CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2, Blinded, Randomized, Placebo-Controlled Study Evaluating the Efficacy and Safety of GS-4875 in Subjects with Moderately to Severely Active Ulcerative Colitis
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number:	143174
EudraCT Number:	2019-001430-33
Clinical Trials.gov Identifier:	NCT04130919
Indication:	Ulcerative Colitis
Protocol ID:	GS-US-365-4237
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Original: 25 March 2019 Amendment 1: 18 July 2019 Amendment 1.1*: 11 December 2019 *Switzerland, Russia, and VHP countries only Amendment 2: 19 June 2020

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

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
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Study Title:	A Phase 2, Blinded, Randomized, Placebo-Controlled Study Evaluating the Efficacy and Safety of GS-4875 in Subjects with Moderately to Severely Active Ulcerative Colitis
IND Number:	143174
EudraCT Number:	2019-001430-33
Clinical Trials.gov Identifier:	NCT04130919
Study Centers Planned:	Approximately 100 centers globally

Objectives and Endpoints:

Primary Objective	Primary Endpoint
To demonstrate the efficacy of GS-4875, compared with placebo control, in achieving Clinical Remission per Modified Mayo Clinic Score (MCS) at Week 10	Clinical Remission per Modified MCS, defined as Stool Frequency subscore ≤ 1 and not greater than baseline, Rectal Bleeding subscore of 0, and Endoscopic subscore ≤ 1 at Week 10
Key Secondary Objectives	**Key Secondary Endpoints**
To demonstrate the efficacy of GS-4875, compared with placebo control, in achieving endoscopic response at Week 10	Endoscopic Response, defined as an Endoscopic subscore ≤ 1 at Week 10
To demonstrate the efficacy of GS-4875, compared with placebo control, in achieving MCS Response at Week 10	MCS Response, defined as a decrease from baseline of ≥ 3 points and at least 30% in MCS, in addition to a ≥ 1 point decrease from baseline in the Rectal Bleeding subscore or a Rectal Bleeding subscore ≤ 1 at Week 10
To demonstrate the efficacy of GS-4875, compared with placebo control, in achieving MCS Remission at Week 10	MCS Remission, defined as a MCS score of ≤ 2 and no individual subscore > 1 at Week 10
To evaluate GS-4875, as compared with placebo control, in achieving histologic remission at Week 10	Histologic remission based upon the Geboes Scale where all of the following must be met at Week 10: Grade 0 of ≤ 0.3, Grade 1 of ≤ 1.1, Grade 2a of ≤ 2A.3, Grade 2b of 2B.0, Grade 3 of 3.0, Grade 4 of 4.0, and Grade 5 of 5.0 (Appendix 5)

Other Secondary Objectives	Other Secondary Endpoints
To evaluate the safety and tolerability of GS-4875	Incidence and characterization of adverse events (AEs) and laboratory abnormalities
	Physical examination (PE) findings, electrocardiogram (ECG), and vital signs

Study Design:

This is a Phase 2, blinded, randomized, placebo-controlled study evaluating the efficacy and safety of GS-4875 for the treatment of subjects with moderately to severely active ulcerative colitis (UC).

This study includes:

- Screening period (Days 30 to 1)
- Baseline/Randomization (Day 1)

  Approximately 180 subjects who meet protocol eligibility criteria will be randomized in a 1:1:1 ratio to 1 of 3 treatment groups as follows:

  Treatment group 1 (n 60): GS-4875 300 mg once daily

  Treatment group 2 (n 60): GS-4875 100 mg once daily

  Treatment group 3 (n 60): Placebo once daily

  Treatment assignments will be stratified according to the sum (≤ 6 or > 6) of 3 MCS subscores for Stool Frequency, Rectal Bleeding, and Endoscopic Findings at screening.

- Blinded Treatment phase (Day 1 up to Week 50)

  At Week 10 visit, all subjects will have an efficacy assessment.

- Open-Label (OL) Treatment phase (OL Day 1 up to OL Week 50)

  At OL Week 10 visit, all subjects will have an efficacy assessment.

- Gilead Data Review Committee (GDRC)

  After approximately 90 subjects complete the Week 10 visit or discontinue from the study prior to Week 10, the GDRC will review endpoint data for potential study termination due to lack of efficacy.

- Unblinding

  The study will be unblinded when all randomized subjects (approximately 180) have completed 10 weeks of blinded study drug, or discontinued from the study, and associated safety and efficacy assessments have been completed.

- Posttreatment (PTx) Assessments

  Subjects who discontinue study drug will return 30 days after the last dose for PTx assessments.

Number of Subjects Planned:	180
Target Population:	Adult subjects with moderately to severely active UC.
Duration of Treatment:	In the Blinded Treatment phase, randomized subjects may receive a maximum of 50 weeks of treatment. Subjects who move to the OL Treatment phase will have received 10 weeks of blinded treatment and may receive up to 50 weeks of OL treatment. Thus, total duration of treatment may be a maximum of 60 weeks.
Diagnosis and Main Eligibility Criteria:	Select Eligibility Criteria: 1) UC of at least 3 months duration before randomization confirmed by endoscopy and histology at any time in the past AND with a minimum disease extent of 15 cm from the anal verge. Documentation of endoscopy and histology consistent with the diagnosis of UC must be available in the source documents prior to the initiation of screening. 2) Moderately to severely active UC as determined during screening by a centrally read endoscopy score ≥ 2, a Rectal Bleeding subscore ≥ 1, a Stool Frequency subscore ≥ 1 and Physicians Global Assessment (PGA) of ≥ 2 as defined by the Mayo Clinic Score (Appendix 4); total MCS must be between 6 and 12, inclusive. 3) Previously demonstrated an inadequate response (primary non-response) or loss of response (secondary non-response) to a TNFα inhibitor (ie, infliximab, adalimumab, golimumab, or biosimilars). The induction treatment regimen resulting in inadequate response or loss of response should have been in accordance with local prescribing information/guidelines.
Study Procedures/ Frequency:	Refer to Appendix 2 and Appendix 3 for the Study Procedures Tables.
Test Product, Dose, and Mode of Administration:	GS-4875 300 mg: 2 GS-4875 150 mg tablets, orally once daily GS-4875 100 mg: 2 GS-4875 50 mg tablets, orally once daily GS-4875 should not be administered with food.
Reference Therapy, Dose, and Mode of Administration:	Placebo: 2 placebo-to-match (PTM) tablets, orally once daily

Criteria for Evaluation:	
Safety:	Assessment of AEs and concomitant medications will continue throughout the duration of the study. Safety evaluations include documentation of AEs, PE (complete or symptom driven), vital signs, clinical laboratory evaluations (hematology, chemistry, urinalysis, stool analysis), and ECG. **Data Monitoring Committee (DMC)** The initial meeting will occur after approximately 20 subjects complete the Week 4 visit or discontinue from the study prior to Week 4. Subsequent DMC meetings for safety review will be held after approximately 60 subjects complete the Week 4 visit or discontinue from the study and after approximately 90 subjects complete the Week 10 visit or discontinue from the study. The frequency of meetings may be adjusted as requested by the DMC.
Efficacy:	Efficacy will be assessed by Clinical Remission per Modified MCS, defined as Stool Frequency subscore ≤ 1 and not greater than baseline, Rectal Bleeding subscore of 0 and an Endoscopic subscore (by central read) ≤ 1 at Week 10.
CCI [redacted]	[redacted] CCI [redacted]
Biomarkers:	**Blood Biomarker Samples** Blood samples will be collected at Day 1 and Weeks 2, 4, 10, 26, and 50.

Mandatory Genomic Samples

Mandatory genomic samples will be collected at the Day 1 visit.

A blood sample will be obtained for genetic analysis of the uridine 5'-diphospho-glucuronosyltransferase family 1 member A1 (UGT1A1)*28 genetic variants.

A blood sample will be obtained to determine the tumor progression locus 2 (TPL2) genotype and single nucleotide polymorphisms (SNPs) associated with inflammatory bowel disease (IBD).

Stool Biomarker Samples

Stool samples will be collected at screening and Weeks 10, 26, and 50.

Statistical Methods:

Primary Analysis

The primary analysis will compare each GS-4875 dose group to placebo on the proportion of subjects achieving Clinical Remission per Modified MCS at Week 10. The Cochran-Mantel-Haenszel (CMH) approach adjusting for stratification factor will be used for hypothesis testing of the primary endpoint. For evaluation of Clinical Remission per Modified MCS at Week 10, MCS score at screening will be used as baseline value.

Subjects who do not have sufficient measurements to determine efficacy endpoints will be considered failures (ie, non-responder imputation [NRI]).

Week 10 Analysis

A Week 10 analysis will be conducted when all randomized subjects (approximately 180) have completed 10 weeks of blinded study drug, or discontinued from the study, and associated safety and efficacy assessments have been completed. The study will be unblinded and safety analysis and Week 10 efficacy analysis (including primary analysis) will be performed. The purpose of these analyses is to inform study discontinuation or further development of GS-4875 for the treatment of UC. If the sponsor concludes that treatment with GS-4875 has an unfavorable benefit-risk profile, the sponsor will request an ad hoc DMC meeting. The DMC will be requested to evaluate the available study data and to make recommendation on whether the study should be stopped, continued, or continued with modifications.

Adjustments of Multiplicity

The following primary and key secondary endpoints will be tested sequentially at a one-sided Type 1 error rate of 2.5% in the following order:

GS-4875 300 mg vs placebo

1. The proportion of subjects with clinical remission per modified MCS at Week 10
2. The proportion of subjects with endoscopic response at Week 10
3. The proportion of subjects with MCS Response at Week 10
4. The proportion of subjects with MCS Remission at Week 10
5. The proportion of subjects with histologic remission at Week 10

GS-4875 100 mg vs placebo

6. The proportion of subjects with clinical remission per modified MCS at Week 10
7. The proportion of subjects with endoscopic response at Week 10
8. The proportion of subjects with MCS response at Week 10
9. The proportion of subjects with MCS remission at Week 10
10. The proportion of subjects with histologic remission at Week 10

Testing will stop with the first of these endpoints failing to reach statistical significance and all subsequent endpoints would not be considered for statistical significance and only nominal p-values will be reported.

Sample Size

A sample size of 60 subjects in the placebo group and 60 subjects in each GS-4875 dose group (n 120 total for GS-4875) will provide approximately 75% power for each GS-4875 dose group comparison to placebo at a 1-sided 0.025 significance level to detect a treatment difference in Clinical Remission per modified MCS response rate of 17.5% (22.5% on GS-4875 and 5% on placebo) based on Fisher's exact test.

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

6-MP	6-mercaptopurine
ADL	Activities of Daily Living
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC_{inf}	area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$
AUC_{0-24}	partial area under the concentration versus time curve from time "0" to time "24 hours"
BAP	Biomarker Analysis Plan
BCRP	breast cancer resistance protein
C difficile	*Clostridium difficile*
CD	Crohn's disease
CI	confidence interval
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	the maximum observed serum/plasma/peripheral blood mononuclear (PBMC) concentration of drug
CMH	Cochran-Mantel-Haenszel
CPK	creatine phosphokinase
CRF	case report form(s)
CRO	contract research organization
CRP	c-reactive protein
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450 enzyme
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form(s)
eGFR	estimated glomerular filtration rate
$eGFR_{cr}$	estimated glomerular filtration rate based on serum creatinine
$eGFR_{cys}$	estimated glomerular filtration rate based on serum cystatin C
EDC	Electronic Data Capture
EMA	European Medicines Agency
ERK	extracellular signal-regulated kinases
EQ-5D	EuroQol 5 dimensions
ET	early termination
EU	European Union

EudraCT	European clinical trials database
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFPE	Formalin Fixed Paraffin Embedded
GCP	Good Clinical Practice (Guidelines)
GDRC	Gilead Data Review Committee
GFR	glomerular filtration rate
GLSM	geometric least-squares mean
Gilead	Gilead Sciences
HBcAb	hepatitis B virus core antibody
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCRU	healthcare resource utilization
HDL	high-density lipoprotein
HDPE	high density polyethylene
HIV	human immunodeficiency virus
HLGT	High-Level Group Term
HLT	High-Level Term
HRQoL	health-related quality of life
IB	Investigator brochure
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IEC	independent ethics committee
IL-1β	interleukin-1 beta
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
IV	intravenous
IWRS	interactive web response system
JAK	Janus Kinase
LDL	low-density lipoprotein
LLT	lower-level term
LLOQ	lower limit of quantification
LOCF	last observation carried forward
LPS	lipopolysaccharides
MATE1	multidrug and toxin extrusion transporter 1
MCS	Mayo Clinic Score

MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	no observed adverse effect level
NRI	non-responder imputation
NSF	normal stool frequency
OATP	organic anion-transporting polypeptide
OL	open-label
P-gp	P-glycoprotein
PBMC	peripheral blood mononuclear cell
PE	physical examination
PGA	Physicians global assessment
PI	principal investigator
PK	Pharmacokinetic(s)
PT	preferred term
PTx	posttreatment
PTM	placebo to match
PVE	Pharmacovigilance and Epidemiology
QD	once daily
RNA	ribonucleic acid
SAC	Safety Assessment Committee
SADR	serious adverse drug reaction
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SF-36	36-Item Short Form Survey
SNP	single nucleotide polymorphism
SOC	system organ class
SOP	standard operating procedure
spp	species
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
TNFα	tumor necrosis factor-alpha
TPL2	tumor progression locus 2
UC	ulcerative colitis
UGT1A1	uridine 5'-diphospho-glucuronosyltransferase family 1 member A1
ULN	upper limit of normal
US	United States
WBC	white blood cell
WPAI-UC	Work Productivity and Activity Impairment-Ulcerative Colitis

1. INTRODUCTION

1.1. Background

Inflammatory bowel diseases (IBD), which include Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory diseases of the gastrointestinal tract characterized by periods of relapses and remission. In UC, the inflammation is limited to the mucosa of the colon and rectum, while in CD any part of the gastrointestinal tract, from mouth to anus, can be affected. Crohn's disease and UC are thought to result from an inappropriate immune response to intestinal microbiota in genetically susceptible hosts, with environmental factors triggering disease initiation and reactivation. This hypothesis implicates reciprocal interactions between host genetics, environmental factors, resident microbiota, and immune responses that normally mediate mucosal homeostasis, but when dysregulated, induce and perpetuate chronic immune-mediated inflammation {Ungaro 2016}.

The incidence and prevalence of UC have been increasing worldwide. In Europe, the incidence and prevalence range from 0.97 57.9 per 100,000 person years and 2.42 505 per 100,000 person years, respectively. However, within Europe there appears to be differences in UC incidence, with countries located in the western and northern regions having higher incidences than eastern countries. In North America, the incidence and prevalence range from 8.8 23.14 per 100,000 person years and 139.8 286.3 per 100,000 person years, respectively. During the 20th century, UC was mainly a disease of westernized countries of North America, Europe, and Oceania. The prevalence of UC in newly industrialized countries is low, but given the rising incidence identified in many of these countries, is expected to climb. This increasing global burden of UC will bring important challenges to health-care systems around the world as they work to care for this complex and costly disease {Ng 2017}.

The most common presentations of UC are blood in the stool and diarrhea. Up to 15% of patients can initially present with severe disease. Symptoms can include urgency, incontinence, fatigue, increased frequency of bowel movements, mucus discharge, nocturnal defecations, and abdominal discomfort (cramps), although abdominal pain tends to be less of a hallmark feature than in CD. Fevers and weight loss can also be present in severe disease. UC is associated with an increased risk of colorectal cancer {Ungaro 2016}. With poorly controlled disease, the risk of developing colorectal cancer increases with time {Jess 2012}.

Treatment of UC is dependent on the severity and the location of disease. Goals of treatment include improved quality of life, reduction in long-term corticosteroid use, and minimization of cancer risk. Mild to moderately active distal colitis may be treated with oral aminosalicylates, topical mesalamine, or topical steroids. For moderately active disease, oral corticosteroids, and immunomodulators such as azathioprine and 6-mercaptopurine (6-MP) may be utilized {Danese 2011}. For more moderately to severely active disease, patients are commonly treated with a tumor necrosis factor-alpha (TNFα) antagonist such as infliximab (Remicade®), adalimumab (Humira®), and golimumab (Simponi®), or an α4β7 integrin antagonist such as vedolizumab (Entyvio®). Tofacitinib, an oral Janus kinase (JAK) inhibitor, and ustekinumab, a monoclonal antibody against IL12/23, are approved for moderately to severely active disease {Harbord 2017, STELARA 2020}.

1.2. Rationale for This Study

Despite the number of available therapeutic options for patients with UC, there remains an unmet medical need because existing agents are limited by low efficacy and safety concerns. Moderately to severely active UC represents a serious, life-threatening disease for which new therapies are needed to interrupt the inflammatory process to: prevent disease progression, restore quality of life, and reduce the risk of colorectal cancer.

GS-4875 is a first-in-class inhibitor of tumor progression locus 2 (TPL2), a cytoplasmic serine/threonine kinase and the primary regulator of extracellular signal-regulated kinase (ERK)-mediated gene expression downstream of multiple pro-inflammatory stimuli including: bacterial products (eg, lipopolysaccharides [LPS] and bacterial peptidoglycans), TNFα, and interleukin-1 beta (IL-1β) {Gantke 2011}. Upon stimulation, the TPL2-ERK pathway is activated in a broad range of immune cells and drives the production of pro-inflammatory cytokines including TNFα, IL-1β, and IL-6; all of which are cytokines involved in the pathogenesis of UC. TPL2 ribonucleic acid (RNA) is upregulated in UC patient colon biopsies and its expression correlates with IBD-associated genes. A TPL2 gain of function polymorphism has been identified as a risk allele in UC {Hedl 2015, Jostins 2012}. Therefore, TPL2 inhibition by GS-4875 has the potential to reestablish a proper homeostasis between intestinal microbiota in the gut and the immune system, potentially enabling the resolution of chronic intestinal inflammation in UC patients.

1.3. GS-4875

1.3.1. General Information

Please refer to the investigator's brochure (IB) for information on GS-4875.

1.3.2. Summary of Additional Nonclinical Experience of GS-4875

1.3.2.1. TX-457-2018

The phototoxic potential of GS-4875 on the eyes and skin of Long-Evans (Crl:LE) pigmented rats was determined in Study TX-457-2018. Crl:LE rats were exposed to ultraviolet B, ultraviolet A, and visible light following systemic exposure to GS-4875 via administration of an intestinally cleaved pro-drug of GS-4875 for 3 days. GS-4875 had no phototoxic liability at the highest doses evaluated ($AUC_{0\ 24}$ 63 µg•h/mL and C_{max} 7.2 µg/mL). The highest exposures ($AUC_{0\ 24}$) tested were 2.8-fold above the human exposure expected to occur with the highest dose of GS-4875 (300 mg once daily) in Study GS-US-365-4237. These results suggest that GS-4875 is not photoreactive; therefore, phototoxicity precautions are not warranted for subjects exposed to GS-4875.

1.3.2.2. TX-365-2016

TX-365-2016 was a 39-week chronic toxicology study of GS-4875 in monkeys with a 26-week interim necropsy and a 4-week recovery period. The 26-week interim necropsy observations have been summarized in the IB. The following data summarize the GS-4875-related observations through the end of 39-weeks of dosing and 4-week recovery period. No GS-4875-related mortality, clinical observations, or alterations in body weight, food consumption or clinical pathology parameters were observed. No GS-4875-related macroscopic or microscopic findings were observed at the end of the dosing or recovery phase. No adverse findings were identified. The no observed adverse effect level (NOAEL) was 60 mg/kg/day, the highest dose evaluated. GS-4875 exposures ($AUC_{0\ 24}$) at NOAEL in the monkey calculated as twice the reported $AUC_{0\ 12}$ values was 88 µg•h/mL. This results in an exposure margin of 3.8-fold above the anticipated steady-state human exposure at the highest dose of GS-4875 (300 mg) in Study GS-US-365-4237.

1.3.3. Summary of Additional Clinical Experience of GS-4875

1.3.3.1. GS-US-365-4235

1.3.3.1.1. Study Design

Study GS-US-365-4235 was an open-label, multiple cohort study designed to evaluate cytochrome P450 enzyme (CYP)-mediated drug-drug interactions between GS-4875 (50, 300, or 450 mg) and various probe drugs in healthy subjects.

1.3.3.1.2. Pharmacokinetic Results

GS-4875 (450 mg once daily) had minimal effect on the pharmacokinetic (PK) of a probe CYP3A substrate (midazolam 2 mg, single dose). Co-administration with GS-4875 did not change midazolam C_{max} (geometric mean ratio [90% CI]: 1.04 [0.88, 1.23]). Midazolam AUC_{inf} was minimally increased by 19% (geometric mean ratio [90% CI]: 1.19 [1.05, 1.36]). Therefore, GS-4875 is considered a weak CYP3A inhibitor. Accordingly, sensitive CYP3A substrates may be administered with GS-4875.

A strong CYP3A inhibitor (voriconazole 200 mg twice daily), when co-administered with GS-4875 (50 mg, single dose), increased GS-4875 exposure (AUC_{inf}) by 2.10-fold (90% CI: 1.74, 2.54) with no change in the C_{max} (geometric mean ratio [90% CI]: 1.06 [0.87, 1.29]). Therefore, administration of GS-4875 with moderate and strong CYP3A inhibitors is not allowed in Study GS-US-365-4237 (see Section 5.4).

A moderate CYP3A inducer (rifampin 10 mg once daily), when co-administered with GS-4875 (300 mg, single dose), reduced GS-4875 plasma exposure (AUC_{inf}) by 27% (geometric mean ratio [90% CI]: 0.73 [0.59, 0.90]) with no change in the C_{max} (geometric mean ratio [90% CI]: 0.96 [0.75, 1.23]). Therefore, moderate and strong CYP3A inducers are not allowed in Study GS-US-365-4237 (Section 5.4).

1.3.3.1.3. Safety Results

All 42 enrolled subjects received at least 1 dose of GS-4875. No deaths, serious adverse events (SAEs), or adverse events (AEs) that led to premature discontinuation of study drug or study were reported during the study. All AEs were mild (Grade 1) or moderate (Grade 2) in severity. The most common AEs included headache, dizziness, decreased appetite, infrequent bowel movements, and nausea. The majority of laboratory abnormalities were Grade 1 or Grade 2.

1.3.3.2. GS-US-365-5588

1.3.3.2.1. Study Design

Study GS-US-365-5588 was a randomized, placebo-controlled study to evaluate the effect of GS-4875 on renal function using the plasma clearance of iohexol as a surrogate marker for measured glomerular filtration rate (GFR). Estimated GFRs, based on serum creatinine ($eGFR_{cr}$) and cystatin C ($eGFR_{cys}$) as calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations (Section 6.9.5.2), were evaluated during the on-treatment period (Days 1 through 10) and during the follow-up period (Days 24 through 66).

1.3.3.2.2. Pharmacokinetic Results

Plasma exposures of GS-4875 (300 mg once daily) on Day 10 were consistent with previous studies. No differences in change from baseline in measured GFR were observed between the GS-4875 and placebo groups on Day 10 (lower bound of CIs for GFRs was above the pre-defined, no-alteration boundary of 85%). Similarly, no differences in change from baseline in $eGFR_{cys}$ were observed between the GS-4875 and placebo groups during the on-treatment and follow-up periods. There was a decrease in the geometric least-squares mean (GLSM) ratio of $eGFR_{cr}$ in the GS-4875 group relative to the placebo group during the on-treatment period (Days 1 through 10) that was reversible, as evidenced by normalization of the GLSM ratio of $eGFR_{cr}$ equivalent to placebo during the follow-up period (Days 24 through 66). These results suggest that changes in serum creatinine observed with GS-4875 treatment at doses up to 300 mg once daily are due to inhibition of the renal transporter multidrug and toxin extrusion transporter 1 (MATE1) and do not represent changes in actual GFR or renal function.

1.3.3.2.3. Safety Results

All 32 enrolled subjects received at least 1 dose of study drug and iohexol. No deaths or SAEs were reported during the study. Most AEs were mild (Grade 1) or moderate (Grade 2) in severity. One subject administered GS-4875 and iohexol experienced a Grade 3 AE (increased creatine phosphokinase) that led to discontinuation of study drug per protocol guidance. The most common AEs included headache, constipation, and dizziness. The majority of laboratory abnormalities were Grade 1 or Grade 2. Two subjects administered GS-4875 and iohexol had Grade 3 laboratory abnormalities. One subject had Grade 3 creatine phosphokinase increases and discontinued study drug; creatine phosphokinase levels returned to normal 5 days later. The other subject had Grade 3 low-density lipoprotein (LDL) increases and a Grade 3 total bilirubin increase without elevations in direct bilirubin. This subject has a known inherited susceptibility

to unconjugated hyperbilirubinemia (homozygous for uridine 5'-diphospho-glucuronosyltransferase family 1 member A1 [UGT1A1]*28 variant allele) and had a Grade 3 LDL at screening. Two subjects administered placebo and iohexol had Grade 3 or higher laboratory abnormalities. One subject had a Grade 3 amylase increase. The other subject had a Grade 4 creatine phosphokinase increase.

1.4. Risk/Benefit Assessment for the Study

No specific risks of GS-4875 have been identified in studies of chronic toxicity in rats and cynomolgus monkeys. A summary of the data from non-clinical chronic toxicity studies are provided in the current edition of the GS-4875 IB and Section 1.3.2.

GS-4875 has been administered to 102 healthy subjects in the Phase 1a first-in-human study, GS-US-365-4233. A summary of the safety and PK data from this study is provided in the current edition of the GS-4875 IB. GS-4875 has been administered to 58 healthy subjects in 2 Phase 1 Studies, GS-US-365-4235 and GS-US-365-5588. A summary of the data from these studies is provided in Section 1.3.3.

In Study GS-US-365-4233, GS-4875 was well-tolerated in healthy subjects when administered for up to 10 days at doses ranging from 15 mg once daily to 450 mg once daily. There were no deaths reported, no SAEs reported, and no subjects discontinued study drug for AEs. Non-clinical studies indicate that GS-4875 is an inhibitor of the organic anion-transporting polypeptide (OATP) isoforms OATP1B1, OATP1B3, and OATP2B1 and is an inhibitor of UGT1A1. Therefore, a cohort of 12 subjects homozygous for the UGT1A1*28 allele (TA7/TA7) was administered placebo or GS-4875 450 mg once daily for 10 days to assess whether GS-4875 would exacerbate hyperbilirubinemia in patients who were genetically susceptible. GS-4875 was well-tolerated in the 8 subjects that received GS-4875 with mild elevations in total bilirubin observed but without elevations in direct bilirubin or symptomatic hyperbilirubinemia.

Non-clinical studies indicate that GS-4875 is an inhibitor of MATE1 and may therefore affect the PK of MATE1 substrates, including creatinine. In Study GS-US-365-5588, increases in serum creatinine and consequently, decreases in $eGFR_{cr}$ were observed in subjects administered GS-4875. However, the results of Study GS-US-365-5588 demonstrated that GS-4875 had no effect on renal function as determined by measured GFR and $eGFR_{cys}$ (See Section 1.3.3.2). Therefore, in order to maintain the study blind, results of serum creatinine and $eGFR_{cr}$ assessments will not be provided to investigators. Assessment of renal function using cystatin C and $eGFR_{cys}$ will be routinely measured, and these data will be provided to investigators.

The unknown risks of GS-4875 are associated with its potential to inhibit inflammatory signaling cascades and thereby impair the immune response in patients with UC. Based on the mechanism of action, there is a potential for immunosuppression but also a theoretical risk that inhibition of TPL2 could exacerbate UC.

These risks are mitigated by the selection of the appropriate patient population as defined by the eligibility criteria, the frequency of scheduled visits during which laboratory and clinical assessments will be performed and the implementation of discontinuation criteria for patients who are not benefitting from treatment with GS-4875 or who have worsening disease. In

addition, an independent and experienced data monitoring committee (DMC) will be convened to monitor the safety of subjects in the study. The frequency of DMC meetings is described in Section 8.11.

GS-4875 is a first-in-class inhibitor of TPL2. The mechanism of action of GS-4875 is novel and treatment effect has not yet been established in patients with UC. Study GS-US-365-4237 is a proof-of-concept study in which GS-4875 may show no treatment effect or lead to disease worsening. In consideration of this early stage of development, efficacy endpoints and disease associated biomarkers will be reviewed by the Gilead Data Review Committee (GDRC) (See Section 5.1.3) allowing for early termination (ET) of the study and avoiding unnecessary exposure to study drug for the subjects. The timing of the GDRC meeting is described in Section 8.2.1.1.

In summary, the benefit-risk profile for GS-4875 is favorable for evaluation in subjects with moderately to severely active UC based on the lack of safety findings in healthy subjects, the lack of concerning non-clinical toxicology findings, the additional oversight from safety and efficacy committees, the beneficial findings in non-clinical models of disease, as well as, the overall safety, tolerability, and PK characteristics of GS-4875.

1.5. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and applicable regulatory requirements. In case of substantial amendment to the protocol, an approval from the Competent Regulatory Authorities will be sought before implementation.

2. OBJECTIVES AND ENDPOINTS

The objectives and associated endpoints of this study are presented in Table 2-1.

Table 2-1. Objectives and Endpoints of Study GS-US-365-4237

Primary Objective	**Primary Endpoint**
To demonstrate the efficacy of GS-4875, compared with placebo control, in achieving Clinical Remission per Modified Mayo Clinic Score (MCS) at Week 10	Clinical Remission per Modified MCS, defined as Stool Frequency subscore ≤ 1 and not greater than baseline, Rectal Bleeding subscore of 0, and Endoscopic subscore ≤ 1 at Week 10
Key Secondary Objectives	**Key Secondary Endpoints**
To demonstrate the efficacy of GS-4875, compared with placebo control, in achieving endoscopic response at Week 10	Endoscopic Response, defined as an Endoscopic subscore ≤ 1 at Week 10
To demonstrate the efficacy of GS-4875, compared with placebo control, in achieving MCS Response at Week 10	MCS Response, defined as a decrease from baseline of ≥ 3 points and at least 30% in MCS, in addition to a ≥ 1 point decrease from baseline in the Rectal Bleeding subscore or a Rectal Bleeding subscore ≤ 1 at Week 10
To demonstrate the efficacy of GS-4875, compared with placebo control, in achieving MCS Remission at Week 10	MCS Remission, defined as a MCS score of ≤ 2 and no individual subscore > 1 at Week 10
To evaluate GS-4875, as compared with placebo control, in achieving histologic remission at Week 10	Histologic remission based upon the Geboes Scale where all of the following must be met at Week 10: Grade 0 of ≤ 0.3, Grade 1 of ≤ 1.1, Grade 2a of ≤ 2A.3, Grade 2b of 2B.0, Grade 3 of 3.0, Grade 4 of 4.0, and Grade 5 of 5.0 (Appendix 5)
Other Secondary Objectives	**Other Secondary Endpoints**
To evaluate the safety and tolerability of GS-4875	Incidence and characterization of AEs and laboratory abnormalities
	Physical examination (PE) findings, electrocardiogram (ECG), and vital signs


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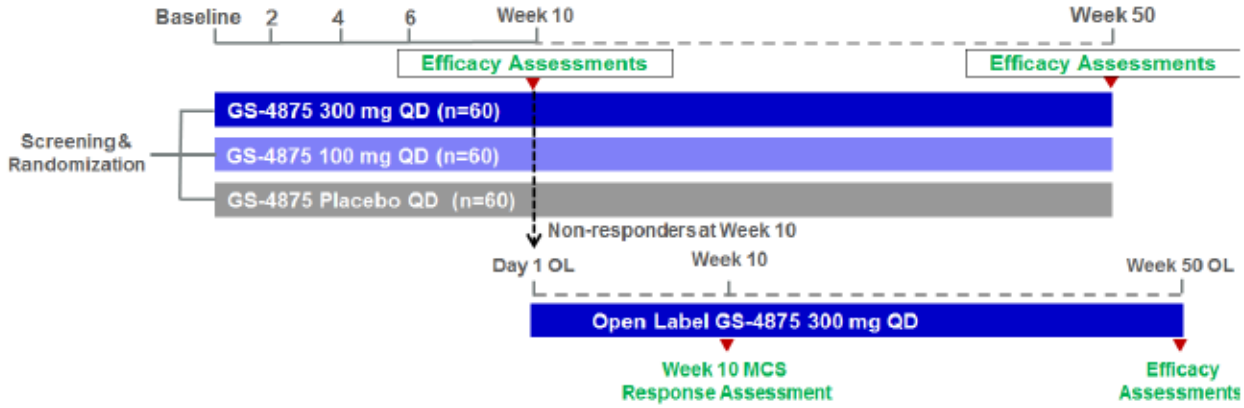
3. STUDY DESIGN

This is a Phase 2, blinded, randomized, placebo-controlled study evaluating the efficacy and safety of GS-4875 for the treatment of subjects with moderately to severely active UC. The objectives and associated endpoints of this study are described in Section 2.

3.1. Study Design

A schematic of this study design is provided in Figure 3-1.

Figure 3-1. Study Design



Abbreviations: QD once daily

This study includes:

- Screening period (Days 30 to 1)
- Baseline/Randomization (Day 1)

  Approximately 180 subjects who meet protocol eligibility criteria will be randomized in a 1:1:1 ratio to 1 of 3 treatment groups as follows:

  Treatment group 1 (n 60): GS-4875 300 mg once daily

  Treatment group 2 (n 60): GS-4875 100 mg once daily

  Treatment group 3 (n 60): Placebo once daily

  Treatment assignments will be stratified according to the sum (≤ 6 or > 6) of 3 MCS subscores for Stool Frequency, Rectal Bleeding, and Endoscopic Findings at Screening.

- Blinded Treatment phase (Day 1 up to Week 50)

  At Week 10 visit, all subjects will have an efficacy assessment.

  - Until response can be assessed based on Week 10 results, subjects will continue on their current assigned study drug regimen. Subjects who achieve MCS Response (Section 2) based on results from Week 10 will continue in the Blinded Treatment phase. All subjects who do not achieve MCS Response will discontinue the Blinded Treatment phase and have the option to enter the open-label (OL) phase.
  - Subjects with insufficient data to assess MCS Response will discontinue study drug and are not eligible for the OL Treatment phase.

- Open-label Treatment phase (OL Day 1 up to OL Week 50)

  OL Day 1 visit should occur within 14 days of Blinded Treatment phase Week 10 visit unless otherwise approved by the medical monitor.

  At OL Week 10 visit, all subjects will have an efficacy assessment.

  - Until response can be assessed based on Week 10 results, subjects will continue OL study drug. Subjects who achieve MCS Response (Section 2) based on results from OL Week 10 will continue in the OL Treatment phase. All subjects who do not achieve MCS Response will discontinue study drug.
  - Subjects with insufficient data to assess MCS Response will discontinue study drug.

- Gilead Data Review Committee

  After approximately 90 subjects complete the Week 10 visit or discontinue from the study prior to Week 10, the GDRC will review endpoint data for potential study termination due to lack of efficacy.

- Unblinding

  The study will be unblinded when all randomized subjects (approximately 180) have either completed the Blinded Treatment phase Week 10 visit and all associated efficacy and safety assessments, or discontinued the study before Week 10.

  After study-wide unblinding, subjects who were receiving placebo will discontinue study drug. Subjects should attend the clinic at their next scheduled study visit or earlier, and undergo the ET assessments followed by the Posttreatment (PTx) assessments 30 days after the last dose of study drug.

  After study-wide unblinding, subjects who were receiving blinded GS-4875 300 mg and GS-4875 100 mg will remain on the same dose. These subjects will continue the Blinded Treatment phase visit schedule up to Week 50.

- Posttreatment (PTx) Assessments

  Subjects who discontinue study drug will return 30 days after the last dose for PTx assessments.

3.2. Duration of Treatment

In the Blinded Treatment phase, randomized subjects may receive a maximum of 50 weeks of treatment.

Subjects, who move to the OL Treatment phase, will have received 10 weeks of blinded treatment and may receive up to 50 weeks of OL treatment. Thus, total duration of treatment may be a maximum of 60 weeks.

3.2.1. Rationale for Study Design

This study is designed as a blinded, randomized, placebo-controlled study.

This study has been designed to minimize bias that could be introduced by subject or physician knowledge of the randomized treatment assignment because the efficacy endpoints utilize subject-reported and physician-reported components in the MCS. Investigators, subjects, and all Sponsor personnel involved in the conduct of the study will be blinded to randomized treatment assignment. As UC has a relapsing and remitting course, the use of a placebo comparison for safety and efficacy endpoints will ensure that a treatment effect is being assessed.

Assessment of the efficacy of treatment will be made after 10 weeks of treatment in the Blinded Treatment phase. This duration is considered appropriate based on evidence from ozanimod and tofacitinib clinical studies demonstrating that 8 weeks of treatment was sufficient for improvement of signs and symptoms of UC {Feagan 2013, Sandborn 2016, Sandborn 2017}. The maintenance of response through Week 50 will be explored in subjects who demonstrate a MCS response at Week 10 in the Blinded Treatment phase.

Subjects who do not demonstrate a MCS response at Week 10 will begin treatment with GS-4875 300 mg for 10 weeks in the OL Treatment phase. The OL Treatment phase will thereby explore the effect of dose escalation in subjects treated with GS-4875 100 mg in the Blinded Treatment phase, who did not achieve MCS response, and will also explore the effect of GS-4875 300 mg for an additional 10 weeks in patients treated with GS-4875 300 mg in the Blinded Treatment phase, who did not achieve MCS response. In addition, placebo-treated subjects who do not achieve MCS response at Week 10 in the Blinded Treatment phase can begin treatment with GS-4875 300 mg in the OL Treatment phase thereby ensuring that every enrolled subject may have access to GS-4875. An assessment of the efficacy of GS-4875 300 mg in the OL Treatment phase will occur after 10 weeks of treatment. Subjects who achieve MCS response in the OL Treatment phase may continue treatment with open-label GS-4875 300 mg until Week 50.

GS-US-365-4237 is a proof-of-concept study of GS-4875, a first-in-class TPL2 inhibitor, in subjects with UC. In consideration of this early stage of development for GS-4875 with a novel and unproven mechanism of action, periodic assessments of GS-4875 safety and efficacy will be performed in this study by the independent DMC and GDRC, respectively. Neither of these committees will include personnel involved in the conduct of the study. Early periodic efficacy and safety assessments in this Phase 2 proof-of-concept study with GS-4875 will appropriately balance the safety of subjects that participate in this clinical trial with the ability to inform pivotal Phase 3 clinical trials based on the results from an adequately powered and blinded study.

When all randomized subjects (approximately 180) have either completed the Blinded Treatment phase Week 10 visit and all associated efficacy and safety assessments, or discontinued the study before Week 10, a Week 10 safety and efficacy analysis will be performed to inform study discontinuation or further development of GS-4875 for the treatment of UC. For further details, see Section 8.2.2 Week 10 Analysis.

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 180 subjects who meet all eligibility criteria at screening will be randomized to receive GS-4875 100 mg, GS-4875 300 mg, or placebo in a 1:1:1 ratio.

It is the responsibility of the investigator to ensure that subjects are eligible to participate in the study prior to randomization or enrollment and throughout the study. Entry into screening does not guarantee enrollment into the study. In order to manage the total trial enrollment, Gilead may suspend screening and/or enrollment at any site or trial-wide at any time.

4.2. Inclusion Criteria

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

1) Must have the ability to understand and sign a written informed consent form, which must be obtained prior to initiation of any study procedures.

2) Males, or non-pregnant, non-lactating females, at least 18 years of age based on the date of the screening visit.

3) UC of at least 3 months duration before randomization confirmed by endoscopy and histology at any time in the past AND a minimum disease extent of 15 cm from the anal verge. Documentation of endoscopy and histology consistent with the diagnosis of UC must be available in the source documents prior to the initiation of screening.

4) Moderately to severely active UC as determined during screening by a centrally read endoscopy score ≥ 2, a Rectal Bleeding subscore ≥ 1, a Stool Frequency subscore ≥ 1, and Physicians Global Assessment (PGA) of ≥ 2 as defined by the Mayo Clinic Score (Appendix 4); total MCS must be between 6 and 12, inclusive.

5) Previously demonstrated an inadequate response (primary non-response) or loss of response (secondary non-response) to a TNFα inhibitor (ie, infliximab, adalimumab, golimumab, or biosimilars). The induction treatment regimen resulting in inadequate response or loss of response should have been in accordance with local prescribing information/guidelines or as outlined below.

   a) Infliximab: 5 mg/kg at Weeks 0, 2, and 6

   b) Adalimumab: 160 mg on Day 1 (given in 1 day or split over consecutive days), followed by 80 mg 2 weeks later (Day 15), 40 mg 2 weeks later (Day 29) and every 2 weeks thereafter until Day 57

   c) Golimumab: 200 mg on Day 1 followed by 100 mg at Week 2

6) May be receiving concomitant therapy for UC at the time of enrollment as specified in Section 5.4, provided the dose prescribed has been stable as indicated prior to randomization.

7) A surveillance colonoscopy is required prior to screening in subjects with a history of UC for 8 or more years, if one was not performed in the prior 24 months.

8) Meet the following tuberculosis (TB) screening criteria:

   a) No evidence of active TB, latent TB, or inadequately treated TB as evidenced by 1 of the following:

      i) A negative QuantiFERON test or equivalent assay reported by the central lab at screening or within 90 days prior to randomization date.

      OR

      ii) A history of fully treated active or latent TB according to local standard of care. Investigator must verify adequate previous anti-TB treatment and provide documentation; these subjects do not require QuantiFERON testing and eligibility must be approved by the sponsor prior to enrollment in the study.

   AND

   b) A chest radiograph (views as per local guidelines with the report or films available for investigator review) taken at screening or within the 4 months prior to randomization without evidence of active or latent TB infection.

9) Laboratory assessments at screening within the following parameters:

   a) Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and total bilirubin $\leq 2 \times$ upper limit of normal (ULN)

   b) Estimated glomerular filtration rate (eGFR) $\geq$ 60 mL/min (1.0 mL/sec) as calculated by the CKD-EPI {Inker 2012}cystatin C formula as described in Section 6.9.5.2.

   c) Hemoglobin $\geq$ 8 g/dL ($\geq$ 80 g/L)

   d) Absolute neutrophil count (ANC) $\geq 1.5 \times 10^3/\mu L$ ($\geq$ 1.5 GI/L)

   e) Platelets $\geq 100 \times 10^3/\mu L$ ($\geq$ 100 GI/L)

   f) White blood cells (WBC) $\geq 3 \times 10^3/\mu L$ ($\geq$ 3 GI/L)

   g) Absolute lymphocyte count $\geq 0.75 \times 10^3/\mu L$ ($\geq$ 0.75 GI/L)

10) Stool sample test result negative for enteric pathogens

11) Stool sample test result negative for ova and parasites unless approved by the medical monitor.

12) Negative HIV antibody test.

13) Negative hepatitis B virus (HBV) surface antigen test. Subjects with negative hepatitis B virus surface antigen (HBsAg) test and positive hepatitis B virus core antibody (HBcAb) test must have a HBV DNA < lower limit of quantification (LLOQ).

14) Negative hepatitis C virus (HCV) antibody test or HCV RNA < LLOQ as described in Section 6.9.5.6.

15) Negative urine drug screen result. A positive drug screen will exclude subjects unless it can be explained by the use of a medication (prescription or nonprescription) that is being used under the direction of a physician. Cocaine use is exclusionary.

16) Females of childbearing potential (as defined in Appendix 8) must have a negative pregnancy test result at screening and Day 1 prior to randomization.

17) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must be willing to use protocol-specified method(s) of contraception as described in Appendix 8.

4.3. Exclusion Criteria

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

1) Currently displaying clinical signs of acute severe colitis, fulminant colitis, or toxic megacolon.

2) Prior surgery for UC.

3) Subjects who are likely to require any type of major surgery during the study. Cataract surgery, breast surgery without reconstruction, laparoscopic cholecystectomy, laparoscopic tubal ligation and most cutaneous, superficial, endoscopic and arthroscopic procedures can be considered minor surgeries.

4) Have had any major surgery or trauma within 8 weeks prior to randomization.

5) History or evidence of incompletely resected colonic mucosal dysplasia.

6) History of malignancy in the last 5 years except for subjects who have been treated or resected for either non-melanoma skin cancer or cervical carcinoma in situ.

7) History of lymphoproliferative disorder, lymphoma, leukemia, myeloproliferative disorder, or multiple myeloma.

8) Any chronic medical condition (including, but not limited to cardiac or pulmonary disease) or psychiatric problem (including, but not limited to alcohol or drug abuse) that, in the opinion of the investigator or sponsor, would make the subject unsuitable for the study or would prevent compliance with the study protocol.

9) History of immunodeficiency syndrome.

10) Have a stoma or ileoanal pouch.

11) Dependence on total parenteral nutrition.

12) Have a transplanted organ with exception of a corneal transplant.

13) Active clinically significant infection, or any infection requiring hospitalization or treatment with intravenous anti-infectives within 8 weeks of randomization; or any infection requiring oral anti-infective therapy within 6 weeks of randomization.

14) History of opportunistic infection.

15) History of symptomatic herpes zoster within 16 weeks of randomization, or any history of disseminated herpes simplex, disseminated herpes zoster, ophthalmic zoster, or central nervous system zoster.

16) Currently on any chronic systemic (oral or intravenous) anti-infective therapy for chronic infection (such as pneumocystis, cytomegalovirus, herpes zoster, or atypical mycobacteria).

17) Use of prohibited concomitant medications as described in Section 5.4.2.

18) Administration of a live or attenuated vaccine within 4 weeks of randomization (Section 5.5)

19) Females who may wish to become pregnant and/or plan to undergo egg donation or egg harvesting for the purpose of current or future fertilization during the course of the study and up to 7 days after last dose of the study drug.

20) Male subjects unwilling to refrain from sperm donation for at least 7 days after last dose of the study drug.

21) Known hypersensitivity to GS-4875, its metabolites, or formulation excipients.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding, and Treatment Codes

5.1.1. Randomization

An interactive web response system (IWRS) will be employed to manage subject randomization, treatment assignments, and study drug supplies. It is the responsibility of the investigator to ensure that subjects are eligible for the study prior to enrollment. The IWRS will assign subjects with a subject ID at the time of enrollment.

5.1.2. Blinding

This is a blinded study where the sponsor Gilead is unblinded as described in Section 5.1.3 and the investigators and subjects are blinded.

Blinding of study treatment is critical to the integrity of this clinical trial. However, specified personnel may be unblinded based on their study role. Study drug will be dispensed by the study pharmacist, or designee, in a blinded fashion to the subjects. The Pharmacokinetics File Administrator, or designee, in Bioanalytical Operations and/or Clinical Data Management, who facilitates the data transfer of PK files between Gilead and vendors, will be unblinded. Individuals in Clinical Packaging & Labeling or Clinical Supply Management who have an Unblinded Inventory Manager role in the IWRS system for purposes of study drug inventory management will remain unblinded. Individuals in Pharmacovigilance and Epidemiology (PVE) responsible for safety signal detection (Section 7.8), investigational new drug (IND) safety reporting and/or expedited reporting of suspected unexpected serious adverse reactions (SUSARs) may be unblinded to individual case data and/or group level summaries. The contract research organization (CRO) biostatisticians and programmers will be unblinded for the DMC data reviews and safety surveillance.

5.1.3. Planned Interim Unblinding

To assess the efficacy of GS-4875 for potential study termination due to lack of efficacy, a Gilead internal unblinded team, the GS-US-365-4237 GDRC, independent of the blinded study team, will be assembled to review the unblinded study results. The GDRC will consist of at least 1 representative from Gilead Clinical Research, Biostatistics, PVE, and Regulatory Affairs, and may include other personnel as necessary including external consultants with expertise in IBD. The GDRC will keep the unblinded information confidential. Site personnel, subjects, Gilead Medical Monitor, Gilead/CRO staff directly interacting with the study center or members of the GS-US-365-4237 Study Management Team will not be unblinded to the subject treatment assignment and will not have access to unblinded study data. The GDRC will be granted access to unblinded clinical data at the individual subject and/or group summary level, including treatment assignments, to review the interim analysis described in Section 8.2.

The membership, conduct, and meeting schedule of the GDRC will be specified in the Gilead Data Review Committee Charter.

5.1.4. Procedures for Breaking Treatment Codes

Treatment assignment should remain blinded unless knowing a subject's treatment assignment is necessary for medical care. In the event of a medical emergency where breaking the blind is required to provide medical care to the subject, the investigator may obtain treatment assignment directly from the IWRS system for that subject. Gilead recommends, but does not require, that the investigator contact the medical monitor before breaking the blind. The rationale for unblinding must be clearly explained in source documentation, along with the date on which the treatment assignment was obtained. If a subject's treatment assignment is unblinded, the investigator is required to promptly contact the medical monitor and the subject will be discontinued from study drug.

5.2. Description and Handling of GS-4875

5.2.1. Formulation

GS-4875 tablets are available in 50 mg and 150 mg strengths. Both strengths of the GS-4875 tablets are white, plain-faced, capsule-shaped, film-coated tablets. In addition to the active ingredient, GS-4875 tablets also contain copovidone, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, macrogol, and talc.

Placebo tablets to match the GS-4875 tablets will be used for blinding purposes. Placebo-to-match (PTM) GS-4875 tablets are identical in size, shape, color, and appearance to both strengths (50 mg and 150 mg) of active GS-4875 tablets. PTM tablets contain lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, macrogol, and talc.

5.2.2. Packaging and Labeling

GS-4875 tablets and matching placebo tablets are packaged in white, high density polyethylene bottles. Each bottle contains 30 tablets, silica gel desiccant and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum-faced liner.

Study drug(s) to be distributed to centers in the United States (US) and other participating countries shall be labeled to meet applicable requirements of the United States Food and Drug Administration (FDA), European Union (EU) Guideline to Good Manufacturing Practice-Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.2.3. Storage and Handling

GS-4875 and PTM tablets should be stored below 30 °C (86 °F). Storage conditions are specified on the label. Until dispensed to the subjects, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure the stability and proper identification, study drugs should not be stored in a container other than the container in which they were supplied. Keep the container tightly closed to protect from moisture. Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

5.3. Dosage and Administration of GS-4875

The study medication will consist of GS-4875 50 mg tablets, GS-4875 150 mg tablets, and PTM tablets for oral administration.

The treatments administered to each treatment group in the Blinded Treatment phase are as follows:

- **Treatment group 1:** (GS-4875 300 mg) 2 GS-4875 150 mg tablets, orally once daily
- **Treatment group 2:** (GS-4875 100 mg) 2 GS-4875 50 mg tablets, orally once daily
- **Treatment group 3:** (Placebo) 2 PTM tablets, orally once daily

The treatment administered in the OL Treatment phase is as follows:

- **Open-label Treatment:** (GS-4875 300 mg) 2 GS-4875 150 mg tablets, orally once daily

The treatments administered to each treatment group, after the study is unblinded, as described in Section 3, are as follows:

- **Treatment group 1:** (GS-4875 300 mg) 2 GS-4875 150 mg tablets, orally once daily
- **Treatment group 2:** (GS-4875 100 mg) 2 GS-4875 50 mg tablets, orally once daily
- **Treatment group 3:** Placebo subjects discontinue study drug

GS-4875 should not be administered with food.

For missed dose(s) of study medication, subjects should be instructed to take the missed dose(s) of study medication as soon as possible during the same day. If the missed dose is not taken on the original day, then subjects should not take the missed dose and the missed dose should be returned to the study drug bottle. Subjects should be cautioned not to double the next dose (ie, taking the missed dose of study drug with that day's dose).

5.3.1. Rationale for Dose Selection

Given the novelty of targeting the TPL2 pathway, GS-4875 dose selection was guided by the goal to demonstrate a dose/exposure efficacy relationship. The 300 mg dose was selected such that trough drug levels, based on Phase 1 data, would be EC_{60} for the in vitro LPS-stimulated phosphorylated ERK (pERK) assay in human whole blood. The 100 mg dose was selected such

that simulations of trough drug levels, which were based on the Phase 1 data, would be EC_{50} at trough. The selection of these doses of GS-4875 (100 and 300 mg) is supported by the safety and PK data in the first-in-human Study GS-US-365-4233.

5.4. Prior and Concomitant Medications

All medications taken up to 30 days prior to the screening visit through the end of study (30 days after the last dose of study drug) need to be recorded in the source documents and on the electronic case report form (eCRF). At each study visit, the study center will record all medications taken by the subject since the last visit or during the visit (as applicable). All concomitant medications (prescription, peri-procedural medications, over-the-counter medications, including vaccines, vitamins, herbal, dietary supplements, and minerals) must be recorded in the concomitant therapy section of the eCRF.

Subjects using oral contraceptives or patch contraceptives must use other methods of contraception while on study. Please refer to Appendix 8 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

Effective therapies should not be discontinued for the sole purpose of participating in this study. Subjects may receive medications as supportive care or to treat AEs as deemed necessary by the investigator or the subject's physician. Based on their clinical judgment, investigators and treating physicians should do whatever is medically appropriate to manage subjects. As described below, changes in concomitant medications may impact a subject's participation in the study. The medical monitor can be consulted prior to initiation of new medications for the treatment of UC.

5.4.1. Allowed Concomitant Medications for UC

The allowed concomitant medication(s) for UC should be maintained at a stable dose for the duration of the study. Subjects on corticosteroids for the treatment of UC at the time of randomization should initiate a steroid taper after the Week 10 Visit (Section 5.4.1.1).

The allowed medications for UC are as follows:

- Oral mesalamine compounds (5-ASA) provided the dose prescribed has been stable for at least 4 weeks prior to randomization.
- Thiopurines (eg, azathioprine, 6-MP) and methotrexate provided the dosing duration must be for at least 8 weeks prior to randomization and the dose must have been stable for at least 4 weeks prior to randomization
- Systemically absorbed corticosteroids prescribed at a stable dose equivalent to $\leq$ 30 mg/day prednisone or budesonide prescribed at a stable dose of $\leq$ 9 mg/day. The doses prescribed must have been stable for 2 weeks prior to the screening endoscopy.

Due to the potential for drug-drug interactions, sulfasalazine is prohibited from 2 weeks prior to the screening endoscopy and throughout treatment with study drug.

Changes to allowed concomitant medications for UC may confound the efficacy and safety assessments of GS-4875. Therefore, subjects who start or increase the dose (compared with the dose at Day 1) of the above allowed concomitant medications, during either the Blinded Treatment phase or the OL Treatment phase, must discontinue study drug and study participation.

5.4.1.1. Corticosteroid Tapering

A steroid taper should be initiated after MCS Response had been evaluated at Week 10 (Blinded Treatment phase or OL Treatment phase) and it is determined that the subject has achieved MCS response and will continue on study. The timing of the steroid taper is at the discretion of the investigator but should begin no later than Week 14. The dose should be reduced at a rate starting at 2.5 mg per week up to and including 5 mg per week (or equivalent taper if not prednisone) until the subject is no longer on steroids. Subjects who are on budesonide should have their daily dose reduced by 3 mg every 3 weeks until they are completely off steroids. For subjects undergoing taper, steroids may be increased or re-started at doses up to and including their Blinded Treatment phase Day 1 dose if return of symptoms is apparent. Subjects who are unable to steroid taper are allowed to continue in the study. Subjects who need to increase steroid dose or intensify steroid treatment dose over their baseline dose must be discontinued from study drug.

5.4.2. Prohibited Concomitant Medications

Co-administration of CYP3A inhibitors may increase GS-4875 exposure. In a drug-drug interaction study of GS-4875 co-administered with voriconazole (strong CYP3A inhibitor), GS-4875 exposures were significantly increased. Therefore, co-administration of strong or moderate CYP3A inhibitors with study drug are prohibited.

Co-administration of CYP3A inducers may decrease GS-4875 exposure. In a drug-drug interaction study of GS-4875 co-administered with multiple dose rifampin (CYP3A inducer), GS-4875 exposures were reduced. Therefore, co-administration of strong or moderate CYP3A inducers with study drug is prohibited.

In vitro data indicate that GS-4875 is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Co-administration of P-gp and BCRP inhibitors may increase GS-4875 exposure. Therefore, co-administration of P-gp and BCRP inhibitors are not allowed with study drug. Co-administration of P-gp inducers may decrease GS-4875 exposure. Therefore, co-administration of P-gp inducers are not allowed with study drug.

In vitro data suggest that GS-4875 has the potential to inhibit MATE1, OATP1B1, OATP1B3, and OATP2B1. GS-4875 has the potential to increase the exposure of MATE1 and OATP sensitive substrates. Therefore, co-administration of MATE1 and OATP sensitive substrates with study drug is prohibited.

In vitro data suggest that GS-4875 has the potential to inhibit P-gp and BCRP. Co-administration of P-gp and BCRP sensitive substrates with a narrow therapeutic index is prohibited.

Co-administration of GS-4875 with sulfasalazine may increase exposure of sulfasalazine. Therefore, sulfasalazine is prohibited 2 weeks prior to screening endoscopy through the end of treatment. Besides sulfasalazine, other mesalamine-based medications may be co-administered with GS-4875.

For more information around GS-4875 drug-drug interactions refer to the GS-4875 IB and Section 1.3.3.1. Examples of representative medications which are prohibited are presented in Table 5-1. If a prohibited concomitant medication with potential drug-drug interactions is taken by a subject, investigators must contact the medical monitor.

Table 5-1. Examples of Prohibited Concomitant Medications for Potential Drug-Drug Interactions[a,b]

Possible Mechanism of Action or Drug Class	Agents Disallowed	Prohibited Period
Strong CYP3A Inhibitors	clarithromycin, conivaptan, itraconazole, ketoconazole, nefazodone, posaconazole, telithromycin, voriconazole, ritonavir, cobicistat, telaprevir, boceprevir, idelalisib	2 weeks prior to randomization through the end of treatment
Strong CYP3A Inducers	carbamazepine, phenytoin, rifampin, fosphenytoin, pentobarbital, primidone, rifabutin, rifapentine, phenobarbital, oxcarbazepine, mitotane, avasimibe	2 weeks prior to randomization through the end of treatment
Moderate CYP3A Inhibitors	fluconazole, erythromycin, diltiazem, dronedarone, aprepitant, imatinib, verapamil, tofisopam, ciprofloxacin, cimetidine, cyclosporine[c], Schisandra sphenanthera	2 weeks prior to randomization through the end of treatment
Moderate CYP3A Inducers	efavirenz, tipranavir/ritonavir, bosentan, thioridazine, nafcillin, talviraline, lopinavir, modafinil, etravirine, lersivirine, semagacestat, genistein	2 weeks prior to randomization through the end of treatment
P gp Inhibitors	amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, propafenone, quinidine, ranolazine, ritonavir, telaprevir, verapamil	2 weeks prior to randomization through the end of treatment
P gp Inducers	rifampin, phenytoin, carbamazepine, rifabutin, rifapentine	2 weeks prior to randomization through the end of treatment
BCRP Inhibitors	cyclosporine[c], gefitinib, sulfasalazine[c], curcumin, eltrombopag	2 weeks prior to randomization through the end of treatment
OATP1B1, OATP1B3, and OATP2B1 Substrates	asunaprevir, atorvastatin, bosentan, cerivastatin, danoprevir, docetaxel, fexofenadine, paclitaxel, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin	2 weeks prior to randomization through the end of treatment
MATE1 Sensitive Substrates	dofetilide, metformin	2 weeks prior to randomization through the end of treatment
P gp Sensitive Substrates	dabigatran, digoxin, fexofenadine	2 weeks prior to randomization through the end of treatment

Possible Mechanism of Action or Drug Class	Agents Disallowed	Prohibited Period
BCRP Sensitive Substrates	rosuvastatin, sulfasalazine[d]	2 weeks prior to randomization through the end of treatment
Herbal/Natural Supplements[e]	Grapefruit juice, St John's Wort	2 weeks prior to randomization through the end of treatment

a Not all of these example medications may be approved in each of the countries where the study is being conducted; please refer to local product information.
b Table is not all inclusive.
c Cyclosporine is prohibited 2 weeks prior to screening endoscopy through the end of treatment (please refer to Table 5 2).
d Sulfasalazine is prohibited 2 weeks prior to screening endoscopy (please refer to Table 5 2).
e Consult the medical monitor for any herbal/natural supplements not listed that may have potential drug drug interactions with study drug or if it is unknown whether there is a potential drug drug interaction with study drug.

Some medications and treatments may have an impact on the safety of the subjects and/or efficacy assessments of this study. Prohibited concomitant medications that may impact efficacy assessments or impact subject safety are presented in Table 5-2. Subjects that initiate any of these concomitant medications at any time during the Blinded Treatment phase study must be discontinued from study drug and will not be eligible for the OL phase of the study. Subjects that initiate any of these concomitant medications at any time during the OL phase of the study must be discontinued from study drug.

Table 5-2. Prohibited Concomitant Medications that May Impact Efficacy Assessments or Impact Subject Safety

Drug Class	Agents Disallowed	Prohibited Period
TNFα antagonist	infliximab, adalimumab, golimumab, certolizumab, or biosimilar agent	12 weeks prior to randomization or an undetectable serum level on a commercially available assay through the end of treatment
Integrin antagonist	vedolizumab, natalizumab	12 weeks prior to randomization or an undetectable serum level on a commercially available assay through the end of treatment
Interleukin antagonist	ustekinumab	16 weeks prior to randomization or an undetectable serum level on a commercially available assay through the end of treatment
Rectal compounds	rectal mesalamine, rectal corticosteroids	2 weeks prior to screening endoscopy through the end of treatment
Antidiarrheal agents	loperamide, diphenoxylate/atropine	2 weeks prior to screening endoscopy through the end of treatment
UC medication with potential drug-drug interactions	sulfasalazine	2 weeks prior to screening endoscopy through the end of treatment

Drug Class	Agents Disallowed	Prohibited Period
Other (non-biologic)	cyclosporine, thalidomide, tacrolimus, leflunomide, JAK inhibitors, and any investigational agent	2 weeks prior to screening endoscopy through the end of treatment
Investigational biologics	Any investigational biologic agent	12 weeks prior to randomization through the end of treatment (or at least 5 half-lives)
Lymphocyte-depleting therapies	alemtuzumab, cyclophosphamide, total lymphoid irradiation, rituximab, and any other lymphocyte-depleting therapy	Any time before and through the end of treatment

If other prohibited concomitant medications, as presented in Table 5-3 are taken by a subject prior to study participation or initiated during the study, investigators must contact the medical monitor.

Table 5-3. Other Prohibited Concomitant Medications

Drug Class	Agents Disallowed	Prohibited Period
Other biologics	Fecal Microbiota Transplant (FMT), Antibody based or other systemic biologics, eg, denosumab, trastuzumab	Requires medical monitor consultation

5.5. Vaccine Guidelines

- Prior to study participation, it is recommended that the subject's vaccinations be brought up to date according to local vaccination standards.
- Live or attenuated vaccines (including, but not limited to varicella and inhaled flu vaccine) are prohibited within 4 weeks of randomization, throughout the study, and for 12 weeks after the last dose of study drug
- Subjects should be advised to avoid routine household contact with persons vaccinated with live/attenuated vaccine components. General guidelines suggest that a study subject's exposure to household contacts should be avoided for the below stated time periods:

  Varicella or attenuated typhoid fever vaccination avoid contact for 4 weeks following vaccination

  Oral polio vaccination avoid contact for 6 weeks following vaccination

  Attenuated rotavirus vaccine avoid contact for 10 days following vaccination

  Inhaled flu vaccine avoid contact for 1 week following vaccination

- Inactivated vaccines (such as inactivated flu vaccines) should be administered according to local vaccination standards whenever medically appropriate; however, there are no available data on the concurrent use of GS-4875 and its impact on immune responses following vaccination.

5.6. Accountability for Study Drug

The investigator is responsible for ensuring adequate accountability of all used and unused investigational medicinal product (IMP) bottles. This includes acknowledgement of receipt of each shipment of IMP (quantity and condition). All used and unused IMP bottles dispensed to subjects must be returned to the site.

Study drug accountability records will be provided to each study site to:

- Record the date received and quantity of IMP bottles
- Record the date, subject number and the IMP kit number dispensed
- Record the date, quantity of used and unused IMP bottles returned, along with the initials of the person recording the information.

If potential deviations in the manufacture, packaging, or distribution of the medicinal product are identified, then a product complaint should be filed with the sponsor upon identification.

5.6.1. Investigational Medicinal Product Return or Disposal

Please refer to Section 9.1.8.

6. STUDY PROCEDURES

The frequency and timing of study procedures to be conducted for each subject in the Blinded Treatment phase are presented in tabular form in Appendix 2 and in Appendix 3 for the OL Treatment phase. The approximate total amount of blood taken at each visit is included in the Study Procedures Tables in Appendix 2 and Appendix 3. Additional information is provided in the study laboratory manual and vendor manuals.

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

6.1. Subject Informed Consent

At the screening visit, informed consent must be obtained by the investigator or appropriate designee before any protocol-specified procedures occur or any protocol-specified samples are collected. Prior to consenting to the study, each subject should understand the nature of the study and the risks associated with the study as well as the subject participation requirements.

CCI [redacted]

6.2. Sequence of Assessments at Visits

Health-related quality of life (HRQoL) and healthcare resource utilization (HCRU) questionnaires (Sections 6.8.2 and 6.8.3) should be completed prior to any other study procedures.

6.3. Pretreatment Assessments

6.3.1. Screening

Subjects will be screened up to 30 days before randomization to determine eligibility for participation in the study. The following will be completed and documented in source data at screening:

- Obtain written informed consent

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- Review inclusion/exclusion criteria and other protocol restrictions (Section 4)

- The assessments to be completed at the screening visit are outlined in the Study Procedures Table in Appendix 2.

  Important information about safety assessments, clinical laboratory evaluations including serum chemistry, hematology, pregnancy testing, TB, HIV and hepatitis screening, and urinalysis is provided in Section 6.9. Stool samples will be collected at screening to identify any enteric pathogens, for microbiome analysis, and for measuring biomarkers: fecal calprotectin and lactoferrin. The urinalysis at screening will include a drug screen.

- e-Diary instructions

  Subjects must be provided with the electronic diary (e-Diary) device and instructions for daily documentation of Stool Frequency and Rectal Bleeding subscores. These data are used to calculate 2 of the 4 subscores that compose the MCS. Subjects should begin filling out the electronic diary (e-Diary) the day of their initial screening visit and continue to fill it out on a daily basis throughout the remainder of the study.

  Subjects should be counseled that their normal stool frequency (NSF) is the average daily stool count the subject experiences when disease-free (ie, in remission). If the subject has never been in remission, the subject should be counseled that their NSF is when they were healthy (ie, prior to initial onset of signs and symptoms of UC).

- Colonoscopy/Flexible Sigmoidoscopy with biopsies

  Subject diary data and other eligibility criteria should be reviewed prior to scheduling the screening visit endoscopy to ensure a subject is eligible (ie, meets Stool Frequency and Rectal Bleeding requirements) prior to performing the endoscopy, see Appendix 4.

  Collect intestinal biopsies. See Section 6.8.1.2 for more information. Results of screening biopsies will not be provided to the sites; additional samples should be obtained if the investigator requires histological assessment for patient management.

- The Endoscopic Findings subscore will be provided to the sites by the central reader. The value provided by the central reader and the PGA is to be recorded by the investigator (or designee) for central calculation of MCS and determination of study eligibility.

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 30 days of the initiation of screening for randomization into the study. Subjects may be randomized more than 30 days after initial screening if permission is obtained from the medical monitor. If the subject is not randomized within this 30-day window, specific screening evaluation procedures may need to be repeated at the direction of the medical monitor. No more than 1 repeat screening visit is allowed for each subject that was previously screen failed, unless prior written approval has been provided by the sponsor. Refer to Section 6.9.5.1 for more information about laboratory retesting.

6.3.2. Baseline/Day 1 Assessments – Blinded Treatment Phase

The Blinded Treatment phase Day 1 assessments to be completed at this visit are outlined in the Study Procedures Table in Appendix 2 with additional information on assessments provided in Sections 6.8 to 6.12.

Prior to administration of study drug, ensure all Day 1 assessments are completed.

6.3.3. Day 1 Assessments – Open-Label Treatment Phase

The OL Treatment phase Day 1 should occur within 14 days of Blinded Treatment phase Week 10 visit unless otherwise approved by the medical monitor. The OL Treatment phase Day 1 assessments to be completed at this visit are outlined in the Study Procedures Table in Appendix 3 with additional information on assessments provided in Sections 6.8 to 6.12.

Prior to administration of study drug, ensure all Day 1 assessments are completed.

6.4. Randomization and Study Drug Administration – Blinded Treatment Phase

6.4.1. Randomization and Treatment Assignment

Subjects who meet protocol eligibility criteria will be randomized in a 1:1:1 ratio to 1 of 3 treatment groups as described in Section 3.

Randomization, stratification, and study drug dispensing will be managed using an IWR system.

6.4.2. Study Drug Administration

The procedure for administration of the first dose of study drug is as follows:

- Enter subject information in the IWRS to receive treatment assignment
- Dispense study drug as directed by the IWRS
- Instruct the subject on the packaging, storage, and administration of the study drug

  Instruct the subject to take 2 pills at each dosing

  Instruct the subject not to take the study drug with food
- Observe the subject taking the first dose of study drug and record the time of first dose

At each subsequent study drug dispensing visit, authorized personnel will log into the IWRS system for the appropriate bottle number(s) to be dispensed. The bottles dispensed will contain the relevant study medication for the period until the next visit.

6.5. Treatment Assessments

6.5.1. Weeks 2, 4 and 6 – Blinded Treatment & Open-Label Treatment Phases

The Blinded Treatment phase assessments to be completed at these visits are outlined in the Study Procedures Table in Appendix 2 and the OL Treatment phase assessments to be completed at these visits are outlined in the Study Procedures Table in Appendix 3 with additional information on assessments provided in Sections 6.8 to 6.12.

6.5.2. Week 10 – Blinded Treatment & Open-Label Treatment Phases

The Blinded Treatment phase assessments to be completed at this visit are outlined in the Study Procedures Table in Appendix 2 and the OL Treatment phase assessments to be completed at these visits are outlined in the Study Procedures Table in Appendix 3 with additional information on assessments provided in Sections 6.8 to 6.12.

At this visit, all subjects will have an efficacy assessment that includes a Colonoscopy/Flexible Sigmoidoscopy with collection of biopsies. Subject diary data entry should be reviewed prior to performing the Week 10 endoscopy to ensure subjects have sufficient data entry to calculate Week 10 MCS subscores. Following the visit, the Endoscopic Findings will be provided to the sites after central read. The value provided by the central reader and the PGA is to be recorded by the investigator (or designee) for central calculation of MCS and subject MCS Response determination.

Until response can be assessed based on Week 10 results, subjects will continue on their current assigned study drug regimen. In the Blinded Treatment Phase, subjects who achieve MCS Response (Section 2) based on results from Week 10 will continue in the Blinded Treatment phase. Subjects who do not achieve MCS Response (Section 2) at Week 10 will have the option to enter the OL Treatment phase. Subjects with incomplete data to assess MCS Response will discontinue study drug and are not eligible for the OL Treatment phase.

In the OL Treatment phase, subjects who achieve MCS Response (Section 2) at Week 10 will continue in the OL Treatment phase. All other subjects will discontinue the OL Treatment phase. Subjects with incomplete data to assess MCS Response will discontinue study drug.

6.5.3. Weeks 14, 18, 22, 26, 30, 34, 38, 42, and 46 - Blinded Treatment & Open-Label Treatment Phases

The Blinded Treatment phase assessments to be completed at these visits are outlined in the Study Procedures Table in Appendix 2 and the OL Treatment phase assessments to be completed at these visits are outlined in the Study Procedures Table in Appendix 3 with additional information on assessments provided in Sections 6.8 to 6.12.

6.5.4. Week 50 - Blinded Treatment & Open-Label Treatment Phases

The Blinded Treatment phase assessments to be completed at this visit are outlined in the Study Procedures Table in Appendix 2 and the OL Treatment phase assessments to be completed at this visit are outlined in the Study Procedures Table in Appendix 3 with additional information on assessments provided in Sections 6.8 to 6.12.

At this visit, all subjects will have an efficacy assessment that includes a Colonoscopy/Flexible Sigmoidoscopy with collection of intestinal biopsies. Following the visit, the endoscopic findings will be provided to the sites after central read. The value provided by the central reader and the PGA is to be recorded by the investigator (or designee) for central calculation of MCS.

6.6. Early Termination (ET) Assessments

If a subject discontinues study drug (eg, as a result of an AE), every attempt should be made to perform the ET assessment and the Posttreatment (PTx) assessment. If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

The Blinded Treatment phase ET assessments are outlined in the Study Procedures Table in Appendix 2 and the OL Treatment phase ET assessments are outlined in the Study Procedures Table in Appendix 3 with additional information on assessments provided in Sections 6.8 to 6.12.

6.7. Posttreatment (PTx) Assessments

All subjects should complete the PTx assessments 30 days after the last dose of study drug.

The Blinded Treatment phase PTx assessments are outlined in the Study Procedures Table in Appendix 2 and the OL Treatment phase PTx assessments are outlined in the Study Procedures Table in Appendix 3 with additional information on assessments provided in Sections 6.8 to 6.12.

6.8. Efficacy Assessments

6.8.1. Mayo Clinic Score (MCS)

The MCS is a scoring system for assessment of UC activity and utilizes 4 subscores: Stool Frequency, Rectal Bleeding, Endoscopic Findings, and the PGA. Each subscore is graded from 0 to 3 and the sum of the subscores (ranging from 0 to 12) determines the overall MCS. Refer to Appendix 4 for details.

The Stool Frequency and Rectal Bleeding subscores are recorded in the electronic diary (e-Diary) and should be collected daily. The PGA is recorded at all study visits and should be captured in source documents. The Endoscopic Finding subscore is reported by the central reader during Screening, Week 10, and Week 50. The score provided by the central reader will be used for all efficacy assessments.

6.8.1.1. e-Diary Instruction & Review

The Stool Frequency and Rectal Bleeding subscores are recorded daily in an e-Diary. Subjects should be provided with the e-Diary and instructions for daily documentation of Stool Frequency and Rectal Bleeding. Subjects should begin filling it out the day of their initial screening visit and continue to fill it out daily throughout the remainder of the study.

Subjects should be counseled about what is meant by NSF: the average daily stool frequency the subject experienced the last time the subject was in remission. If the subject has never been in remission, the NSF is defined as: the average daily stool frequency before the initial onset of signs and symptoms of UC.

For the daily Stool Frequency question, subjects should be counseled that a stool is defined as a visit to the toilet when they have either a bowel movement, pass blood only, pass mucus only, or pass blood and mucus.

For the Rectal Bleeding question, subjects should be counseled to select the category that describes their most severe rectal bleeding over the last 24 hours. Subjects should be counseled to select "No Blood Seen" if they do not have a stool during a given day.

For the purposes of determining eligibility and efficacy assessments, the MCS subscores for Rectal Bleeding and Stool Frequency will be calculated based on the data recorded in the diary for the week prior to the endoscopy. Thus, sites need to ensure subjects are entering eDiary data daily, especially prior to an endoscopy. Subjects must be instructed to document Stool Frequency and Rectal Bleeding daily and site personnel should be monitoring subject's compliance.

6.8.1.2. Colonoscopy/Flexible Sigmoidoscopy with Biopsies

A colonoscopy or flexible sigmoidoscopy will be performed and recorded for central reader review. The Endoscopic Findings subscore will be provided to the investigator by a vendor responsible for central reading. The value provided by the central reader will be used for calculation of MCS at Screening, Week 10, and Week 50.

As stool frequency and rectal bleeding may be affected by bowel preparation for the endoscopy, the stool frequency and rectal bleeding subscores on the day prior to endoscopy, day of endoscopy and day after endoscopy are not included in the calculation of the MCS. For this reason, extended bowel preparation (> 24 hours prior to the procedure) is discouraged as stool frequency and rectal bleeding subscores during this period may be used for the determination of eligibility and response to treatment.

Intestinal biopsies will be collected during endoscopy for efficacy assessments and as biomarker samples. At screening, a total of 9 biopsies should be collected from the colon. At Weeks 10 and 50, 7 biopsies should be collected from the sigmoid colon. Please refer to the lab manuals for specific collection instructions. The number of biopsies, site of collection, and planned analyses are listed below:

Tissue biopsy collection 10 cm proximal to end of active disease (location will vary by subject) during Screening endoscopy only

- **1x FFPE:** Biopsies will be formalin fixed and paraffin embedded (FFPE) for histological and immunohistochemical/immunofluorescence assessment.
- **1x RNAlater:** Biopsies will be collected in RNAlater to measure changes in gene expression.

Tissue biopsy collection from sigmoid colon during endoscopy at Screening, Weeks 10 and 50

- **1x FFPE:** Biopsies will be FFPE for histological and immunohistochemical/immunofluorescence assessment.
- **1x RNAlater:** Biopsies will be collected in RNAlater to measure changes in gene expression.
- **4x Freezing Media:** Biopsies will be collected in freezing media to allow single cell isolation. Cells will be analyzed for RNA expression or characterized for abundance of immune cell subsets and/or markers of intracellular signaling.
- **1x Flash Frozen:** Biopsies will be flash frozen for tissue microbiome and/or proteomic analysis.

6.8.1.3. PGA for MCS Calculation

The PGA subscore is assessed by the investigator and the score recorded for calculation of MCS. (Appendix 4).

6.8.1.4. Evaluation of Disease Worsening using Partial MCS

Disease worsening starting after Week 10 in the Blinded Treatment phase or OL Treatment Phase should be assessed by the investigator using the following criteria: partial MCS (sum of all MCS subscores except Endoscopic Findings) increase of ≥ 3 points to at least 5 points from the respective Week 10 value on 2 consecutive visits OR an increase in partial MCS to 9 points on 2 consecutive visits if the respective Week 10 partial MCS is > 6. The disease worsening visits may include unscheduled visits.

6.8.2. Health-Related Quality of Life (HRQoL) Surveys

The study includes 4 HRQoL Surveys; SF-36, WPAI-UC, EQ-5D-5L, and IBDQ.

HRQoL surveys are to be completed at the site on the site tablet when indicated in the Study Procedures Table (Appendix 2 and Appendix 3). It is recommended for subjects to complete HRQoL surveys before any other study procedures at these visits.

The SF-36 is a HRQoL instrument consisting of 36 questions belonging to 8 domains in 2 components; physical well-being and mental well-being; and covers a 4-week recall period. The remaining item (health transition) is not part of the above domains but is kept separately. The SF-36 is not disease specific and has been validated in numerous health states.

The WPAI-UC is designed to measure the effect of general health and symptom severity on work productivity and regular activities during the past 7 days.

The EQ-5D is a standardized instrument developed by the EuroQol Group as a measure of HRQoL that can be used in a wide range of health conditions and treatments.

The IBDQ is a disease-specific questionnaire comprised of 32 questions divided into 4 health subscales: bowel symptoms (10 questions); systemic symptoms, including sleep disorders and fatigue (5 questions); emotional function such as depression, aggression and irritation (12 questions); and social function, meaning the ability to participate in social activities and to work (5 questions).

6.8.3. Health Care Resource Utilization Survey

HCRU survey is to be completed when indicated in the Study Procedures Table (Appendix 2 and Appendix 3). During visits, it is recommended for the HCRU surveys to be completed after the HRQoLs and before any other study procedures at these visits.

6.9. Safety Assessments

Safety will be assessed using AEs, concomitant medications, PEs (complete and symptom-driven), vital signs, ECGs, and clinical laboratory results. The timing of safety assessments is summarized in Appendix 2 and Appendix 3.

6.9.1. Review of Adverse Events

From the time of obtaining informed consent through the first administration of investigational medicinal product, record all SAEs, as well as any AEs related to protocol-mandated procedures.

Following initiation of study medication, record all AEs, regardless of cause or relationship, until 30-days after last administration of study drug.

For more information on AEs and SAEs, see Section 7.

6.9.2. Review of Concomitant Medications

Review all medications taken up to 30 days prior to the screening visit through the end of study (30 days after the last dose of study drug). At each study visit, record all medications taken by the subject since the last visit or during the visit (as applicable). All concomitant medications (prescription, peri-procedural medications, over-the-counter medications, including vaccines, vitamins, herbal, dietary supplements, and minerals) must be recorded.

6.9.3. Physical Examination

A PE should be performed at the time points indicated in the Study Procedures Table (Appendix 2 and Appendix 3). Any changes from screening will be recorded. At screening, a complete PE including, vital signs, body weight, and height will be performed. Subjects should be instructed to remove shoes prior to measurement of height. Vital signs and weight will be collected at every visit.

A complete PE will include source documentation of general appearance and the following body systems: head, neck, and thyroid; eyes, ears, nose, throat, mouth and tongue; chest (excluding breasts); respiratory; cardiovascular; lymph nodes; abdomen; skin, hair, nails; musculoskeletal; and neurological. Symptom-driven PEs will be performed at all other visits based on reported signs and symptoms.

Vital signs should be taken after the subject has been resting in the seated or supine position for at least 5 minutes and will include pulse rate, respiratory rate, systolic and diastolic blood pressure, and temperature.

6.9.4. 12-lead Electrocardiogram

A resting 12-lead ECG will be performed at the time points indicated in the Study Procedures Table (Appendix 2 and Appendix 3).

The ECG should be obtained after the subject has been resting in the supine position for at least 5 minutes and will include heart rate, inter-beat, QRS, uncorrected QT, morphology, and rhythm analysis. Electrocardiograms will be interpreted by the investigator (or qualified designee) for clinical significance and results will be entered into the eCRF.

6.9.5. Clinical Laboratory Assessments

The clinical laboratory assessments will be performed at the central laboratory. Reference ranges will be supplied by the central laboratory and will be used by the investigator to assess the laboratory data for clinical significance and pathological changes. The details of sample handling and shipment instructions will be provided by the central laboratory in a separate laboratory manual. Refer to the Study Procedures Table (Appendix 2 and Appendix 3) for collection time points and to the Clinical Laboratory Assessment Table (Appendix 7) for more information.

6.9.5.1. Laboratory Retesting Guidance

A single retest of screening labs is permitted only if there is reason to believe the retest value will be within accepted parameters, or if the initial value was either due to a sample processing error or due to an extenuating circumstance.

Laboratory values outside the normal range will be flagged and clinical relevance will be assessed by the investigator. More frequent sampling as well as additional tests may be performed as deemed necessary by the investigator.

Note that in the case where clinically significant laboratory test results are a potential reason for discontinuation from study drug and/or withdrawal from the study, retesting of the affected parameter(s) should be prompt (eg, within 7 days, except serum cystatin C, which should be retested within 14 days).

6.9.5.2. Hematology and Chemistry

Blood samples will be collected by venipuncture [redacted] in the arm at the time points indicated in the Study Procedures Table (Appendix 2 and Appendix 3).

Results of serum creatinine and $eGFR_{cr}$ will not be provided to investigators. Refer to Section 1.4 for more details.

In order to allow for assessment of renal function, cystatin C and $eGFR_{cys}$ will be routinely measured and these data will be provided to investigators.

Values for $eGFR_{cys}$ by the CKD-EPI equation {Inker 2012} are shown below.

Male: $133 \times Min(\frac{SCys}{0.8}, 1)^{-0.499} \times Max(\frac{SCys}{0.8}, 1)^{-1.328} \times 0.996^{Age}$,

Female: $133 \times Min(\frac{SCys}{0.8}, 1)^{-0.499} \times Max(\frac{SCys}{0.8}, 1)^{-1.328} \times 0.996^{Age} \times 0.932$,

where SCys is serum cystatin C in mg/L and age is in years.

6.9.5.3. Urinalysis

Urine samples for clinical laboratory assessments will be collected during study visits for complete urinalysis.

A urine drug test will be performed at screening. A positive drug test result excludes subjects unless it can be explained by a medication that is being used under the direction of a physician (prescription or nonprescription). Cocaine is exclusionary.

6.9.5.4. Stool Samples for Enteric Infections

Samples will be collected to test for enteric pathogens (eg. *Clostridium difficile* toxin, pathogenic *Escherichia coli*, Salmonella species (spp), Shigella spp, Campylobacter spp, Yersinia spp), as well as ova and parasites.

A stool sample should also be collected at any time during the study for culture for pathogenic bacteria, ova and parasites, and *C difficile* toxin assay when a subject becomes symptomatic, including worsening or return of disease activity.

6.9.5.5. Tuberculosis Screening

A TB assessment (QuantiFERON test or equivalent assay) performed by the central lab must be conducted at screening unless the subject has a history of active or latent TB that has been fully treated and the subject's eligibility has been confirmed by the sponsor. Positive or negative TB assessment results must not be repeated. An indeterminate result can be repeated once and the second result (if positive or negative) will be considered final. Two sequential indeterminate results constitute a screen failure. Refer to Section 4.2 for chest radiograph requirements.

6.9.5.6. HBV, HCV, and HIV Screening

Subjects with positive HCV antibody at screening must have further testing for HCV RNA. Subjects with HCV RNA ≥LLOQ will not be eligible for the study. Subjects with positive HCV antibody but HCV RNA < LLOQ are eligible.

Subjects with positive HBsAg will be excluded from the study. Subjects with negative HBsAg and positive HBcAb must have further testing for HBV DNA. Subjects with HBV DNA ≥ LLOQ will not be eligible for the study. Subjects with HBV DNA < LLOQ will be eligible.

Subjects who have HIV infection (positive antibody test) regardless of virologic status are excluded from the study.

6.9.5.7. HBV Monitoring

Subjects with negative HBsAg and positive HBcAb at Screening require HBV DNA monitoring per the Study Procedures Table (Appendix 2 and Appendix 3).

6.9.5.8. Pregnancy Testing

All females of childbearing potential (Appendix 8) must have a serum pregnancy test at screening that will be performed by the central lab and an in-clinic urine pregnancy test on Day 1. Thereafter, in-clinic urine pregnancy tests must be completed every 4 weeks at a minimum. If any pregnancy test is positive, study drug should be immediately interrupted, and the subject should have a serum pregnancy test in clinic performed by the central lab. Confirmed pregnancies should be reported as outlined in Section 7.7.2.1.

CCI [redacted]

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CCI [redacted]

[redacted]

6.11. Biomarker Assessments

Biological specimens will be collected in this study to evaluate the association between systemic and localized biomarkers with disease activity, and treatment response (including efficacy and/or AEs). Biomarkers associated with UC, inflammation, and the TPL2 pathway will be assessed in blood, stool, urine, and colonic biopsies.

Because biomarker science is a rapidly evolving area of investigation, it is not possible to specify prospectively all analyses that will be done on the specimens collected. The analyses outlined below are based upon the current state of scientific knowledge. They may be modified during or after the end of the study based upon new scientific knowledge.

Biomarker sample collection frequency is listed in Study Procedures Table (Appendix 2 and Appendix 3). Samples collected for biomarker assessments will be destroyed no later than 15 years after the end of study.

6.11.1. Blood Biomarker Samples

Blood samples will be collected at Day 1 and Weeks 2, 4, 10, 26, and 50 as outlined in the Study Procedures Table (Appendix 2 and Appendix 3). Please refer to the lab manual for specific collection instructions for the following samples:

- **Blood Sample**: whole blood collected for measurement of the percentages and absolute numbers of immune cell populations, and for potential B-cell/T-cell receptor repertoire sequencing.
- **Plasma and Serum**: whole blood collected to assess levels of circulating proteins, metabolites and miRNAs.
- **Blood Transcriptome**: whole blood collected for RNA isolation to assess changes in gene expression.
- **Peripheral Blood Mononuclear Cells (PBMC)**: whole blood collected for PBMC isolation to characterize immune cell subsets (including transcriptomic analysis of key immune cell subsets), intracellular signaling and/or cell function.

6.11.2. Mandatory Genomic Samples

A blood sample will be obtained for genetic analysis of the UGT1A1*28 genetic variants. Results of the test will be made available to the investigator and the medical monitor to identify subjects for monitoring purposes who may be more susceptible to GS-4875-related hyperbilirubinemia. Results of this test will not be used for determination of eligibility.

A blood sample will be obtained to determine the TPL2 genotype and single nucleotide polymorphisms (SNPs) associated with IBD. The TPL2 genotype and IBD-associated SNPs of each patient will be used to study associations with disease activity and response to GS-4875. Results of the test will not be made available to sites and will not be used for determination of eligibility.

Mandatory genomic samples will be collected at the Day 1 visit.

CCI [redacted]

6.11.4. Stool Biomarker Samples

Stool samples will be collected at Screening and Weeks 10, 26, and 50. Samples can be collected at home by the subject. Please refer to the lab manual for specific collection instruction for the following samples:

- **Stool Microbiome and Metabolome**: samples to assess the stool microbiome and stool metabolome.

- **Stool Calprotectin, Lactoferrin**: samples to assess changes in these markers of inflammation.
- **Additional Stool Aliquot**: samples to assess levels of proteins, metabolites, RNA, and miRNA.

CCI [redacted]

[redacted]

6.12. Study Drug Dispensing

Refer to Section 5.3 for details on study drug dispensation.

6.13. Criteria for Interruption or Discontinuation of Study Treatment

6.13.1. General Considerations

Subjects administered GS-4875 may experience elevations in indirect (unconjugated) bilirubin due to the inhibition of hepatic transporters and UGT1A1 by GS-4875. Subjects with Gilbert's syndrome may be more susceptible to GS-4875-mediated elevations in indirect bilirubin. Hepatic transaminase elevations that occur with hyperbilirubinemia should be evaluated for alternative etiologies.

Increases in serum creatinine have been observed in subjects administered GS-4875 due to inhibition of the renal transporter MATE1 by GS-4875. Consequently, decreases in $eGFR_{cr}$ were observed in subjects administered GS-4875 in Study GS-US-365-5588 (See Section 1.3.3.2). To maintain the study blind, results of serum creatinine and $eGFR_{cr}$ assessments will not be provided to investigators. To allow for assessment of renal function, cystatin C and $eGFR_{cys}$ will be routinely measured and these data will be provided to investigators.

Any subject who develops a new infection during the study should undergo prompt diagnostic testing appropriate for an immunocompromised individual, and the subject should be closely monitored.

6.13.2. Study Drug Interruption Considerations

When feasible, the medical monitor should be consulted prior to study drug interruption. The medical monitor must be informed of all cases of study drug interruption for medical reasons.

Study drug interruption must occur in the following circumstances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree.
- Positive urine pregnancy test.

- Subject is scheduled for elective or emergency surgery (excluding minor skin procedures under local or no anesthesia).

- Any Grade 3 AE assessed as related to study drug.

During the time of study drug interruption for any of the above, the subject may continue to have study visits and to take part in procedures and assessments if deemed medically appropriate by the investigator.

6.13.3. Study Drug Discontinuation Considerations

When feasible, the medical monitor should be consulted prior to study drug discontinuation. The medical monitor must be informed of all cases of study drug discontinuation.

Study drug must be permanently discontinued in the following instances:

- Any Grade 3 or greater rash associated with constitutional symptoms

- Any Grade 4 AE assessed as related to study drug

- Any confirmed Grade 4 laboratory abnormality assessed as related to study drug with the exception of cholesterol, triglyceride, glucose, creatine kinase (CK), or bilirubin abnormalities that are assessed as not clinically significant

- Subjects in the Blinded Treatment phase and OL Treatment phase that initiate or increase the dose above their Blinded Treatment phase Day 1 dose of the following medications for the treatment of UC: oral mesalamine compounds, thiopurines, methotrexate, or systemically absorbed corticosteroids, see Section 5.4.1

- Subject experiences significant disease worsening or loss of response based on 1 or more of the following:

  Investigator judgment

  Initiation of a prohibited medication that may impact efficacy assessments or subject safety (Table 5-2), or surgical intervention for UC

  Disease worsening as described in Section 6.8.1.4

- Any opportunistic infection

- Any infection that meets SAE reporting criteria.

- Febrile neutropenia (temperature $\geq$ 38.3° C or a sustained temperature of $\geq$ 38° C for more than one hour) with absolute neutrophil count of $< 1 \times 10^3/\mu L$ (< 1 GI/L)

- 2 sequential hemoglobin levels < 7.0 g/dL (70 g/L), or anemia requiring transfusion regardless of hemoglobin value

- Complicated herpes zoster infection (with multi-dermatomal, disseminated, ophthalmic, or central nervous system involvement)
- Evidence of active Hepatitis C Virus (HCV) during the study, as evidenced by a HCV RNA ≥ LLOQ
- Evidence of active Hepatitis B Virus (HBV) during the study, as evidenced by a HBV DNA ≥ LLOQ
- Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromises the subject's ability to continue study-specific procedures or is considered to not be in the subject's best interest
- Subject request to discontinue for any reason
- Subject noncompliance
- Pregnancy during the study; refer to Section 7.7.2.1 and Appendix 8
- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC).
- Any of the following abnormal laboratory findings confirmed by immediate repeat testing:

  2 sequential AST or ALT elevations > 3 × ULN AND at least one of the following confirmed values or symptoms:

  - Total bilirubin > 2 × ULN
  - International normalized ratio (INR) > 1.5
  - Symptoms consistent with hepatic injury

  For any subject with an initial AST or ALT elevation > 3 × ULN, at the time of the second confirmatory draw, an INR, prothrombin time) and partial thromboplastin time (PTT) must also be drawn

  Two sequential AST or ALT > 5 × ULN

  Two sequential values for eGFR < 30 mL/min (< 0.5 mL/sec) based on the CKD-EPI cystatin C formula {Inker 2012}

Subjects withdrawing from the study should complete the ET visit, followed by posttreatment assessments 30 days after the last dose of study drug.

Reasonable efforts should be made to contact subjects who are lost to follow up. All contacts and contact attempts must be documented in the subject's file.

6.14. Instructions for Drug Assignments after Study Unblinding

After study-wide unblinding, subjects receiving placebo will discontinue study drug. Subjects should attend the clinic at their next scheduled study visit or earlier and undergo the ET assessments as described in Section 6.6 followed by the Posttreatment assessments 30 days after the last dose of study drug in Section 6.7.

After study-wide unblinding, subjects who were receiving GS-4875 will continue to receive the same dose (as received blinded) of GS-4875. Subjects should attend the clinic at their next scheduled study visit to receive OL GS-4875 and complete study procedures as per their next scheduled study visit.

6.15. End of Study

End of Study is defined as when all subjects have completed treatment plus 30 days follow-up or discontinued from the study.

6.16. Post Study Care

After the subject has completed their study participation, the long-term care of the participant will remain the responsibility of the primary treating physician.

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 medicinal product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or posttreatment complications that occur as a result of protocol specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and must be reported.
- Pre-existing 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 (Section 7.7.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history case report form (CRF).

7.1.2. Serious Adverse Events

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

- Death
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization

- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

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 IMP therapy using clinical judgment and the following considerations:

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

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 using the modified Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 (Appendix 6). For each episode, the highest grade attained should be reported.

If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening) or Grade 5 (fatal) to describe the maximum intensity of the AE. For purposes of consistency with the CTCAE, these intensity grades are defined in Table 7-1.

Table 7-1. Grading of Adverse Event Severity

Grade	Adjective	Description
Grade 1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate	Local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4	Life-threatening	Urgent intervention indicated
Grade 5	Death	Death related AE

* Activities of Daily Living (ADL) Instrumental ADL refer to opening preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
** Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

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

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

7.3.1. Adverse Events

Following initiation of study medication, report all AEs, regardless of cause or relationship, until 30 days after last administration of study IMP must be reported to the CRF/eCRF database as instructed.

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

7.3.2. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occurs after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the protocol-required post treatment follow-up period, must be reported to the CRF/eCRF database and Gilead PVE as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Any SAEs and deaths that occur after the post treatment follow-up visit but within 30-days of the last dose of study IMP, regardless of causality, should also be reported.

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

All AEs and SAEs will be recorded in the CRF/eCRF database within the timelines outlined in the CRF/eCRF completion guideline.

Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead PVE within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.
- If for any reason it is not possible to record the SAE information electronically, ie, the eCRF database is not functioning, record the SAE on the paper SAE reporting form and submit within 24 hours to:
- Gilead PVE Fax: PPD
  Email: PPD
- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines.
- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.
- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.
- Additional information may be requested to ensure the timely completion of accurate safety reports.
- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's CRF/eCRF and the event description section of the SAE form.

7.4. 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, serious adverse drug reactions (SADRs), or 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 GS-4875 IB or relevant local label as applicable.

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

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

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) independent of the underlying medical condition that require medical or surgical intervention or lead to investigational medicinal product interruption 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, and vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE (or SAE) as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (ie, anemia) not the laboratory result (ie, decreased hemoglobin).

Severity should be recorded and graded according to the CTCAE Grading Scale for Severity of AEs and Laboratory Abnormalities (Appendix 6). For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.6. Toxicity Management

The investigator is responsible for monitoring of AEs and laboratory parameters for graded toxicities. Refer to Section 6.13, for guidance on further actions in case of treatment-emergent toxicities.

Management of AEs and laboratory toxicities not covered by Section 6.13 is at the discretion of the investigator. For Grade 3 and 4 toxicities, relationship to study drug, clinical status of subject, and the investigator assessment of subject safety should inform study drug interruption and subsequent re-introduction or permanent discontinuation. Abnormal laboratory values should be repeated when necessary and followed until resolution when clinically appropriate.

Any questions regarding toxicity management or management of specific laboratory values should be directed to the study medical monitor.

7.7. Special Situations Reports

7.7.1. Definitions of Special Situations

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

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

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

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

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labeling (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).

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

7.7.2. Instructions for Reporting Special Situations

7.7.2.1. Instructions for Reporting Pregnancies

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

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

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

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

A spontaneous abortion is always considered to be an SAE and will be reported as described in Sections 7.1.2 and 7.3.2. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead PVE

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

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to Gilead PVE using the pregnancy and pregnancy outcome forms within 24 hours of the investigator becoming aware of the situation.

Monitoring of the subject should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE, fax number PPD or email PPD

Refer to Appendix 8 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.7.2.2. Reporting Other Special Situations

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

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

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

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

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

7.8. Safety Surveillance

Gilead PVE periodically reviews accumulating safety data across completed and ongoing studies within the GS-4875 development program to detect serious and unexpected suspected adverse reactions and clinically important increased rates of previously recognized serious adverse reactions. If, during the periodic review of safety data from clinical studies, a significant numerical imbalance is observed for an AE across treatment groups based on predefined reporting thresholds, a Safety Assessment Committee (SAC) will review unblinded safety data and determine if any actions are necessary to protect subjects involved in the GS-4875 development program. In order to preserve the scientific integrity of the trial data, the SAC members will be Gilead employees who are not involved in the conduct and analysis of studies within the GS-4875 development program.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The objectives of the study are described in Section 2.

8.1.2. Study Endpoints

The study endpoints are listed in Section 2.

8.2. Planned Analyses

8.2.1. Interim Analysis

8.2.1.1. Planned Internal Unblinded Analysis

The GDRC defined in Section 5.1.3 will perform the data review of study data after 90 subjects complete the Week 10 visit or early discontinue from the study. Based on the interim analysis, the GDRC may propose changes in the study design, including potential termination of study due to futility. Ad hoc data reviews at additional timepoints may also be conducted by the GDRC if needed.

The study data that will be provided to the GDRC may be unblinded at individual subject level and/or group level, including the following clinical, endoscopic, histologic and biomarker endpoints: Clinical remission per modified MCS, MCS response, endoscopic response, UC-100, Geboes remission, fecal calprotectin, fecal lactoferrin, and CRP.

Additional data may be provided to the GDRC upon request.

If, based on the review of study data, the GDRC concludes that treatment with GS-4875 does not positively impact the disease under study, the GDRC may request an ad-hoc DMC meeting to further evaluate whether continuation of the trial warranted.

8.2.2. Week 10 Analysis

A Week 10 analysis will be conducted when all randomized subjects (approximately 180) have completed 10 weeks of blinded study drug or discontinued from the study, and associated safety and efficacy assessments have been completed. The study will be unblinded and Week 10 safety and efficacy analyses (including primary analysis [See Section 8.5.1]) will be performed. The purpose of these analyses is to inform study discontinuation or further development of GS-4875 for the treatment of UC. If the sponsor concludes that treatment with GS-4875 has an unfavorable benefit-risk profile, the sponsor will request an ad-hoc DMC meeting. The DMC will be requested to evaluate the available study data and to make recommendation on whether the study should be stopped, continued, or continued with modifications.

8.3. Analysis Conventions

8.3.1. Analysis Sets

8.3.1.1. Efficacy

The primary analysis set for efficacy analysis is the Full Analysis Set (FAS), defined as all randomized subjects who received at least 1 dose of study drug.

Subjects will be analyzed according to the treatment group they were randomized to for the analysis period.

8.3.1.2. Safety

The primary analysis set for safety analyses is the Safety Analysis Set, defined as all subjects who receive at least one dose of study drug.

Subjects will be analyzed according to the study drug they actually received for the analysis period.

All data collected during treatment up to the date of last dose of IMP plus 30 days will be included in the safety summaries.

CCI [redacted]

[redacted]

CCI [redacted]

8.3.1.4. Biomarkers

The Biomarker Analysis Set includes all subjects who receive at least one dose of study drug and have the necessary baseline and on-study measurements to provide interpretable results for the specific parameters of interest.

8.4. Data Handling Conventions

Procedures for handling missing data for MCS (and components) will be described in the statistical analysis plan (SAP).

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The primary analysis will compare each GS-4875 dose group to placebo on the proportion of subjects achieving Clinical Remission per Modified MCS at Week 10. The Cochran-Mantel-Haenszel (CMH) approach adjusting for stratification factors will be used for hypothesis testing of the primary endpoint. For evaluation of clinical remission per modified MCS at Week 10, MCS score at screening will be used as baseline value.

Subjects who do not have sufficient measurements to determine efficacy endpoints will be considered failures (ie, non-responder imputation [NRI]).

8.5.2. Secondary Analyses

The same statistical methods used for analyzing the primary efficacy endpoint will be utilized for analyzing the binary secondary endpoints. Subjects who do not have sufficient measurements to determine the efficacy endpoints will be considered failures (ie, NRI).

CCI [redacted]

[redacted]

8.6. Safety Analysis

All safety data collected on or after the date that IMP was first dispensed up to the date of last dose of IMP plus 30 days will be summarized by treatment group (according to the IMP received). Data for the pretreatment will be included in data listings.

8.6.1. Extent of Exposure

A subject's extent of exposure to IMP data will be generated from the IMP administration data. Exposure data will be summarized by treatment group.

8.6.2. Adverse Events

Clinical and laboratory AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System organ class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT) will be attached to the clinical database.

Treatment-emergent adverse event (TEAE) will be defined as 1 or both of the following:

- Any AE with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug.
- Any AE leading to premature discontinuation of study drug

Summaries (number and percentage of subjects) of TEAEs (by SOC, and PT) will be provided by treatment group. TEAEs will also be summarized by relationship to study drug and severity. In addition, TEAEs leading to premature discontinuation of study drug will be summarized and listed.

8.6.3. Laboratory Evaluations

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

Graded laboratory abnormalities will be defined using the CTCAE in Appendix 6.

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

8.6.4. Other Safety Evaluations

Individual data for PE findings, prior and concomitant medications and medical history will be provided. Twelve-lead ECGs and vital signs measurements will be listed by subject and summarized by incidence of events/abnormalities or descriptive statistics as appropriate.

8.7. Adjustments for Multiplicity

There are no interim analyses for efficacy and no plans to stop this study early for favorable efficacy. The following primary and key secondary endpoints will be tested sequentially at a one-sided Type 1 error rate of 2.5% in the following order:

GS-4875 300 mg vs placebo

1. The proportion of subjects with clinical remission per modified MCS at Week 10
2. The proportion of subjects with endoscopic response at Week 10
3. The proportion of subjects with MCS response at Week 10
4. The proportion of subjects with MCS remission at Week 10
5. The proportion of subjects with histologic remission at Week 10

GS-4875 100 mg vs placebo

6. The proportion of subjects with clinical remission per modified MCS at Week 10
7. The proportion of subjects with endoscopic response at Week 10
8. The proportion of subjects with MCS response at Week 10
9. The proportion of subjects with MCS remission at Week 10
10. The proportion of subjects with histologic remission at Week 10

Testing will stop with the first of these endpoints failing to reach statistical significance and all subsequent endpoints would not be considered for statistical significance and only nominal p-values will be reported. In this way, the overall one-sided Type I error rate in testing these endpoints is controlled at a 2.5% level.

CCI [redacted]

CCI [redacted]

CCI [redacted]

8.9. Biomarker Analysis

Descriptive statistics of baseline and change in biomarkers will be provided at each sampling time by treatment. To evaluate treatment effect, a mixed-effect analysis of variance model will be used to calculate a point estimate and 2-sided 95% CI for the mean percent change from baseline in biomarker level for each treatment group at individual time points. The estimate and 95% CI of difference in mean percent change from baseline between each GS-4875 dose group and placebo will be provided as well.

CCI [redacted]

8.10. Sample Size

A sample size of 60 subjects in the placebo group and 60 subjects in each GS-4875 dose group (n 120 total for GS-4875) will provide approximately 75% power for each GS 4875 dose group comparison to placebo at a 1-sided 0.025 significance level to detect a treatment difference in clinical remission per modified MCS response rate of 17.5% (22.5% on GS-4875 and 5% on placebo) based on Fisher's exact test.

Study GS-US-365-4237 compares GS-4875 to placebo in subjects who previously demonstrated an inadequate response or loss of response to a TNFα inhibitor (TNFα failures). Results from previously conducted studies indicate that placebo response rates for TNFα failures are low, 2.5% to 6.9%, compared to the rates for subjects naive to TNFα inhibitors, 8.7% to 11% {Sandborn 2020a, Sandborn 2012}. Further, across available clinical study results, the definition for clinical remission can vary between studies. For Study GS-US-365-4237, the definition for clinical remission is nearly identical to that used by 2 recently published studies in which the placebo response rates in TNFα failures subgroups were 2.5% and 0% {Sandborn 2020a, Sandborn 2020b}. Accordingly, a conservative placebo response rate of 5% has been utilized in the sample size calculation.

To justify further development, GS-4875 should be as good or better than other drug candidates in development or on the market. A minimum treatment difference of 17.5% was selected for Study GS-US-365-4237 based on data from a similar Phase 2 study in UC which demonstrated a 19.6% treatment difference between study drug and placebo as assessed by Clinical Remission per the Modified Mayo Clinical Score {Sandborn 2020b}. The patient population in this study consisted mainly of biologically experienced subjects (78%) and thus should be similar to the patient population enrolled in Study GS-US-365-4237. In summary, a treatment difference of 17.5% and a placebo response rate of 5% is assumed in the sample size calculation for GS-US-365-4237.

8.11. Data Monitoring Committee

An external multidisciplinary DMC will review the progress of the study and perform interim reviews of study data and provide recommendation to Gilead whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the ET of the study, whether the study should continue as planned, or the study should continue with modifications. The DMC may also provide recommendations as needed regarding modifications to study design.

The initial DMC safety review meeting will occur after approximately 20 subjects either complete the Week 4 visit or discontinue from the study prior to Week 4.

Subsequent DMC meetings for safety review will be held after approximately 60 subjects either complete the Week 4 visit or discontinue from the study and after approximately 90 subjects either complete Week 10 visit or discontinue from the study. The frequency of meetings may be adjusted as requested by the DMC.

The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct and meeting schedule.

While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of the study.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with ICH E6 (R2) Good Clinical Practices 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, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study subject activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC any modifications made to the protocol or any accompanying material to be provided to the subject after initial 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 consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject and the person conducting the consent discussion, and also by an impartial witness if required by IRB or IEC or local requirements. For pharmacogenomics testing, the consent form will inform subjects about genomic testing and sample retention, and their right to receive clinically relevant genomic analysis results. For more information see Section 6.1.

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 or 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 trial. 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 IMP, 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 or IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

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

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria, ie, history, PE, 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 IMP, 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, United States, 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. 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 source data verification within the electronic data capture (EDC) 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 trial, 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, IMP should be destroyed at the site. At the start of the study, the study monitor will evaluate each study center's IMP disposal procedures and provide appropriate instruction for disposal or return of unused IMP supplies. If the site has an appropriate SOP for drug destruction as determined by Gilead Sciences, the site may destroy used (empty or partially empty) and unused IMP supplies as long as performed in accordance with the site's SOP. This can occur only after the study monitor has performed drug accountability during an on-site monitoring visit.

A copy of the site's IMP Disposal SOP or written procedure (signed and dated by the principal investigator [PI] or designee) will be obtained for Gilead site files. If the site does not have acceptable procedures in place, arrangements will be made between the site and Gilead Sciences (or Gilead Sciences' representative) for return of unused study drug supplies.

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

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

9.1.9. Inspections

The investigator will make available all source documents and other records for this trial to Gilead's appointed study monitors, to IRBs or 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 or IEC in accordance with local requirements and receive documented IRB or 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 report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

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

the results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years

The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.

No such communication, presentation, or publication will include Gilead's confidential information (Section 9.1.5).

The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, 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 trial 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.

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11. APPENDICES

Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGEMENT

A Phase 2, Blinded, Randomized, Placebo-Controlled Study Evaluating the Efficacy and Safety of GS-4875 in Subjects with Moderately to Severely Active Ulcerative Colitis

Amendment 2, 19 June 2020

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

PPD

Name (Printed)
Study Director

PPD

Signature

19 June 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 – Blinded Treatment

Period	Screen		Blinded Treatment														Follow-up	
Week		**0**	**2**	**4**	**6**	**10**	**14**	**18**	**22**	**26**	**30**	**34**	**38**	**42**	**46**	**50**	**PTx**	**ET**
Study Day	**-30 to -1**	**1**	**15**	**29**	**43**	**71**	**99**	**127**	**155**	**183**	**211**	**239**	**267**	**295**	**323**	**351**		
Visit Window			**±3**	**±3**	**±3**	**±5**	**±5**	**±5**	**±5**	**±5**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±3**	
Informed Consent	X																	
12 lead ECG	X					X					X					X		X
Physical Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review of Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review of Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Dispensing		X		X	X	X	X	X	X	X	X	X	X	X	X			
Colonoscopy/Flexible Sigmoidoscopy with Biopsies	X					X										X		
PGA for MCS Calculation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Evaluation of Disease Worsening using Partial MCS							X	X	X	X	X	X	X	X	X			
eDiary instruction & review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Stool Sample for Enteric Infections	X																	
Stool Biomarker Samples	X					X				X						X		
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CCI																		
Pregnancy Test	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TB Assessment	X																	

Period	Screen		Blinded Treatment														Follow-up	
Week		0	2	4	6	10	14	18	22	26	30	34	38	42	46	50	PTx	ET
Study Day	-30 to -1	1	15	29	43	71	99	127	155	183	211	239	267	295	323	351		
Visit Window			±3	±3	±3	±5	±5	±5	±5	±5	±7	±7	±7	±7	±7	±7	±3	
HBV, HCV, HIV screening	X																	
HBV Monitoring, As Needed						X			X			X			X			
Hematology & Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fasting Lipids		X	X			X				X						X		
Blood Biomarker Samples		X	X	X		X				X						X		
Mandatory Genomic Samples		X																
CCI																		
CCI																		
CCI																		
HRQoL Surveys		X				X										X		
HCRU Questionnaire		X	X	X	X	X		X		X		X		X		X		
Approximate Total Amount of Blood Taken at This Visit	23.5 mL	44.5 mL	34.0 mL	34.0 mL	12.0 mL	34.0 or 40.0 mL	8.0 mL	8.0 mL	8.0 or 14.0 mL	30.0 mL	8.0 mL	8.0 or 14.0 mL	8.0 mL	8.0 mL	8.0 or 14.0 mL	30.0 mL	8.0 mL	8.0 mL

Appendix 3. Study Procedures Table – Open-Label Treatment

Period	Open-Label Treatment															Follow-up	
Week	**0**	**2**	**4**	**6**	**10**	**14**	**18**	**22**	**26**	**30**	**34**	**38**	**42**	**46**	**50**	**PTx**	**ET**
Study Day	**1**	**15**	**29**	**43**	**71**	**99**	**127**	**155**	**183**	**211**	**239**	**267**	**295**	**323**	**351**		
Visit Window		**±3**	**±3**	**±3**	**±5**	**±5**	**±5**	**±5**	**±5**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±3**	
12 lead ECG					X					X					X		X
Physical Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review of Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review of Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Dispensing	X		X	X	X	X	X	X	X	X	X	X	X	X			
Colonoscopy/Flexible Sigmoidoscopy with Biopsies					X										X		
PGA for MCS Calculation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Evaluation for Disease Worsening using Partial MCS						X	X	X	X	X	X	X	X	X			
eDiary instruction & review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Stool Biomarker Samples					X				X						X		
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CCI																	
Pregnancy Test	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBV Monitoring					X			X			X			X			
Hematology & Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fasting Lipids					X				X						X		
Blood Biomarker Samples	X	X	X		X				X						X		
HRQoL Surveys	X				X										X		

Period	Open-Label Treatment															Follow-up	
Week	**0**	**2**	**4**	**6**	**10**	**14**	**18**	**22**	**26**	**30**	**34**	**38**	**42**	**46**	**50**	**PTx**	**ET**
Study Day	**1**	**15**	**29**	**43**	**71**	**99**	**127**	**155**	**183**	**211**	**239**	**267**	**295**	**323**	**351**		
Visit Window		**±3**	**±3**	**±3**	**±5**	**±5**	**±5**	**±5**	**±5**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±3**	
HCRU Questionnaire	X	X	X	X	X		X		X		X		X		X		
Approximate Total Amount of Blood Taken at This Visit	30.0 mL	34.0 mL	34.0 mL	12.0 mL	34.0 or 40.0 mL	8.0 mL	8.0 mL	8.0 or 14.0 mL	30.0 mL	8.0 mL	8.0 or 14.0 mL	8.0 mL	8.0 mL	8.0 or 14.0 mL	30.0 mL	8.0 mL	8.0 mL

Appendix 4. Modified Mayo Scoring System for Assessment of Ulcerative Colitis Activity

Stool Frequency – *Each subject serves as his or her own control to establish the degree of abnormality of the stool frequency*	☐ 0 Normal number of stools for subject ☐ 1 1 to 2 stools per day more than normal ☐ 2 3 to 4 stools per day more than normal ☐ 3 ≥ 5 stools per day more than normal
Rectal Bleeding – *The daily bleeding score represents the most severe bleeding of the day.*	☐ 0 No blood seen ☐ 1 Streaks of blood with stool less than half the time ☐ 2 Obvious blood (more than just streaks) or streaks of blood with stool most of the time ☐ 3 Blood alone passes
Endoscopic findings – *Assessed by Central Reader (include only for MCS assessment)*	☐ 0 Normal or inactive disease ☐ 1 Mild Disease *(erythema, decreased vascular pattern)* ☐ 2 Moderate Disease *(marked erythema, lack of vascular pattern, friability, erosions)* ☐ 3 Severe Disease *(spontaneous bleeding, ulceration)*
Physician's Global Assessment – *The physician's global assessment acknowledges the three other criteria, the subject's daily recollection of abdominal discomfort and general sense of well being, and other observation, such as physical findings and the subject's performance status.*	☐ 0 Normal ☐ 1 Mild disease ☐ 2 Moderate disease ☐ 3 Severe disease

Appendix 5. Geboes Histological Score Grades

	Subgrades	Structural (Architectural Change)
Grade 0	0.0	No abnormality
	0.1	Mild abnormality
	0.2	Mild or moderate diffuse or multifocal abnormalities
	0.3	Severe diffuse or multifocal abnormalities
Grade 1		**Chronic inflammatory infiltrate**
	1.0	No increase
	1.1	Mild but unequivocal increase
	1.2	Moderate increase
	1.3	Marked increase
Grade 2		**Lamina propria neutrophils and eosinophils**
	2A Eosinophils	
	2A.0	No increase
	2A.1	Mild but unequivocal increase
	2A.2	Moderate increase
	2A.3	Marked increase
	2B Neutrophils	
	2B.0	None
	2B.1	Mild but unequivocal increase
	2B.2	Moderate increase
	2B.3	Marked increase
Grade 3		**Neutrophils in epithelium**
	3.0	None
	3.1	< 5% crypts involved
	3.2	< 50% crypts involved
	3.3	> 50% crypts involved
Grade 4		**Crypt destruction**
	4.0	None
	4.1	Probable local excess of neutrophils in part of crypt
	4.2	Probable marked attenuation
	4.3	Unequivocal crypt destruction
Grade 5		**Erosion or ulceration**
	5.0	No erosion, ulceration, or granulation tissue
	5.1	Recovering epithelium + adjacent inflammation
	5.2	Probable erosion focally stripped
	5.3	Unequivocal erosion
	5.4	Ulcer or granulation tissue

Appendix 6. CTCAE Grading Scale for Severity of Adverse Events

Please refer to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, which can be found at:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae_v5.0.xlsx

For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

Appendix 7. Clinical Laboratory Assessment Table

Hematology	Chemistry	Urinalysis	Other
Hematocrit Hemoglobin Platelet count Red blood cell (RBC) count White blood cell (WBC) count Differentials (absolute and percentage), including: Lymphocytes Monocytes Neutrophils Eosinophils Basophils Reticulocyte count Mean corpuscular volume (MCV)	Alkaline phosphatase Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Direct and indirect bilirubin Total protein Albumin Bicarbonate Blood urea nitrogen (BUN) Calcium Chloride Serum creatinine Serum cystatin C Glucose Phosphorus Magnesium Potassium Sodium Creatine phosphokinase (CPK) $eGFR_{cr}$ $eGFR_{cys}$	Appearance: Blood Color Glucose Leukocyte esterase pH Protein Urobilinogen **Serology** Hepatitis B Surface Ag Hepatitis B Surface Ab Hepatitis B Core Ab HBV DNA Hepatitis C Ab HCV RNA HIV **Pregnancy** *In females of childbearing potential:* Serum pregnancy Urine pregnancy **Lipids** Triglycerides Total cholesterol High-density lipoprotein [HDL] – cholesterol Low-density lipoprotein [LDL] – cholesterol	Urine drug screen for: Amphetamines Cocaine Barbiturates Opiates Benzodiazepines C-reactive protein (hs - CRP) TB Analysis (QuantiFERON or equivalent assay) Stool Samples Microbiome and Metabolome Calprotectin, Lactoferrin Bacterial Stool Culture *C difficile* Toxin Ova and Parasites (O&P) Pharmacokinetics (PK) Serum Immunoglobulin Prothrombin Time Partial thromboplastin time (PTT) International Normalized Ratio (INR)

Appendix 8. 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 post-menopausal, unless permanently sterile or with medically documented ovarian failure. Women who do not meet below criteria for being post-menopausal, are not permanently sterile, or do not have medically documented ovarian failure must have pregnancy testing as outlined by the protocol.

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.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age. Bilateral tubal ligation is not considered permanent sterilization.

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 sterilized by bilateral orchidectomy or has medical documentation of permanent male infertility. Vasectomy is not considered permanent sterilization.

2) Contraception for Female Subjects

a) Study Drug Effects on Pregnancy and Hormonal Contraception

GS-4875 is contraindicated in pregnancy because its teratogenicity/fetotoxicity profile is unknown. GS-4875 is not genotoxic. Clinically relevant drug-drug interactions between hormonally-based contraceptives and GS-4875 are not expected. In vitro studies in HepaRG cells using reference substrates indicate that GS-4875 does not induce CYP1A2, CYP2B6, or CYP3A4 enzymes involved in metabolism of common hormonal contraceptives. The lack of induction potential of GS-4875 on CYP3A4 was further confirmed in a clinical drug-drug interaction study, where multiple dose administration of 450 mg GS-4875 did not affect the pharmacokinetics of midazolam (a prototypical in vivo probe CYP3A4 substrate) (see Section 1.3.3.1). Additionally, clinically relevant inhibition of CYPs during GS-4875 treatment is unlikely, based on in vitro and clinical data. Based on the totality of the in vitro and clinical data, clinically relevant drug interactions between GS-4875 with hormonal contraceptives are not expected . Therefore, hormonal contraceptives may be allowed as a component of a highly effective contraceptive regimen but only when used in conjunction with a barrier method, preferably a male condom (see below). Please refer to the latest version of the GS-4875 IB for additional information.

b) Contraception for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of *highly effective* contraceptive measures. Women must have a negative serum pregnancy test at screening and a negative urine pregnancy test on the Day 1 visit prior to randomization. Pregnancy tests will be performed as defined by the schedule of assessments in the Study Procedures Tables (Appendix 2 and Appendix 3). In the event of a delayed menstrual period (> 1 month between menstruations), a pregnancy test must be performed to rule out pregnancy. This also applies for women of childbearing potential with infrequent or irregular periods.

Female subjects must agree to use 1 of the following methods from screening until 7 days following the last dose of study drug:

- 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:

  Intrauterine device (IUD) with a failure rate of < 1% per year

  Intrauterine hormone-releasing system (IUS) with a failure rate of < 1% per year

  Tubal sterilization

  Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)

  Essure® micro-insert system (provided confirmation of success 3 months after procedure)

OR

- Combination of hormonal contraceptives and barrier methods. Female subjects who wish to use a hormonally-based method must use it in conjunction with a barrier method, preferably a male condom. Female subjects who utilize a hormonal contraceptive as one of their birth control methods must have consistently used the same method for at least 3 months prior to study dosing. Hormonally-based contraceptives and barrier methods permitted for use in this protocol are as follows:

  Barrier methods (each method must be used with a hormonal method)

  - Male condom (with or without spermicide)
  - Female condom (with or without spermicide)
  - Diaphragm with spermicide

- Cervical cap with spermicide
- Sponge with spermicide

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

- Oral contraceptives (either combined or progesterone only)
- Injectable progesterone
- Subdermal contraceptive implant
- Transdermal contraceptive patch
- Contraceptive vaginal ring

All female subjects must also refrain from egg donation and in vitro fertilization during treatment and until at least 7 days after the last study drug dose.

3) Contraception Requirements for Male Subjects

It is theoretically possible that a relevant concentration of study drug may be achieved in a female partner from exposure to the male subject's seminal fluid. Therefore, male subjects with female partners of childbearing potential must use condoms during study participation and for 7 days after the last study of drug dose. Female partners of male study subjects should consider using one of the above methods of contraception as well.

Male subjects must also refrain from sperm donation during treatment and until at least 7 days after the end of study drug dosing.

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. Female condom and male condom should not be used together.

5) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they (or their partner if subject is male) become pregnant at any time during the study, or within 7 days of last study drug dose. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. Male subjects whose partner has become pregnant or suspect she is pregnant during the study are to report the information to the investigator.

Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.7.2.1.

6) Pregnancy Testing

All females of childbearing potential will have urine pregnancy testing every 4 weeks, at a minimum, (in clinic) during their study participation. If a urine pregnancy test is positive, the subject should stop study drug immediately, contact the investigator, and have confirmatory serum pregnancy test in clinic.