 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] GGT Glucose LDH Lipase Cholesterol Triglycerides Amylase Magnesium Phosphorus/phosphates Potassium Sodium Total bilirubin[b] Direct bilirubin Total protein	Color and appearance Specific gravity pH Occult blood Protein Glucose Bilirubin Leukocyte esterase Nitrite Urobilinogen Ketones Microscopic[b]	WBC and differential count Hemoglobin Hematocrit Platelet count ANC MCH MCHC MCV RBC <u>Differential</u> Eosinophils Lymphocytes Monocytes Neutrophils **Coagulation** Prothrombin time (INR) aPTT	Serum β−hCG or urine pregnancy test[c] Endocrine Function Tests TSH and freeT4[d] Basal cortisol HIV, HBsAg, and HCV antibody viral testing in subjects with current or prior history of HIV, HBV, and HCV infection, respectively.[b] CD4+ count will also be performed in subjects with current or prior history of HIV.

β hCG beta human chorionic gonadotropin; ALT alanine aminotransferase; ANC absolute neutrophil count; aPTT activated partial thromboplastin time; AST aspartate aminotransferase; BUN blood urea nitrogen; CD4+ cluster determinant 4 positive; Free T4 free thyroxine; GGT gamma glutamyltransferase; HBsAg hepatitis B surface antigen; HBV hepatitis B virus; HCV hepatitis C virus; HIV human immunodeficiency virus; INR international normalized ratio; LDH lactate dehydrogenase; MCH mean corpuscular hemoglobin; MCHC mean corpuscular hemoglobin concentration; MCV mean corpuscular volume; RBC red blood cell; 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 h 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 performed 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. Treatment Assessments

Subject should continue to receive all assessments as defined in the Treatment Phase (C1D1 until EOT) of the Schedule of Assessments (Appendix 2) while they are actively receiving study treatment.

6.4. 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 on the eCRFs.

6.5. Pharmacokinetic, Pharmacodynamic, Genetic, and Other Assessments

6.5.1. Pharmacokinetic Assessments

Intensive PK will be collected in all subjects in Phase 1b dose cohorts between 400 mg and 1500 mg QD. In the 1000 mg BID dose escalation cohort, intensive PK will be collected at select sites and in at least 6 subjects. Intensive PK samples will be collected predose on Cycle 1 Days 1 and 15, followed by 0.5, 1, 1.5, 2.5, 4, 6, 12 (1000 mg BID dose cohort) and 0.5, 1, 1.5, 2.5, 4, 6 and 24 (400-1500 mg QD dose cohorts) hours postdose relative to the AM dose. For the 1000 mg BID cohort, the 12 hours postdose samples will be collected prior to the PM dose. Every effort should be made to collect intensive PK samples at the indicated time; actual sample collection time should be recorded.

Predose PK samples will be collected on the indicated days as described in the Study Procedures Table (Appendix 2) in all subjects in Phase 1b who also have intensive PK collection (all subjects in dose cohorts between 400 mg and 1500 mg QD and at least 6 subjects in 1000 mg BID dose cohort).

CCI [redacted]

CCI [redacted]

Postdose PK samples for the Sparse PK collection will be collected between 30 minutes and 4 hours after the clinic dose on Day 1 and Day 8.

6.5.1.1. Pharmacokinetic Parameters

GS-4224 plasma concentrations will be determined by a validated method. The PK parameters to be estimated and reported may include, but may not be limited to, time of last observable plasma concentration (T_{last}), maximum observed drug concentration at steady-state (C_{max}), observed concentration at the end of the dosing interval at steady-state (C_{trough}), area under the concentration-time curve from time zero to last time point with measurable concentration (AUC_{last}), area under the concentration-time curve from time zero to the end of the dosing interval (AUC_{tau}), time to maximum observed concentration (T_{max}), terminal disposition rate constant (λz), terminal elimination half-life ($t_{1/2}$), systemic clearance after oral administration (CL/F), and volume of distribution after oral administration (V/F), etc. Noncompartmental (NCA) techniques will be used to analyze the PK. Compartmental modeling (eg, population pharmacokinetics [PopPK]) analysis may be conducted.

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

CCI [redacted]

6.5.2.2. Phase 2 Dose Expansion Biopsies:

For the Dose Expansion Cohort B1, subjects must have available sufficient and adequate formalin-fixed tumor tissue sample 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.

CCI [redacted]

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

6.6. Disease Assessments

6.6.1. CT with Contrast or MRI Scan

Subjects will be assessed by CT scan with contrast (or MRI, if unable to tolerate CT contrast) of the chest, abdomen, and pelvis to document metastatic disease, identify target lesions, and to assess response as per RECIST v1.1 (refer to Appendix 6) for solid tumors and per Lugano 2014 response criteria (refer to Appendix 7) for cHL. The same assessment methods should be used for the subject throughout all treatment cycles. CT or MRI scans will be obtained at the applicable study visits per the Study Procedures Table (Appendix 2) and transferred to a central vendor for storage.

In subjects who cannot tolerate iodinated contrast, a CT of the lung without contrast and MRI of the abdomen, pelvis, and cervical region should be performed. Imaging by CT scan (with contrast) or MRI or applicable scan will be performed at screening (or within 6 weeks before C1D1 if the scan was performed as part of standard medical practice) and then every 6 weeks after C1D1 for the first 2 scans and then every 9 weeks during the treatment period regardless of cycle number or dose interruption. During the treatment, scans may be performed at time points other than specified in the protocol, as clinically indicated, to assess tumor progression.

Note on PET-CT scans in subjects with cHL: Low dose or attenuation correction CT portions of a combined PET-CT are of limited use in anatomically based efficacy assessments and should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically based measurements. However, if a site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with contrast) then the CT portion of the PET-CT can be used for measurements.

6.6.2. PET-CT

As cHL is a fluorodeoxyglucose (18F) (FDG)-avid lymphoma, PET-CT is recommended to assess disease at baseline and postbaseline, using the Deauville 5-point scale (5-PS) with subassessments to describe the FDG-avidity of disease.

For subjects with cHL, in addition to CT or MRI scan, a baseline PET-CT is required at screening (or within 6 weeks before C1D1 if the scan was performed as part of standard medical practice), Cycle 3 Day 1, and Cycle 5 Day 1.

PET-CT will be used in lieu of a bone marrow biopsy/aspirate to assess bone marrow involvement. Per Lugano 2014 criteria, PET-CT is required to confirm radiographic CR in subjects with bone marrow involvement at screening. Thus, in subjects with bone marrow involvement at screening and at a time point where CR is suspected, PET-CT will be required to confirm CR if CR was not achieved at Cycle 3 and/or 5.

6.6.3. Response Assessment

For subjects with solid tumors, RECIST v1.1 {Eisenhauer 2009} [Appendix 6] will be used for assessment of tumor responses for the purposes of study evaluation, managing subjects on protocol treatment, and decision making for discontinuation of study therapy due to disease progression, with some modifications to account for atypical responses which may occur with immune-based therapies {Swaika 2015}. Given that anti-PD-1 agents produce antitumor effects by potentiating endogenous cancer-specific immune responses, the response patterns seen with these agents may extend beyond the typical time course of responses seen with cytotoxic agents. In addition, anti-PD-1 therapies can occasionally manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions (“tumor flare” or “pseudoprogression”) {Topalian 2014}. In these cases, standard RECIST may not provide an accurate response assessment of anti-PD-1 agents. Therefore, RECIST v1.1 will be used (see Appendix 6) with the following adaptations:

- If imaging shows a CR or PR, tumor imaging should be repeated at least 4 weeks (≥ 4 weeks) later to confirm response, per RECIST v1.1 guidelines. Subjects will then return to regular scheduled imaging starting with the next protocol-specified imaging time point. Subjects who obtain a confirmatory scan do not need to undergo scheduled imaging assessment ≤ 2 weeks later (eg, if a subject obtains a scan at Week 22 to confirm a Week 16 response, they will not also be required to complete the scheduled Week 24 scan).

- If imaging shows PD, it is at the discretion of the investigator to keep the subject on study treatment or to stop study treatment until imaging is repeated ≥ 4 weeks later in order to confirm PD (adapted from the immune-related response criteria recommendations) {Wolchok 2009}. Subjects that are deemed clinically unstable or who have biopsy-proven new metastatic lesions are not required to have repeat imaging for confirmation. The decision to continue a subject on study while awaiting PD confirmation will be based on clinical judgment of a patient's overall clinical condition, including performance status, clinical symptoms, and laboratory data.

- Subjects should not present clinical symptoms or signs indicating clinically significant disease progression; no decline in performance status; absence of rapid disease progression or threat to vital organs or critical anatomical sites (eg, CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention; no significant, unacceptable or irreversible toxicities related to study treatment.

For subjects with cHL, Lugano 2014 response criteria should be used {Cheson 2014} [Appendix 7].

For additional details and instructions regarding imaging requirements, refer to the study imaging manual.

6.7. End of Study

End of study will be defined when the last subject reaches the last scheduled follow-up time point, is lost to follow up, withdraws from the study, dies, or the time at which the sponsor closes the study.

6.8. Posttreatment Assessments

6.8.1. End of Treatment Visits

The EOT visit requirements are outlined in Appendix 2. There is an EOT visit 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 EOT visit should occur at the time the last dose of study drug is discontinued for any reason. If the EOT visit occurs 30 days (±7 days) from the last dose of study treatment, at the time of the mandatory 30-day safety follow-up visit, procedures do not need to be repeated. Procedures at the time of discontinuation are detailed in Appendix 2. Subjects that discontinue from the study treatment for reasons other than PD will continue to have imaging/CT scans at the predefined schedule until documented PD or initiation of a new treatment (refer to Section 6.6).

6.8.1.2. 30-Day Safety 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 treatment, whichever comes first. Subjects who miss the 30-day safety follow-up visit will be contacted by phone 30 days (± 7 days) after the last dose of study treatment to assess AEs.

6.9. Assessments for Premature Discontinuation from Study

If a subject discontinues study dosing (eg, 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, 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

Treatment with GS-4224 should be discontinued if any of the following occur:

- 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 sponsor.
- Disease progression, defined by RECIST v1.1 or Lugano 2014 response criteria for cHL as defined in Section 6.6, unless the subject is considered to derive clinical benefit from the treatment by the investigator, is clinically stable, and there is agreement with the sponsor.
- Occurrence of any condition that fulfills criteria for permanent treatment discontinuation, as defined in Section 3.5
- Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest
- Pregnancy during the study; refer to Appendix 5
- Use of a non-permitted concomitant and/or prohibited medication, as defined in Sections 5.5.1 and 5.5.3, in which the predefined consequence is withdrawal from study drug (sponsor may be contacted to discuss whether study drug must be discontinued).
- Subject Noncompliance
- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree.
- Subject request to discontinue for any reason

6.10.2. Discontinuation from Disease Response Evaluation

Subjects should be discontinued from tumor evaluation in the event of progression of disease (compared to baseline assessment) or confirmed disease progression, defined as progression confirmed by a second, consecutive assessment ≥ 4 weeks apart, in a clinically stable subject as defined in Section 6.6 with the option for continuing treatment while awaiting radiographic confirmation of progression where feasible.

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
- Study terminated by sponsor
- Adverse event
- PD
- Investigator's discretion

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 a study drug, 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 a study drug, whether or not considered related to the study drug. AEs may also include pre- or posttreatment complications that occur as a result of protocol-specified procedures or special situations (Section 7.1.3).

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 adverse event 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 (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.1.3)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the ICF is signed and not related to a protocol-associated procedure is not an AE, but rather considered to be preexisting and should be documented on the medical history CRF.

Preexisting events that increase in severity or change in nature after study drug initiation or during or as a consequence of participation in the clinical study will also be considered AEs.

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], the death can be reported as an SAE.)

- A life-threatening situation (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 Serious Adverse Event Definitions

Protocol-specific SAE reporting exemptions:

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 due to underlying disease
- Death from disease progression due to underlying disease

Disease progression and death from disease progression should be reported as SAEs by the investigator only if it is assessed that the study drugs caused or contributed to the disease.

7.1.3. Study Drugs and Gilead Concomitant Therapy Special Situations Reports

Special situation reports (SSRs) include all reports of medication error, abuse, misuse, overdose, occupational exposure, drug interactions, exposure via breastfeeding, unexpected benefit, transmission of infectious agents via the product, counterfeit of falsified medicine, and pregnancy regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, preparation for administration or administration of a study drug while the medication is in the control of a health care professional, patient, or consumer. Medication errors may be classified as a medication error without an AE, which includes situations of missed dose, medication error with an AE, intercepted medication error, or potential medication error.

Abuse is defined as persistent or sporadic intentional excessive use of a study drug by a subject.

Misuse is defined as any intentional and inappropriate use of a study drug 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 study drug given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labeling (as it applies to the daily dose of the subject in question). 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).

Occupational exposure is defined as exposure to a study drug as a result of one's professional or nonprofessional occupation.

Drug interaction is defined as any drug/drug, drug/food, or drug/device interaction.

Unexpected benefit is defined as an unintended therapeutic effect where the results are judged to be desirable and beneficial.

Transmission of infectious agents is defined as any suspected transmission of an infected agent through a Gilead study drug.

Counterfeit or falsified medicine: Any study drug with a false representation of (a) its identity, (b) its source, or (c) its history.

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 (eg, preexisting condition, underlying disease, intercurrent illness, concomitant medication).

- **Yes**: There is reasonable possibility that the AE 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 (eg, 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 (eg, venipuncture).

7.2.2. Assessment of Severity

The severity of AEs will be graded and recorded throughout the study and during the follow-up period according to NCI-CTCAE version 5.0. 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

Refer to Appendix 4 for more information.

7.3. Investigator Reporting Requirements and Instructions

7.3.1. Requirements for Collection Prior to Study Drug Initiation

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

7.3.2. Adverse Events

Following initiation of study drug, collect all AEs, regardless of cause or relationship, until 30 days after last administration of study drug and report them on the eCRFs as instructed.

All AEs should be followed 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.

7.3.3. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occur after the subject first consents to participate in the study (ie, signing the ICF) and throughout the duration of the study, including the 30-day safety follow-up visit, must be reported on the applicable eCRFs and Gilead GLPS as instructed below in this section. This also includes any SAEs resulting from protocol-associated procedures performed after the ICF is signed.

Any SAEs and deaths that occur within 30 days of the last dose of study drug, regardless of causality, should also be reported (See Section 7.1.2.1. for protocol-specified exceptions).

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 GLPS.

Instructions for reporting SAEs are described in Section 7.4.1.

7.3.4. Study Drug Special Situations Reports

All study drug SSRs that occur from study drug initiation and throughout the duration of the study, including the 30-day safety follow-up visit, must be reported to Gilead GLPS (Section 7.4.2.). Adverse events and SAEs resulting from SSRs must be reported in accordance to the AE and SAE reporting guidance (Section 7.3).

7.3.5. Concomitant Therapy Reports

7.3.5.1. Gilead Concomitant Therapy Special Situations Report

Special situation reports involving a Gilead concomitant therapy (not considered study drug), that occurs after the subject first consents to participate in the study (ie, signing the ICF) and throughout the duration of the study, including the posttreatment follow-up visit, must be reported to Gilead GLPS utilizing the paper SSR (Section 7.4.2.2).

7.3.5.2. Non-Gilead Concomitant Therapy Report

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.

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

7.4. Reporting Process for Serious Adverse Events and Special Situation Reports

7.4.1. Serious Adverse Event Reporting Process

For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be transmitted by email 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 eCRF and the SAE narrative section of the Safety Report Form eCRF.

7.4.1.1. Electronic Serious Adverse Event Reporting Process

- Site personnel will record all SAE data on the applicable eCRFs and from there transmit the SAE information to Gilead GLPS within 24 hours of the investigator's knowledge of the event from ICF signature throughout the duration of the study, including the protocol-required posttreatment follow-up period.

If it is not possible to record and transmit the SAE information electronically, record the SAE on the paper SAE reporting form and transmit within 24 hours:

Gilead GLPS
Email: PPD
or
Fax: PPD

If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary. If the database is not locked, any SAE reported via paper must be transcribed as soon as possible on the applicable eCRFs and transmitted to GLPS.

7.4.2. Special Situations Reporting Process

7.4.2.1. Paper Special Situations Reporting Process for Study Drug

- All SSRs will be recorded on the special situations report form and transmitted by emailing or faxing the report form within 24 hours of the investigator's knowledge of the event to the attention of Gilead GLPS from study drug initiation throughout the duration of the study, including the protocol-required posttreatment follow-up period.

Gilead GLPS
Email: PPD
or
Fax: PPD

7.4.2.2. Reporting Process for Gilead Concomitant Medications

Special situations that involve Gilead concomitant medications that are not considered study drug must be reported within 24 hours of the investigator's knowledge of the event to Gilead GLPS utilizing the paper special situations report form to:

Gilead GLPS
Email: PPD
or
Fax: PPD

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.

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

7.4.2.3. Pregnancy Reporting Process

The investigator should report pregnancies in female study subjects and/or female partners of male subjects that are identified after initiation of study drug and throughout the study, including the after study drug follow-up period, to Gilead GLPS using the pregnancy report form within 24 hours of becoming aware of the pregnancy. Contact details for transmitting the pregnancy report form are as follows:

Gilead GLPS
Email: PPD
or
Fax: PPD

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

All other premature terminations of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE, as described in Section 7.4.1. 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 7.4.1. Furthermore, any SAE occurring as an adverse pregnancy outcome after study must be reported to the Gilead GLPS.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome of the pregnancy/partner pregnancy should be reported to Gilead GLPS using the pregnancy outcome report form. If the end of the pregnancy/partner pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead GLPS. Gilead GLPS contact information is as follows: email: PPD and fax: PPD.

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

7.5. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA 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 which may be in the form of line-listings, serious adverse drug reactions (SADRs), 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 IB 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.

7.5.1. 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 (eg, 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 (eg, 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 (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

For specific information on handling of clinical laboratory abnormalities in this study, please refer to Section 7.6.

7.6. Toxicity Management

Severity should be recorded and graded according to NCI-CTCAE version 5.0 (Appendix 4).

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objectives of this study are as follows:

Phase 1b Dose Escalation

- Characterize the safety and tolerability of GS-4224 in subjects with advanced solid tumors
- Determine the MTD and RP2D of GS-4224 in subjects with advanced solid tumors

The secondary objectives of this study are as follows:

Phase 1b Dose Escalation

- Evaluate the PK of GS-4224 in subjects with advanced solid tumors

Phase 2 Dose Expansion

- Evaluate the safety and tolerability of GS-4224 in subjects with advanced solid tumors

CCI

[redacted]

8.1.2. Primary Endpoint

The primary endpoints of this study are as follows:

Phase 1b Dose Escalation

- Incidence of DLT as defined in Section 3.2.

8.1.3. Secondary Endpoint

The secondary endpoints are as follows:

Phase 1b Dose Escalation

- PK parameters (T_{last}, T_{max}, C_{max}, C_{trough}, AUC_{last}, AUC_{tau} and $t_{1/2}$, as applicable) for GS-4224 in subjects with advanced solid tumors

Phase 2 Dose Expansion

- Incidence of Grade ≥ 3 TEAEs in Cohort B1 subjects with advanced solid tumors
- Incidence of Grade ≥ 3 treatment-emergent laboratory abnormalities in Cohort B1 subjects with advanced solid tumors

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

8.2. Planned Analyses

8.2.1. Interim Analysis

8.2.1.1. Analyses for Dose Escalation Decisions

To support dose escalation decision, safety data, including DLTs and other AEs may be listed and summarized, if appropriate. Supportive data including demographic, disease history, concomitant medication, and drug administration may be listed. The analysis will occur when all subjects enrolled in a dose level have been followed for at least 21 days after the first dose of GS-4224 or two DLTs have been observed, whichever is earlier.

8.2.1.2. Analyses for Dose Expansion Decisions

To support dose expansion decision, available and relevant clinical data from all subjects treated in the escalation phase may be listed and summarized, if appropriate. The analysis will occur when all subjects enrolled in the last cohort of dose escalation phase have been followed for at least 21 days after the first dose of GS-4224 or two DLTs have been observed, whichever is earlier.

8.2.1.3. Primary Analysis

The study primary analysis will be conducted when all enrolled subjects have discontinued the study or have been on treatment of GS-4224 for at least 48 weeks and completed response assessment of Week 48.

Prior to the final analysis, interim analyses may be conducted, and the analyses may be submitted to regulatory agencies to seek guidance for the overall clinical development program.

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 analyses of subject characteristics.

8.3.1.2. Full Analysis Set

The Full Analysis Set (FAS) includes all subjects who took at least 1 dose of study treatment. It will be used in the analyses of efficacy endpoints.

8.3.1.3. Safety Analysis Set

The Safety Analysis Set includes all subjects who enrolled to the study and receive at least 1 dose of study treatment, with treatment assignments designated according to the actual treatment received. This analysis set will be used in the analyses of safety variables as well as study treatment administration.

8.3.1.4. DLT-Evaluable Analysis Set

The DLT-Evaluable Analysis Set includes all subjects in the Safety Analysis Set who enroll to the dose escalation cohorts (up to the first 6 subjects in the 1000 mg BID dose escalation cohort; CCI [redacted]), complete ≥ 75% of the prescribed study treatment and have safety assessments through the protocol-specified DLT assessment window (first 21 days of study dosing, inclusive) or have experienced a DLT prior to the completion of first 21 days of study dosing. Safety assessment relevant to the DLT-Evaluable Analysis Set definition will include laboratory serum chemistry tests and hematology tests as specified in the protocol. Determination of the MTD will be based on the DLT-Evaluable Analysis Set.

8.3.1.5. Pharmacokinetics (PK) Analysis Set

The PK Analysis Set includes subjects in the Safety Analysis Set who have received the study drug and have at least 1 sample with detectable drug concentration.

CCI [redacted]

[redacted]

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 analysis set), n (number with data), mean, standard deviation, 95% CIs on the mean, median, minimum, and maximum. Summary tables for categorical variables will include: N, n, percentage, and 95% CIs on the percentage. Unless otherwise indicated, 95% 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 cohort, analysis set, and time point.

The baseline value will be the last (most recent) pretreatment value before or on the first dosing date of study drug. As appropriate, changes from baseline to each subsequent time point will be described and summarized. Graphical techniques (eg, waterfall plots, Kaplan-Meier [KM] curves, line plots) may be used when such methods are appropriate and informative. 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 Data and Baseline Characteristics

Demographic and baseline measurements will be summarized by cohort, indication, and treatment using standard descriptive methods.

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

Baseline data will include summaries of body weight, height, ECOG performance status score, 12-lead ECG, and PD-L1 expression (TPS or CPS).

8.6. Efficacy Analysis

In efficacy analysis, ORR will be evaluated by tumor type and treatment in FAS. Tumor types with less than 5 subjects enrolled will be pooled for ORR summary. Subjects who do not have sufficient baseline or on-study tumor assessment to characterize response will be counted as nonresponders. Estimates and the corresponding 95% CIs based on the Clopper-Pearson exact method will be provided. The potential impact of subject baseline characteristics on treatment response may be explored with logistic regression modeling.

Medians, first quartile (Q1), third quartile (Q3) of the PFS distribution, and the proportion of subjects who are progression-free at Weeks 12, 24, and 48 from the first dosing date will be estimated by tumor type using the KM method along with the corresponding 95% CIs. KM curves will be provided.

The similar ORR and PFS analyses will be conducted using the investigator assessments and independent review committee (IRC) assessments if available.

8.7. Safety Analysis

Safety will be assessed via AEs, clinical laboratory tests, and concomitant medications.
All safety data collected on or after the date that study drug was first administered up to the date of last dose of study drug plus 30 days will be summarized by cohort, indication and treatment in the Safety Analysis Set. Information regarding study drug administration,
study drug compliance, and other safety variables will be summarized. Data for the pretreatment will be included in data listings.

8.7.1. Extent of Exposure

A subject's extent of exposure to study drug data will be generated from the study drug administration data. Descriptive information will be provided by cohort, indication and treatment regarding the number of doses of study drug prescribed, the total number of doses taken, the duration of exposure to study drug, and the number and timing of prescribed dose interruptions.

GS-4224 compliance will be described in terms of the proportion of study drug actually taken based on returned pill count relative to the amount that was dispensed (taking into account physician-prescribed interruptions).

8.7.2. Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High-Level Group Term, High-Level Term, Preferred Term (PT), and Lower-Level Term will be attached to the clinical database. The severity of AEs will be graded by the investigator according to the NCI-CTCAE, version 5.0, whenever possible. If a NCI-CTCAE criterion does not exist for a specific type of AE, the grade corresponding to the appropriate adjective will be used by the investigator to describe the intensity of the AE: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life threatening), or Grade 5 (fatal). The relationship of the AE to the study drug will be categorized as related or unrelated.

All AEs will be listed. The focus of AE summarization will be on TEAEs. A TEAE is defined as any AE with onset date on or after the date of first dose of study drug up to 30 days after permanent study drug discontinuation or any AEs leading to premature study drug discontinuation. Summaries (number and percentage of subjects) of TEAEs by SOC and PT will be provided by cohort, indication, and treatment.

Summary tables will be presented to show the number and percentage of subjects reporting TEAEs by severity grade and corresponding percentages. A subject who reports multiple TEAEs within the same PT (or SOC) is counted only once for that PT (or SOC) using the worst severity grade. Separate listings and summaries will be prepared for the following types of TEAEs:

- Study drug-related AEs
- AEs that are Grade ≥ 3 in severity
- AEs leading to study drug interruption and/or dose modification
- AEs leading to study drug discontinuation
- SAEs

8.7.3. Laboratory Evaluations

Selected laboratory data will be summarized based on observed data. Data and change from baseline at all scheduled time points will be summarized. The focus of laboratory data summarization will be on treatment-emergent laboratory abnormalities. A treatment-emergent laboratory abnormality is defined as an abnormality that, compared to baseline, worsens by ≥ 1 grade in the period from the first dose of study drug to 30 days after the last dose of study treatment. If baseline data are missing, then any graded abnormality (ie, an abnormality that is Grade ≥ 1 in severity) will be considered treatment emergent.

Graded laboratory abnormalities will be defined using the NCI-CTCAE version 5.0 when applicable. Summary tables will be presented for each relevant assay to show the number of subjects by CTCAE severity grade with corresponding percentages. For parameters for which a CTCAE scale does not exist, the frequency of subjects with values below, within, and above the normal ranges will be summarized. Subjects will be characterized only once for a given assay, based on their worst severity grade observed during a period of interest (eg, during the study or from baseline to a particular visit).

Shift tables for selected laboratory data may also be presented by showing change in CTCAE severity grade from baseline to the worst grade after baseline. For parameters for which a CTCAE scale does not exist, shift tables presented will show change in results from baseline to the worst grade after baseline. Separate listings and summaries will be prepared for laboratory abnormalities that are Grade ≥ 3 in severity.

CCI [redacted]

CCI [redacted]

8.10. Sample Size

The sample size of the study will be determined based on the number of dose levels evaluated and the emerging GS-4224-related toxicities and efficacy. The study is planned to enroll approximately 120 subjects.

Approximately 44 subjects will be enrolled in the dose escalation phase (Phase 1b) CCI

Approximately 40 subjects will be enrolled into the Dose Expansion Cohort B1.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use) (ICH) E6(R2) GCPs and applicable laws and regulations.

9.1.2. Financial Disclosure

The investigator and subinvestigators will provide documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug under 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/Independent Ethics Committee Review and Approval

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, ICF, 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 IRB/IEC 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 and before undertaking any study-related procedures.
The investigator must use the most current IRB or IEC approved ICF for documenting written informed consent. Each ICF (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 local requirements. The ICF 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 the sponsor, 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 showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the study. 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 IB, 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; CRF and query forms; IRB/IEC and governmental approval with correspondence; ICF; 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 (name, date of birth, gender)
- Documentation that subject meets eligibility criteria, ie, 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, and including causality and severity)
- 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 will be completed by an authorized study staff member whose training for this function is documented according to study procedures. An eCRF should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. The Eligibility Criteria eCRF should be completed only after all data related to eligibility have been received. Subsequent to data entry, a study monitor will perform SDV within the electronic data capture system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), 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. The eCRF capture the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff,

who routinely review the data for completeness, correctness, and consistency. The site coordinator 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). At the conclusion of the study, Gilead will provide the site 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. Investigational Medicinal Product Accountability and Return

Where possible, study drug should be destroyed at the site. If the site has an appropriate 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 central files. If study drug is destroyed on site, the investigator must maintain accurate records for all study drug destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drug. 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 eventual destruction. The study monitor will provide instructions for return.

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

9.1.9. Inspections

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

9.1.10. 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 (CSR) will be prepared and provided to the regulatory agency(ies). Gilead will ensure that the CSR meets the standards set out in the ICH Guideline for Structure and Content of CSRs (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.

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, eg, attendance at Investigator's 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

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the accuracy of the data recorded in the CRF/eCRF.

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 on 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 the sponsor 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 appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

10. REFERENCES

Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations For Initial Evaluation, Staging, and Response Assessment Of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. J Clin Oncol 2014;32 (27):3059-68.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (Version 1.1). Eur J Cancer 2009;45 (2):228-47.

Swaika A, Hammond WA, Joseph RW. Current state of anti-PD-L1 and anti-PD-1 agents in cancer therapy. Mol Immunol 2015;67 (2 Pt A):4-17.

Topalian SL, Sznol M, McDermott DF, Kluger HM, Carvajal RD, Sharfman WH, et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. J Clin Oncol 2014;32 (10):1020-30.

Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbe C, et al. Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria. Clin Cancer Res 2009;15 (23):7412-20.

11. APPENDICES

Appendix 1. Investigator Signature Page
Appendix 2. Study Procedures Table
Appendix 3. Tumor Specific Inclusion/Exclusion Criteria
Appendix 4. NCI-CTCAE Grading Scale for Severity of Adverse Events and Laboratory Abnormalities
Appendix 5. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements
Appendix 6. Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1)
Appendix 7. Response Assessment for Classic Hodgkin Lymphoma (Lugano Classification)
Appendix 8. Pandemic Risk Assessment and Mitigation Plan

Appendix 1. Investigator Signature Page

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

A Phase 1b/2 Dose Escalation/Expansion Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of GS-4224 in Subjects with Advanced Solid Tumors

Protocol Version 6.0 dated 02 October 2020

STUDY ACKNOWLEDGEMENT

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

PPD

Name (Printed)
Author

PPD

Signature

07 October, 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 Table

Study Phase Cycle Day	Screening Day -28 to Day 1	Cycle 1 (First 21 Days)						C2D1	C3D1	C4D1	C5D1	Every 3 weeks	Every 6 weeks	Every 9 weeks	EOT [f]	30 day Safety Follow -up[f]
		Cycle 1 Day 1	Day 2	Day 4	Day 8	Day 11	Day 15									
Window (day)	**-28**	**±0**	**±0**	**±0**	**±1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	**±7**	**±7**
Informed Consent	X															
Medical and Medication History[a]	X															
Physical Examination[b]	X	X	X	X	X	X	X	X	X	X	X	X			X	
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X	X			X	
12 lead ECG[d]	X	X			X		X	X	X	X	X	X[d]			X	X
Adverse events/ Concomitant medications[e]	X	X	X	X	X	X	X	X	X	X	X	X			X	X
Study Drug Dispensing		X						X	X	X	X	X				
Dosing Diary Accountability		X	X	X	X	X	X	X	X	X	X	X				
IXRS Registration	X	X						X	X	X	X	X			X	
CBC with differential	X[g]	X		X	X	X	X	X	X	X	X	X			X	
Coagulation	X[g]	X		X	X	X	X	X	X	X	X	X			X	
Chemistry	X[g]	X		X	X	X	X	X	X	X	X	X			X	
TSH		X											X			
Basal Cortisol		X											X			
Urinalysis		X			X			X	X	X	X	X			X	
Pregnancy Test[h]	X	X						X	X	X	X	X			X	

Study Phase Cycle Day	Screening Day -28 to Day 1	Cycle 1 (First 21 Days)						C2D1	C3D1	C4D1	C5D1	Every 3 weeks	Every 6 weeks	Every 9 weeks	EOT [f]	30 day Safety Follow -up[f]
		Cycle 1 Day 1	Day 2	Day 4	Day 8	Day 11	Day 15									
Window (day)	**-28**	**±0**	**±0**	**±0**	**±1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	**±7**	**±7**
HIV/CD4+/HBV/HCV Testing[i]	X															
CCI																
CCI																
CCI																
CCI																
CCI																
CCI																
Tumor PD L1 IHC[p]	X															
Archival Tumor Tissue or pre treatment biopsy[q]	X															

Study Phase Cycle Day	Screening Day -28 to Day 1	Cycle 1 (First 21 Days)						C2D1	C3D1	C4D1	C5D1	Every 3 weeks	Every 6 weeks	Every 9 weeks	EOT [f]	30 day Safety Follow -up[f]
		Cycle 1 Day 1	Day 2	Day 4	Day 8	Day 11	Day 15									
Window (day)	**-28**	**±0**	**±0**	**±0**	**±1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	**±7**	**±7**	**±7**
CCI																
CCI																
CT Scan with Contrast or MRI[t]	X								X		X			X	X[s]	
PET CT[u]	X								X		X					
ECOG Performance Status	X	X			X		X								X	

a Medical history includes significant past medical events (eg, prior hospitalizations or surgeries), a review of the disease under study, prior anti cancer therapies, and any concurrent medical illnesses.

b Screening and end of treatment Physical Examinations will be a complete physical examination. Beginning on C1D1, a modified physical examination will be performed to monitor for any changes (eg, lymph nodes, lung, cardiac, abdomen, skin, neurologic, and any systems, as clinically indicated). Weight (without shoes) should be measured at each PE. Height (without shoes) should be measured at screening only.

c Vital signs will be taken within 15 min pre GS 4224 dose. C1D1 vitals will also be collected at 2 and 4 hours postdose (± 15 min); vital signs will be taken predose only at all subsequent visits.

d A triplicate 12 lead ECG will be collected at screening, at predose on Cycle 1 Day 1, Cycle 1 Day 8, 1.5 hours postdose (± 9 min) on Cycle 1 Days 1 and 15, at the EOT visit and at the 30 Day Safety Follow up visit. Triplicate ECGs should be taken 5 minutes apart. Single 12 lead ECGs will be collected predose on Day 1 of Cycles 2 6.

e Adverse events will be assessed at pre and post GS 4224 dosing during applicable clinic visits. Subjects will also return to clinic at 30 day after last study drug dose, to assess AEs and SAEs. If the subject cannot return to the clinic, the site will contact the study subject by phone approximately 30 days after the last dose of study drug to assess AEs.

f End of treatment (EOT) and 30 day follow up visit are to be done 30 days after last dose of GS 4224. Subjects who miss the 30 day Safety follow up visit will be contacted by phone 30 days (± 7 days) after the last dose to assess AEs.

g Screening chemistry, hematology, and coagulation to be collected within 10 days of Study Day 1/C1D1.

h If applicable (females of child bearing potential). Serum pregnancy will be conducted at screening. Urine pregnancy will be conducted predose on Day 1 of each cycle and at EOT.

i HIV, HBsAg, and HCV antibody viral testing in subjects with current or prior history of HIV, HBV, and HCV infection, respectively. CD4+ count will also be performed in subjects with current or prior history of HIV.

[redacted]

p Where required for enrollment and if not already known, PD L1 expression will be determined.

q Archival tumor tissue for biomarker analysis will be collected. The tissue should preferably be obtained either at the time of or after the diagnosis of advanced disease has been made and from a site not previously irradiated. Tissue must be collected between screening and Cycle 2. If archival tissue is not available, a pre treatment biopsy will be collected from enrolled subjects. For the 1000 mg BID dose escalation cohort, subjects with melanoma, Merkel cell, MSI H cancers, and classical Hodgkin lymphoma are not required to have archival or fresh biopsy tissue

[redacted]

t Tumor evaluation by CT/MRI will be performed during screening (within 28 days of Day 1) and every 6 weeks for the first 2 scans and then every 9 weeks. A baseline scan within 6 weeks of Day 1 is acceptable. Cycle 3 Day 1 and Cycle 5 Day 1 scans can have a 7 day window. The same radiographic procedure used to define measurable lesions must be used throughout the study for each subject.

u PET CT to be completed at screening (within 28 days of Day 1), Cycle 3 Day 1, and Cycle 5 Day 1 only for subjects with cHL. Per Lugano 2014 criteria, PET CT is required to confirm radiographic CR in subjects with bone marrow involvement at screening. In subjects with bone marrow involvement at screening and at a time point where CR is suspected, PET CT will be required to confirm CR if CR was not achieved at Cycle 3 and/or 5.

Appendix 3. Tumor Specific Inclusion/Exclusion Criteria

DOSE ESCALATION 1000 MG BID COHORT AND BASKET COHORT (COHORT B1)

Non-Small Cell Lung Cancer (NSCLC):

Inclusion Criteria:

1) Subjects must have histologically or cytologically confirmed NSCLC with disease progression on or after targeted therapy, platinum-containing chemotherapy, or a checkpoint inhibitor, unless they have no access to a checkpoint inhibitor or refused intravenous checkpoint inhibitor therapy.

2) Tumor PD-L1 expression with a TPS ≥ 1% (Basket Cohort) and TPS ≥ 10% (1000 mg BID Cohort)

Melanoma:

Inclusion Criteria:

1) Subjects must have a histologically or cytologically confirmed diagnosis of melanoma with advanced disease (previously treated, therapy-refractory or recurrent Stage III (unresectable) or Stage IV); disease no longer controlled by surgery, chemotherapy, or radiotherapy; and disease refractory to or relapsed after standard therapy (including, but not limited to, chemotherapy and/or interleukin-2). All melanomas regardless of primary site of disease will be allowed.

Renal:

Inclusion Criteria:

1) Subjects must have histologically or cytologically confirmed renal cell carcinoma (RCC) (clear cell component) with advanced or recurrent and progressing disease that is not amenable to cure by surgery or other means, and must have failed at least 1 prior systemic therapy, including, but not limited to, treatment with Sunitinib, Temsirolimus, Sorafenib, IL-2, prior anti-angiogenic therapy, and/or chemotherapy.

2) Clinical evidence of or biopsy-proven metastatic disease to a site or sites distant from the primary tumor, that are not deemed to be surgically curative, or the subject is not a surgical candidate.

3) Tumor PD-L1 expression with a CPS ≥ 1 (Basket Cohort) and CPS ≥ 10 (1000 mg BID Cohort)

Urothelial:

Inclusion Criteria:

1) Subjects must have histologically or cytologically confirmed locally advanced or metastatic urothelial carcinoma and are not eligible for cisplatin-containing therapy.

2) Tumor PD-L1 expression with a CPS ≥ 10

Gastric:

Inclusion Criteria:

1) Subjects must have histologically or cytologically confirmed recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors expression PD-L1 with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy.

2) Tumor PD-L1 expression with a CPS ≥ 1

Head and Neck Squamous Cell Cancer (HNSCC):

Inclusion Criteria:

1) Subjects must have histologically or cytologically confirmed recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.

2) Tumor PD-L1 expression with a CPS ≥ 1

Hepatocellular Carcinoma:

Inclusion Criteria:

1) Subjects must have histologically or cytologically confirmed hepatocellular carcinoma (HCC) with disease progression after sorafenib or lenvatinib treatment unless the subject does not have access to either treatments. Subjects who do not have access to sorafenib or lenvatinib treatment may enroll to receive GS-4224 in the first-line setting.

2) Child-Pugh Class A liver score within 7 days of first dose of study drug

3) Tumor PD-L1 expression with a CPS ≥ 10 (1000 mg BID Cohort)

Exclusion Criteria:

1) Esophageal or gastric variceal bleeding within the last 6 months

2) Clinically apparent ascites on physical examination

3) Portal vein invasion at the main portal (Vp4), inferior vena cava, or cardiac involvement of HCC based on imaging

4) Encephalopathy in the last 6 months. Participants on rifaximin or lactulose to control their encephalopathy are not allowed

MSI-H Cancer:

Inclusion Criteria:

1) Subjects with unresectable or metastatic, MSI-H or mismatch repair deficient solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options

2) For subjects with colorectal cancer, progression following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

Merkel Cell Carcinoma:

Inclusion Criteria:

1) Subject with biopsy-proven metastatic Merkel cell carcinoma (MCC) or locoregional MCC that has recurred following standard locoregional therapy with surgery and/or radiation therapy.

2) No prior systemic therapy for MCC

Classical Hodgkin Lymphoma (cHL):

Inclusion Criteria:

1) Subjects with refractory cHL or who have relapse after 3 or more prior lines of therapy.

Esophageal Squamous Cell Carcinoma:

Inclusion Criteria:

1) Subjects with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus with disease progression after one or more prior lines of systemic therapy.

2) Tumor PD-L1 expression with a CPS ≥ 1 (Basket Cohort) and CPS ≥ 10 (1000 mg BID Cohort)

Cutaneous Squamous Cell Carcinoma:

Inclusion Criteria:

1) Subjects with recurrent or metastatic cutaneous squamous cell carcinoma that is not curable by surgery or radiation

2) Tumor PD-L1 expression with a CPS ≥ 1 (Basket Cohort) and CPS ≥ 10 (1000 mg BID Cohort)

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

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.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 < 54 years of age with amenorrhea of ≥ 12 months may also be considered postmenopausal if their follicle stimulating hormone (FSH) 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 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-4224 is contraindicated in pregnancy because a malformation effect has been demonstrated/suspected or is unknown, taking into consideration class effects or a strong suspicion of human teratogenicity/fetotoxicity in early pregnancy based on nonclinical data. GS-4224 has demonstrated/suspected or has insufficient data to exclude the possibility of a clinically relevant interaction with hormonal contraception that results in reduced contraception efficacy. Therefore, hormonal contraception is not recommended as a contraceptive method either solely or as a part of a contraceptive regimen. Refer to the latest version of the IB for additional information.

b. Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of highly effective contraceptive measures with a failure rate of < 1% per year. They must also not rely on hormone-containing contraceptives as a form of birth control during the study. They must have a negative serum pregnancy test at screening and a negative pregnancy test at the Admission (Day -1) visit prior to enrollment. Pregnancy tests will be performed at monthly intervals thereafter until the end of contraception requirement (30 days after last dose of study drug).

Duration of required contraception for female subjects in this clinical study should start from Screening visit until 30 days after the last dose of study drug.

Female subjects must agree to one of the following contraceptive methods:

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.

Or

Consistent and correct use of 1 of the following methods of birth control listed below:

- Non-hormonal intrauterine device (IUD)
- Bilateral tubal occlusion (upon medical assessment of surgical success)
- Vasectomy in the male partner (upon medical assessment of surgical success)

Inclusion of methods of contraception in this list of permitted methods does not imply that the method is approved in any country or region. Methods should only be used if locally approved.

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until the end of contraception requirement (30 days after last dose of study drug).

3. Contraception Requirements for Male Subjects

It is theoretically possible that a relevant systemic concentration of study drug may be achieved in a female partner from exposure of the male subject's seminal fluid and poses a potential risk to an embryo/fetus. Therefore, male subjects with female partners of childbearing potential must use condoms during treatment until 90 days after the last dose of study drug. If the female partner of childbearing potential is not pregnant, additional contraception recommendations should also be considered.

Male subjects must also refrain from sperm donation during treatment and until the end of contraception requirement (90 days after last dose of study drug).

4. Unacceptable Birth Control Methods

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

5. Procedures to be Followed in the Event of Pregnancy

Female subjects will be instructed to notify the investigator if they become pregnant or suspect they are pregnant at any time from start of the study to 30 days after last study drug dose. Study drug must be discontinued immediately.

Male subjects whose partner has become pregnant or suspects she is pregnant from start of study to within 90 days of last dose of study drug must also report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.4.2.3.

Appendix 6. Response Evaluation Criteria in Solid Tumors (RECIST Version 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 ≥ 15 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 exam 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 × 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 (eg, '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

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

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

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).

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 = inevaluable.

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

CR = complete response, PD = progressive disease, and NE = inevaluable.

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 trials so to assign this category when no lesions can be measured is not advised.

Appendix 7. Response Assessment for Classic Hodgkin Lymphoma (Lugano Classification)

Revised Criteria for Response Assessment		
Response and Site	**PET-CT–Based Response**	**CT-Based Response**
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3 with or without a residual mass on 5PS† It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to < 1.5 cm in LDi No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment (EOT), these findings indicate residual disease	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value When no longer visible, 0 × 0 mm For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase

Revised Criteria for Response Assessment		
Response and Site	**PET-CT–Based Response**	**CT-Based Response**
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or EOT	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable

Revised Criteria for Response Assessment

Response and Site	PET-CT–Based Response	CT-Based Response
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following PPD progression:
Individual target nodes/nodal masses Extranodal lesions	Score 4 or 5 with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or EOT assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by > 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to Lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5 point scale; CT, computed tomography; EOT, end of treatment; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.
*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and

should include, where applicable, mediastinal and retroperitoneal areas. Non nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).
†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.
Please reference {Cheson 2014} for further information on Lugano Classifications for cHL.

Appendix 8. Pandemic Risk Assessment and Mitigation Plan

During an ongoing pandemic, potential risks associated with subjects being unable to attend study visits have been identified for this study.

These risks can be summarized as follows:

1) Study drug supplies to subjects and sites:

    a) Subjects may be unable to return to the site for a number of visits to get the study drug, or the site may be unable to accept any subject visits. Without study drugs, the subject would not be able to stay on the study drug as planned per protocol.

        Mitigation plan: Study drug supplies may be provided to the subject from the site without a clinic visit, once it is confirmed that the subject may safely continue on study drug as determined by the principal investigator (PI). A virtual study visit, via phone or video conferencing, must be performed prior to remote study drug resupply. At the earliest opportunity, the site will schedule in-person subject visits and return to the protocol's regular schedule of assessments. A qualified courier may be utilized to ship the study drug from sites to study subjects if permitted by local ethic committee (EC)/institutional review boards (IRB)/Regulatory Authority as applicable and with sponsor's approval.

    b) Shipments of study drug could be delayed because of transportation issues. Without study drug subject would not be able to stay on the study drug as planned per protocol.

        Mitigation plan: The sites' study drug inventory should be closely monitored. Site staff should notify the sponsor or delegate if they foresee shortage in study drug inventory or if there is any interruption in local shipping service. The sponsor will continue to monitor inventory at the study drug depot and study sites. Manual shipments will be triggered as necessary.

2) Subject safety monitoring and follow up:

    a) Subjects may be unable or unwilling to come to the study site for their scheduled study visits as required per protocol.

        Mitigation plan: For subjects who may be unable or unwilling to visit the study site for their scheduled study visits as required per protocol, the PI or qualified delegate will conduct a virtual study visit, via phone or video conferencing, to assess the subject within target visit window date whenever possible. During the virtual study visit, the following information at minimum will be reviewed:

        i) Confirm if subject has experienced any adverse events (AEs)/serious adverse events (SAEs)/special situations (including pregnancy) and follow up on any unresolved AE/SAEs.

ii) Review current list of concomitant medications and document any new concomitant medications.

iii) If applicable, confirm subjects study drug supply is sufficient to last until the next planned visit date. If study drug resupply is needed it will be provided as described above in (1).

iv) If applicable, remind subject to maintain current dosing and to keep all dispensed study drug kits for return at the next on-site visit.

b) Subjects may be unable or unwilling to travel to the site for planned assessments (eg, safety blood draws); hence samples may not be sent for central lab analyses.

Mitigation plan: Local labs may be utilized as appropriate to monitor subject safety until the subject can return to the site for their regular follow up per protocol. Any laboratory assessments conducted at a local lab due to the pandemic will be documented accordingly. Pregnancy testing may be performed using a home urine pregnancy test if local lab pregnancy testing is not feasible.

c) Subjects may be unable or unwilling to attend the study visit to sign an updated informed consent form (ICF) version.

Mitigation plan: The site staff will follow their approved consent process and remain in compliance with local EC/IRB and national laws and regulations. Remote consent will be allowed if has been approved by the local EC/IRB. The consent process will be documented and confirmed by normal consent procedure at the earliest opportunity.

3) Protocol and monitoring compliance:

a) Protocol deviations may occur, in case scheduled visits cannot occur as planned per protocol.

Mitigation plan: If it is not possible to complete a required procedure, an unscheduled visit should be conducted as soon as possible when conditions allow. The situation should be recorded and explained as a protocol deviation. Any missed subject visits or deviation to the protocol due to the pandemic must be reported in the eCRF and described in the clinical study report (CSR). Any virtual study visits that are conducted in lieu of clinic visits due to the pandemic will be documented as a protocol deviation related to the pandemic.

b) Monitors may be unable to carry out source data review (SDR) or source data verification (SDV), or study drug accountability or assess protocol and GCP compliance. This may lead to delays in SDV, an increase in protocol deviations, or under reporting of AEs.

Mitigation plan: The study monitor is to remain in close communication with the site to ensure data entry and query resolution. The study monitor is to reference the Study Monitoring Plan for guidance on how to conduct a remote monitoring visit. The study staff is to save and document all relevant communication in the study files. The status of sites that cannot accept monitoring visits and/or subjects on site, must be tracked centrally and updated on a regular basis.

4) Missing data and data integrity:

a) There may be an increased amount of missing data due to subjects missing visits/assessments. This could have an impact on the analysis and the interpretation of clinical trial data.

Mitigation plan: Implications of a pandemic on methodological aspects for the study will be thoroughly assessed and documented, and relevant actions will be taken as appropriate (ie, modification of the statistical analysis plan) and in compliance with Regulatory Authorities' guidance. Overall, the CSR will describe the impact of the pandemic on the interpretability of study data.

Risks will be assessed continuously, and temporary measures will be implemented to mitigate these risks as part of a mitigation plan, as described above. These measures will be communicated to the relevant stakeholders as appropriate and are intended to provide alternate methods that will ensure the evaluation and assessment of the safety of subjects who are enrolled in this study.

Since these potential risks are considered mitigated with the implementation of these measures, the expected benefit-risk assessment of GS-4224 in study subjects remains unchanged.