CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1, Open-Label, Multiple Dose Study to Evaluate the Pharmacokinetics of Entospletinib in Subjects with Normal and Impaired Hepatic Function	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404	
IND No.:	116416	
EudraCT Number:	Not Applicable	
ClinicalTrials.gov Identifier:	NCT02521376	
Indication:	Oncology	
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PROTOCOL SYNOPSIS
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Study Title:	A Phase 1, Open-Label, Multiple Dose Study to Evaluate the Pharmacokinetics of Entospletinib in Subjects with Normal and Impaired Hepatic Function
IND Number: **EudraCT Number:**	116416 Not Applicable
Study Centers Planned:	Multiple centers in the United States and New Zealand
Objectives:	The primary objective of this study is as follows: • To evaluate the pharmacokinetics of Entospletinib (ENTO) and/or its metabolites (if applicable) in subjects with impaired hepatic function (stratified by smoking status, as appropriate) relative to matched, healthy controls The secondary objectives of this study are as follows: • To evaluate the safety and tolerability of administration of ENTO in subjects with normal and impaired hepatic function • To evaluate the potential impact of smoking on the PK of ENTO in subjects with moderate hepatic impairment
Study Design:	Phase 1, open-label, parallel-group, adaptive, multiple dose study
Number of Subjects Planned:	A minimum of 40 subjects and a maximum of 80 subjects total. **<u>Cohort 1 (Moderate Hepatic Impairment) initial cohort</u>** Up to 40 subjects: 20 with moderate hepatic impairment (10 smokers [at least 8 evaluable] and 10 non-smokers]at least 8 evaluable]), 20 matched healthy controls (at least 8 evaluable healthy controls matched to smokers with moderate impairment, and at least 8 evaluable healthy controls matched to non-smokers with moderate hepatic impairment). **<u>Adaptive Cohort 2 (Severe Hepatic Impairment)</u>** Up to 20 subjects: 10 with severe impairment, up to 10 matched healthy controls, for 8 evaluable subjects per group. Data from healthy subjects in previous cohort who are an appropriate match for a severe hepatic impairment subject may be used.

Adaptive Cohort 3 (Mild Hepatic Impairment)

Up to 20 subjects: 10 with mild impairment, up to 10 matched healthy controls, for 8 evaluable subjects per group. Data from healthy subjects in previous cohort who are an appropriate match for a mild impairment subject may be used.

The 90% CIs will be examined to determine if a meaningful change (≥ 2-fold mean difference from matched controls) in the exposures of ENTO and/or metabolite (if applicable) is identified which would be clinically interpreted. A decision to enroll subjects in adaptive Cohort 2 (Severe Hepatic Impairment) and/or adaptive Cohort 3 (Mild Hepatic Impairment) will be enrolled as determined by safety (treatment-emergent AEs, treatment-emergent laboratory abnormalities, vital signs, safety ECGs) and/or PK data from Cohort 1 (Moderate Hepatic Impairment). Specifically, Cohort 2 will be initiated if supported by safety (treatment-emergent AEs, treatment-emergent laboratory abnormalities, vital signs, safety ECGs) and PK findings from subjects in Cohort 1. Cohort 3 will be enrolled if a clinically meaningful change (≥ 2-fold mean difference from matched healthy controls) in the exposures of ENTO and/or metabolite (if applicable) exposure is identified in non-smoking hepatic impairment subjects in Cohort 1.

Target Population: Male and non-pregnant, non-lactating females subjects aged ≥ 18 years, with varying degrees of hepatic impairment and matched healthy controls. Those with hepatic impairment will be categorized based upon the Child-Pugh-Turcotte (CPT) classification system for hepatic impairment (CPT Class A, B, or C) as recommended by the United States Food and Drug Administration (FDA) and international guidance documents. Within the CPT system, subjects will be assigned to Class A, B, or C based on a cumulative score evaluating the presence and severity of hyperbilirubinemia, hypoalbuminemia, prolongation of international normalized ratio (INR) for coagulation time, ascites, and hepatic encephalopathy. Designations of hepatic impairment will be assigned as follows:

- Class A (mild): CPT score 5-6
- Class B (moderate): CPT score 7-9
- Class C (severe): CPT score 10-15

The control group will consist of matched healthy subjects with normal hepatic function.

Cohort 1 enrollment of hepatic impairment subjects will be an approximate even distribution of subjects who are active cigarette smokers (at least 10 cigarettes/day) and subjects who are current

	non-smokers (no use of tobacco, nicotine-containing or THC-containing products within the last 14 days). Hepatic impairment subjects enrolled in adaptive Cohorts 2 and 3 will be current non-smokers (no use of tobacco, nicotine-containing or THC-containing products within the last 14 days).
Duration of Dosing:	5 days
Study Duration:	20 days
Main Eligibility Criteria:	Eligible subjects will be male and non-pregnant, non-lactating female subjects, aged ≥ 18 years, 18 ≤ BMI ≤ 40, with either impaired hepatic function of CPT classification A, B, or C or with normal hepatic function. Hepatic impairment must have been stable during the 3 months (90 days) prior to study drug administration. Each subject in the control group will be matched to a subject with impaired hepatic function by age (± 10 years), gender, and body mass index (± 20%). Subjects with use of moderate or strong CYP3A or CYP2C9 inducers, or strong CYP2C9 inhibitors within 2 weeks prior to study drug administration and subjects with use of substrates of Pgp, OATP1B1 and OATP1B3 within 7 days of study drug administration should be excluded (e.g.,Rifaximin) will be excluded since these agents may affect the PK of ENTO. Subjects with use of proton pump inhibitors within 1 week prior to study drug administration will be excluded.
Study Procedures/ Frequency:	Following completion of Screening and Day -1 assessments, eligible subjects will be enrolled in Cohort 1 (followed by Cohorts 2 and/or 3 pending PK/Safety review) and receive multiple doses of 100 mg twice a day (BID) ENTO (1 × 100 mg tablet) starting on Day 1. When feasible, dosing in a matched control subject with normal hepatic function will occur after the subject with impaired hepatic function has completed the PK assessments, except if data exist from a subject with normal hepatic function in a previous cohort, this will be used instead of enrolling an additional normal healthy control subject as permitted in adaptive Cohorts 2 and 3. Subjects in adaptive Cohort 2 (Severe Hepatic Impairment) and/or adaptive Cohort 3 (Mild Hepatic Impairment) will be enrolled as determined by safety and/or PK data from Cohort 1 (Moderate Hepatic Impairment). Specifically, Cohort 2 will be initiated if supported by safety and PK findings from the non-smoking hepatic impairment subjects and matching, healthy control subjects in Cohort 1. Cohort 3 will be enrolled if a clinically meaningful change (≥ 2-fold mean difference from matched healthy controls) in the

exposures of ENTO and/or metabolite (if applicable) exposure is identified in non-smoking hepatic impairment subjects in Cohort 1. (Refer to Section 8.7, Sample Size)

Study Visits and Confinement

Eligible subjects will be confined to the study center beginning Day -1 until the completion of assessments on Day 9. Subjects will return for an in-clinic follow-up visit 14 (±1) days after the last dose of study drug (i.e., Day 19).

Study Drug Administration

All study treatments will be administered at approximately the same time each day with 240 mL of water following an overnight fast (no food or drinks except water, for at least 8 hours).

When ENTO is administered twice a day, the evening dose of ENTO will be administered approximately 12 hours after the AM dose. Subjects should continue fasting for 2 hours post AM dose and 2 hours before and 2 hours after the PM dose.

Only the AM dose of ENTO will be given on Day 5.

On the days of intensive pharmacokinetic sampling, study treatments will be administered in the morning following an overnight fast (no food or drinks except water, for at least 8 hours). Subjects will continue to fast until after collection of the 4-hour pharmacokinetic samples, relative to study drug dosing.

Additionally, subjects will be restricted from water consumption 1 hour before until 2 hours after dosing, except for the 240 mL given with the study treatment.

Pharmacokinetic Assessments

Serial blood samples will be collected relative to the AM dose on the following days and timepoints for ENTO and/or metabolites (if applicable).

Day 1: 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 (pre-PM dose) hours postdose

Day 5: 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 60, 72, 84, and 96 hours postdose

Trough Sampling: Days 2 and 4: 0 (pre-AM dose, at approximately the same time each day)

Plasma concentrations for ENTO and/or its metabolites (if applicable) will be determined and PK parameters evaluated. Protein binding of ENTO and/or its metabolites (if applicable), may be assessed at their T_{max} time point(s) as well as another later time point.

An additional Trough PK sample will be collected at the follow-up visit for assessing plasma concentrations for ENTO and/or its metabolites (if applicable).

Safety Assessments

Complete physical exam: Screening and at the follow-up visit or the Early Termination visit (if applicable)

Symptom driven physical exam: Day -1, Day 3, Day 7, and prior to discharge on Day 9

Vital signs (blood pressure, pulse, respiration rate, and temperature): Screening, Day -1, Day3, Day 7, prior to discharge on Day 9, at the follow-up visit, and at the early termination visit, if applicable.

Clinical laboratory tests (hematology, blood chemistry, and urinalysis): Screening, Day -1, Day 7, prior to discharge on Day 9, at the follow-up visit, and at the early termination visit, if applicable.

Urine Drug and Alcohol Assessments: Screening, Day -1, Day 5, prior to discharge on Day 9, at the follow-up visit, and at the early termination visit, if applicable.

12-lead ECG: Screening, Day -1, Day 3, Day 7, prior to discharge on Day 9, at the follow-up visit, and at the early termination visit, if applicable.

Serum Pregnancy Test (women of childbearing potential only): Screening, Day -1, Day 4, prior to discharge on Day 9, at the follow-up visit, and at the early termination visit, if applicable.

Serology Test (HBV, HCV, HIV): Screening

FSH testing (females of childbearing potential only): Screening

Other Assessments

Height: Screening

Weight: Screening, Day -1

Assessment of adverse events and concomitant medications will continue throughout the study.

Genetic Testing

A separate, mandatory blood specimen will be collected for the extraction of deoxyribonucleic acid (DNA) for genotyping to identify polymorphisms of drug metabolizing enzymes (such as CYP2C9, CYP3A4/5, CYP1A2 and UGT1A1) and transporters (such as OATP 1B1/3, P-gp, BCRP and MATE1) to optimize the therapeutic strategy for ENTO. This sample should be collected on Day -1, before administration of the first dose of study drug, but may be collected at any time during clinic confinement.

Test Product, Dose, and Mode of Administration:	ENTO 100 mg [1 × 100 mg tablet] twice a day
Reference Therapy, Dose, and Mode of Administration:	Not applicable
Criteria for Evaluation:	
Safety:	Safety will be evaluated by assessment of periodic physical examinations including vital sign and 12-lead ECGs performed at various time points during the study, by the documentation of adverse events, and by intervention with concomitant medications.
Efficacy:	Not applicable
Pharmacokinetics:	The following plasma pharmacokinetic parameters will be calculated: C_{max}, T_{max}, C_{last}, T_{last}, λ_z, AUC_{last}, AUC_{inf}, $\%AUC_{exp}$, $T_{½}$, CL/F, and V_z/F, and as appropriate, AUC_{tau}, C_{tau}.
Statistical Methods:	Pharmacokinetic parameters for ENTO and/or its metabolites (if applicable) will be listed and summarized by hepatic function group (normal or CPT Class A, B, or C) and smoking status (Cohort 1 only) using descriptive statistics (e.g., sample size, arithmetic mean, geometric mean, % coefficient of variation, standard deviation, median, minimum, an maximum). An analysis of variance appropriate for a parallel design will be fit to the natural logarithm-transformed pharmacokinetic parameters (AUC and C_{max}). The 90% confidence intervals (CIs) will be constructed for the least-squares geometric mean (GLSM) ratios of pharmacokinetic parameters for ENTO and/or its metabolite (if applicable), in groups of subjects with hepatic impairment (for Cohort 1 only, stratified by smoking status) versus the appropriate group of matched, healthy controls. Protein binding of ENTO and/or its metabolites (if applicable) at their T_{max} and another later time point will be summarized by hepatic function group and smoking status (Cohort 1 only) using descriptive statistics (if applicable). Safety data will be listed by subject and summarized by hepatic function groups, and frequency of event/abnormality or descriptive statistical summaries, as appropriate. A sample size of 8 evaluable subjects per hepatic function group (for Cohort 1, it is 8 evaluable subjects per hepatic function group within

each smoking status group) will provide a ≥ 89% probability for the 90% CI for the GLSM ratio of pharmacokinetic parameters (AUC or C_{max}) for ENTO in the hepatic impairment/dysfunction group(s) versus the appropriate group of matched, healthy controls, to be within limits of 50% to 200%. The calculation assumes an expected ratio of geometric means of 1.0 in pharmacokinetic parameters and inter-subject standard deviation of 0.455 for the natural logarithm-transformed pharmacokinetic parameters for ENTO. The assumption is based on the data obtained from a prior clinical study of ENTO (Study GS-US-339-0111).

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

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

° C	degrees Celsius
° F	degrees Fahrenheit
AE	adverse event
ALL	acute lymphoid leukemia
AML	acute myeloid leukemia
ALT	alanine aminotransferase
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the ENTO concentration versus time curve
$AUC_{0\text{-last}}$	area under the plasma concentration-time curve from time 0 to the last measurable concentration
AUC_{inf}	area under the plasma/serum/PBMC concentration versus time curve extrapolated to infinite time, calculated as $AUC_{0\text{-last}} + (Clast/\lambda_z)$
AUC_{tau}	area under the plasma/serum/PBMC concentration versus time curve over the dosing interval
BID	twice a day
BLQ	below limit of quantification
BMI	body mass index
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
CLL	chronic lymphocytic leukemia
CL/F	apparent oral clearance
C_{last}	last observed quantifiable serum/plasma/PBMC concentration of the drug
C_{max}	maximum observed ENTOconcentration of drug
CPK	creatine phosphokinase
CPT	Child-Pugh-Turcotte
CrCl	creatinine clearance
CRF	case report form(s)
CRO	contract (or clinical) research organization
CSR	clinical study report
CTA	clinical trial application
Ctau	observed drug concentration at the end of the dosing interval
CV	coefficient of variation
DNA	deoxyribonucleic acid
DSPH	Drug Safety and Public Health

EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form(s)
EDC	electronic data capture
ENTO	entospetenib
eSAE	electronic serious adverse event
ET	early termination
EU	European Union
FDA	(United States) Food and Drug Administration
FSH	follicle stimulating hormone
FU	follow up
GCP	Good Clinical Practice (Guidelines)
Gilead	Gilead Sciences, Inc.
GLSM	geometric least square mean
HBV	hepatitis B virus
HCV	hepatitis C virus
HDPE	high density polyethylene
HIV	human immunodeficiency virus
HLGT	high-level group term
HLT	high-level term
IB	investigator's brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ID	Identification
IND	Investigational New Drug (Application)
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
LLT	lower-level term
LLOQ	lower-limit of quantitation
LOEL	lowest observable effect level
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
NHL	non-Hodgkin lymphoma
NOEL	no observable effect level
OTC	over the counter
PD	pharmacodynamics
PI	principal investigator
PI3K	phosphatidylinositol 3-kinase
PK	pharmacokinetic(s)

PT	preferred term
PT	prothrombin time
Q1	first quartile
Q3	third quartile
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave representing the time for both ventricular depolarization and repolarization to occur
QTcF	QT interval corrected for heart rate using the Fridericia formulation
RA	rheumatoid arthritis
SADR	serious adverse drug reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	System Organ Class
SOP	standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
SYK	spleen tyrosine kinase
TEAE	treatment-emergent adverse event
THC	Tetrahydrocannabinol
T_{last}	time (observed time point) of C_{last}
T_{max}	the time (observed time point) of C_{max}
$T_{1/2}$	an estimate of the terminal elimination half-life of the drug in ENTO calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
US	United States
Vz/F	apparent volume of distribution of the drug
λz	terminal elimination rate constant; estimated by linear regression of the terminal elimination phase of the log serum/plasma/PBMC concentration versus time curve of the drug

1. INTRODUCTION

1.1. Background

Spleen tyrosine kinase (SYK) is a non-receptor cytoplasmic tyrosine kinase that is primarily expressed in cells of hematopoietic lineage and is an important mediator of immunoreceptor signaling in macrophages, neutrophils, mast cells, and B cells. SYK contains 2 adjacent Src Homology 2 (SH2) domains that bind to immunoreceptor tyrosine-based activation motifs (ITAMs) to autophosphorylate and activate the enzyme. This allows SYK to phosphorylate its specific substrates, including other enzymes and adaptor proteins, orchestrating a complex series of cellular responses such as cell proliferation, differentiation, survival, and phagocytosis in these cells.

Recent studies have suggested a role for the dysregulation of SYK in B-cell malignancies. SYK is expressed in B cells and is essentially involved in multiple signal transduction pathways downstream of the B-cell receptor (BCR). In this process, SYK trans-autophosphorylates and activates effector molecules such as phospholipase C gamma (PLCγ), phosphatidylinositol 3-kinase (PI3K), and mitogen-activated protein kinase (MAPK), and their associated signaling pathways, to induce an array of B-cell responses, including: proliferation, survival, differentiation, and apoptosis. Inhibition of BCR-mediated SYK activity is therefore an attractive therapeutic target for hematopoietic B-cell malignancies where SYK inhibition could inhibit the proliferation and survival of malignant B cells.

1.2. Entospletinib (ENTO, GS-9973)

The generic name of GS-9973 is entospletinib (ENTO).

1.2.1. General Information

Entospletinib (ENTO) is a potent and highly selective inhibitor of SYK, orally bioavailable and is being developed for the treatment of hematologic malignancies. Entospletinib is currently in a Phase 2 clinical trial in subjects with acute myeloid leukemia (AML)/acute lymphoid leukemia (ALL)/chronic lymphocytic leukemia (CLL)/non-Hodgkin lymphoma (NHL).

Further information is available in the Investigator's Brochure (IB) for GS-9973.

1.2.2. Preclinical Pharmacology and Toxicology

ENTO was evaluated in a standard battery of safety pharmacology studies to assess potential effects on central nervous, cardiovascular, and respiratory systems. ENTO had no effect on central nervous and respiratory system parameters evaluated in rats. In a cardiovascular safety pharmacology study in dogs, small increases in heart rate (up to a 25% increase) were observed in male dogs given ENTO at 15, 50, or 150 mg/kg. While the higher heart rates were considered ENTO-related, the relevance of these changes to humans is not known. Due to the observed increases in heart rate, a NOEL was not identified and the lowest observed effect level (LOEL) was 15-mg/kg. ENTO had no effect on ECGs or arterial blood pressure values at oral doses up to 150 mg/kg, the highest dose tested. Consistent with the lack of effect on ECG parameters, ENTO has no meaningful effect on the human-ether-a-go-go related gene (hERG), indicating that ENTO would not be expected to induce clinical QT prolongation.

The toxicity of ENTO has been characterized in animal genotoxicity, embryo-fetal reproductive toxicity, and phototoxicity studies. Recently published data demonstrated that species-specific GI toxicity and lymphoid changes, similar to that which was observed following ENTO administration to dogs, can occur in dogs but not rats, cynomolgus monkeys, or humans treated with p38 map kinase and MAP kinase activated protein kinase-2 (MK2) small molecule kinase inhibitors that inhibit pathways that overlap with SYK signaling pathways {Morris et al 2010}. Oral administration of ENTO to rats for up to 26 weeks or cynomolgus monkeys for up to 39 weeks showed no evidence of GI toxicity or lymphoid changes at exposures which overlapped with or exceeded those that resulted in acute toxicity in dogs. Furthermore, ENTO has been previously investigated in healthy human subjects at doses up to 1200 mg twice a day for 7 days and in subjects with RA at doses up to 900 mg for 26 days and no evidence of GI or lymphoid toxicity was observed in these clinical studies. Therefore, the relevance of these findings to humans is not known.

ENTO inhibits uridine disphosphate glucuronosyltransferase 1A1 (UGT1A1) with an IC_{50} of 2 μM. This enzyme is involved in glucuronidation of bilirubin, and inhibitors of UGT1A1 have the potential to produce increased levels of total and indirect (unconjugated) bilirubin in the circulation {Zhang et al 2005}.

ENTO is considered non-genotoxic and administration of ENTO did not result in skin reactions indicative of phototoxicity in mice.

Administration of ENTO to pregnant female rats and rabbits from implantation to the closure of the hard palate (International Conference on Harmonisation [ICH] Harmonised Tripartite Guideline stages C to D) resulted in dose-dependent developmental findings including increased incidence of early and late fetal resorptions and reduced fetal weights, and delays in ossification of the forelimb phalanges (rats and rabbits) and metacarpals (rabbits only). These fetal findings occurred at ENTO doses that caused maternal toxicity as demonstrated in both studies by dose-dependent decreases in body weight gain and/or body weight loss and decreased food consumption of the dams. Maternal toxicity was also demonstrated in these studies at doses that did not result in developmental findings.

1.2.3. Clinical Trials of Entospletinib

Positive results have been reported from a Phase 2 clinical trial with the putative SYK inhibitor fostamatinib showing objective anti-tumor responses in CLL and NHL subjects. {Friedberg et al 2010} These responses occurred despite off target toxicities that limited drug exposure. Entospletinib is a highly selective inhibitor of SYK and hence has the potential for an improved efficacy and tolerability profile in subjects with hematologic malignancies.

To date, 8 clinical studies have been initiated with ENTO including a total of 486 subjects (including 304 healthy subjects, 7 subjects with rheumatoid arthritis (RA), 80 subjects with chronic lymphocytic leukemia (CLL), 95 subjects with non-Hodgkins lymphoma (NHL); 26 subjects receiving placebo) in Phase 1 and Phase 2 clinical studies. Of the 460 subjects receiving ENTO in these studies, ENTO has generally been well tolerated.

Entospletinib is being evaluated in an ongoing Phase 2 clinical trial in subjects with relapsed or refractory CLL/NHL, and aPhase 1b/2 clinical trial in subjects with entospletinib monotherapy and in combination with chemotherapy in subjects with AML and ALL.

ENTO given at doses up to 1200 mg twice a day (2400 mg/day) for 7 days was well tolerated in healthy human subjects, and doses of up to 900 mg twice a day (1800 mg/day) given in combination with methotrexate were well tolerated for 26 days in subjects with RA and at 800 mg BID (1600 mg/day) was well tolerated in subjects with relapsed or refractory CLL/NHL for a median duration of exposure for 15 weeks.

Treatment emergent adverse events (AEs) that were commonly reported across the studies included headache, somnolence, and GI symptoms (nausea and abdominal pain), all of which were mild and reversible. ENTO administered for 26 days at a dose of 900 mg twice a day was well tolerated by subjects with RA on stable doses of methotrexate. This dose and treatment schedule produced levels of drug exposure similar to what we expect in subjects with hematologic malignancies receiving doses of ENTO at 800 mg twice a day.

Increased transaminases were noted in some subjects observed approximately 2 weeks after completion of study drug. In the cohort of subjects with RA, 2 subjects had elevated transaminases, which were also observed after completion of study drug. One subject with RA had elevated AST/ALT concurrent with bronchopneumonia while the other was diagnosed with acute hepatitis.

ENTO is expected to produce asymptomatic and transient elevations of unconjugated (indirect) bilirubin due to inhibition of UGT1A1. Eight of 178 healthy subjects treated developed asymptomatic indirect bilirubin elevations (6 Grade 1, 1 Grade 2, and 1 Grade 3) that resolved following discontinuation of the drug. Three of 7 subjects with RA who received ENTO for 26 days developed asymptomatic indirect bilirubin elevations (2 Grade 1 and 1 Grade 3) which improved despite continued dosing.

Common AEs from an on-going Phase 2 study evaluating chronic administration of entospletinib monotherapy in 186 subjects with hematologic malignancies are fatigue (53.2%), nausea (45.2%), diarrhea (38.7%), decreased appetite (24.7%), constipation (23.7%), cough (21.0%), and headache (21.0%) as of 21 November 2014.

1.3. Rationale for the Current Study

Hepatic disease may alter absorption, disposition, and elimination of drugs resulting in pharmacokinetic and subsequently pharmacodynamic changes. Available data indicate a hepatic role in the disposition of ENTO. Hence, the objective of this study is to investigate potential alterations in the pharmacokinetics, pharmacodynamics, and safety of ENTO (and/or its metabolites, if applicable) in the context of hepatic insufficiency. The data from this study will directly inform dosing recommendations for patients who have liver dysfunction.

This study will be conducted in an adaptive manner. The initial subjects to be enrolled will have moderate (Child-Pugh Classification B {Pugh et al 1973}) hepatic functional impairment; data from these subjects will be compared to matched subjects with normal hepatic function. Based upon adequate safety and assessment of the pharmacokinetics in these subjects with moderate hepatic impairment (CPT Class B), the study will subsequently evaluate subjects with mild (CPT Class A) and/or severe (CPT Class C) hepatic impairment. The planned, staged approach of this study design is consistent with recommendations included in the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling" {U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER); Center for Biologics Evaluation and Research (CBER) 2003}. Such a design enhances subject safety by minimizing the potential for exposing subjects to supratherapeutic exposures of ENTO and/or its metabolites (if applicable). Specifically, the study will first generate pharmacokinetic and safety data in the setting of moderate hepatic impairment where adequate numbers of subjects with stable hepatic dysfunction are available and are suitable for evaluation in a Phase 1 study. Results obtained from these subjects with moderate impairment are also likely to yield determinative data that indicate either, a) the lack of an effect of moderate hepatic impairment, thus obviating the need for evaluation in subjects with mild disease or, alternatively, b) the potential for large changes in the exposure of ENTO in the setting of end-organ dysfunction that may provide evidence for a need for caution with respect to an evaluation in the setting of severe hepatic dysfunction.

In vitro studies indicate that ENTO is primarily metabolized by CYP2C9, and to a lesser extent by CYP3A and CYP1A2. Use of nicotine-containing or THC-containing products may induce CYP1A2, which has the potential to affect ENTO metabolism. Due to lower observed ENTO exposure in smokers in Cohort 1, enrollment in Cohort 1 has been expanded to enroll 10 smokers with moderate hepatic impairment (for 8 evaluable) and appropriate matched healthy controls, in order to further investigate the impact of smoking on ENTO PK. To avoid the potentially confounding effect of smoking on the assessment of hepatic impairment on ENTO PK, additional non-smoking subjects with moderate hepatic impairment will also be enrolled in Cohort 1 (10 enrolled for 8 evaluable, and appropriate healthy, matched controls). In Cohorts 2 and 3, only non-smoking subjects with hepatic impairment will be enrolled so that an accurate assessment of the effect of hepatic impairment on ENTO PK can be made, without the potentially confounding effect of smoking.

The trial will enroll subjects with chronically impaired hepatic function and healthy controls, matched for body mass index, age, and sex. This study will proceed in a staggered fashion. Dosing of subjects with mild and/or severe hepatic impairment will occur only after the review of safety and PK from smoking and non-smoking subjects with moderate hepatic impairment. Specifically, Cohort 2 will be initiated if supported by safety and PK findings from subjects in Cohort 1. Cohort 3 will be enrolled if a clinically meaningful change (≥ 2-fold mean difference from matched healthy controls) in the exposures of ENTO and/or metabolite (if applicable) exposure is identified in non-smoking hepatic impairment subjects in Cohort 1.

1.3.1. Rationale for the Dose Selection

A therapeutic dose of ENTO 400 mg twice a day is being evaluated in the Phase 2 program in subjects with CLL (Study 339-0102). Safety results from clinical studies to date indicate that ENTO is well tolerated when administered to healthy subjects at 400 mg BID. In this study, a lower dose of ENTO (100 mg) compared to therapeutic dose will be used to evaluate the effect of hepatic insufficiency on the PK, PD and safety of ENTO (and/or its metabolites, if applicable) to allow for a potential increase in ENTO exposures due to impaired hepatic metabolism.

ENTO exhibited non-linear PK (i.e. time and dose dependency in pharmacokinetic parameters) in Phase 1 studies. Per the FDA's recommendation {U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER); Center for Biologics Evaluation and Research (CBER) 2003}, a multiple dose hepatic impairment study is desirable when the drug or an active metabolite is known to exhibit nonlinear or time dependent PK. Therefore, the current study involves administration of ENTO 100 mg BID for 5 days.

1.4. Compliance

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

2. OBJECTIVES

The primary objective of this study is as follows:

- To evaluate the pharmacokinetics of Entospletinib (ENTO) and/or its metabolites (if applicable) in subjects with impaired hepatic function (stratified by smoking status, as appropriate) relative to matched, healthy controls

The secondary objectives of this study are as follows:

- To evaluate the safety and tolerability of administration of ENTO in subjects with normal and impaired hepatic function

- To evaluate the potential impact of smoking on the PK of ENTO in subjects with moderate hepatic impairment

3. STUDY DESIGN

3.1. Study Design

This protocol describes an open-label, parallel-group, adaptive, multiple-dose, Phase 1 study evaluating the pharmacokinetics of ENTO and/or its metabolites (if applicable), in subjects with impaired hepatic function relative to matched, healthy controls.

This study will enroll a minimum of 20 and a maximum of 80 subjects using an adaptive study design that includes up to 3 enrolled cohorts of subjects with hepatic impairment as well as matched healthy controls. Eligible subjects will be male and nonpregnant, nonlactating female subjects, aged ≥ 18 years, 18 ≤ BMI ≤ 40, with either impaired hepatic function of CPT classification A, B, or C or with normal hepatic function. Each subject in the control group will be matched to a subject with impaired hepatic function by age (± 10 years), gender, and body mass index (± 20%).

When feasible, dosing in a matched control subject with normal hepatic function will occur after the subject with impaired hepatic function has completed the PK assessments, except if data exist from a subject with normal hepatic function in a previous cohort, this will be used instead of enrolling an additional normal healthy control subject, as permitted in adaptive Cohorts 2 and 3.

Cohort 1 enrollment of hepatic impairment subjects will be an approximate even distribution of subjects who are active cigarette smokers (at least 10 cigarettes/day) and subjects who are current non-smokers (no use of tobacco, nicotine-containing or THC-containing products within the last 14 days). Hepatic impairment subjects enrolled in adaptive Cohorts 2 and 3 will be current non-smokers (no use of tobacco, nicotine-containing or THC-containing products within the last 14 days).

Based on safety and/or PK results from the non-smoking subjects with moderate hepatic impairment and matching, healthy controls (Cohort 1), subjects with severe hepatic impairment (Cohort 2) and/or mild hepatic impairment (Cohort 3) will be enrolled as follows:

- Cohort 1 (CPT Class B, Moderate Hepatic Impairment)
  Up to 40 subjects total:
  20 with moderate impairment, (10 smokers]at least 8 evaluable] and 10 non-smokers]at least 8 evaluable]), 20 matched healthy controls (at least 8 evaluable healthy controls matched to smokers with moderate impairment, and at least 8 evaluable healthy controls matched to non-smokers with moderate impairment).

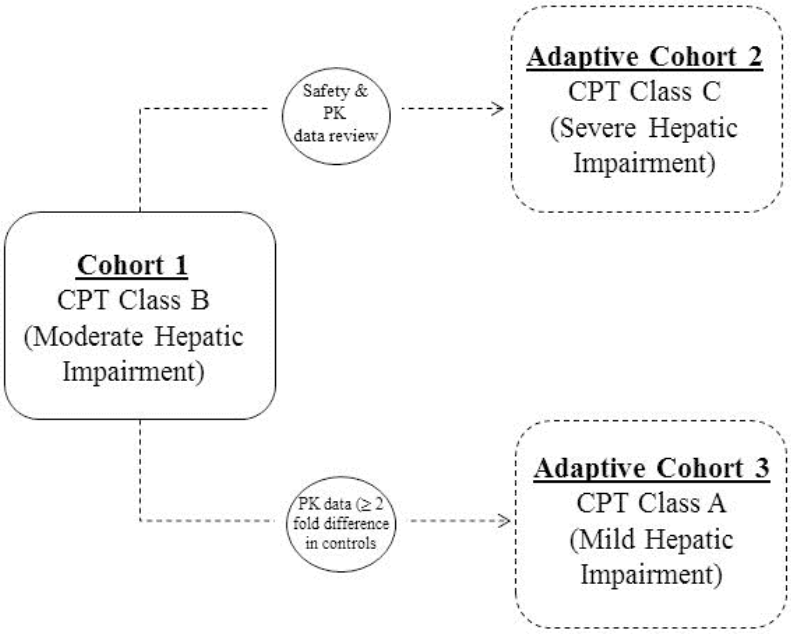
- Adaptive Cohort 2 (CPT Class C, Severe Hepatic Impairment)
  Up to 20 subjects:
  10 with severe impairment, up to 10 matched healthy controls if none of the healthy subjects from a previous cohort is an appropriate match for a severe impairment subject, for 8 evaluable per group.

- Adaptive Cohort 3 (CPT Class A, Mild Hepatic Impairment)
  Up to 20 subjects:
  10 subjects with mild impairment, up to 10 matched healthy control subjects if none of the healthy subjects from a previous cohort is an appropriate match for a mild impairment subject, for 8 evaluable per group

The 90% CIs will be examined to determine if a meaningful change (≥ 2-fold mean difference from matched controls) in the exposures of ENTO and/or metabolite (if applicable) is identified which would be clinically interpreted. A decision to enroll subjects in adaptive Cohort 2 (Severe Hepatic Impairment) and/or adaptive Cohort 3 (Mild Hepatic Impairment) will be enrolled as determined by safety (treatment-emergent AEs, treatment-emergent laboratory abnormalities, vital signs, safety ECGs) and/or PK data from non-smoking moderate hepatic impairment subjects and matching, healthy controls in Cohort 1. Specifically, Cohort 2 will be initiated if supported by safety (treatment-emergent AEs, treatment-emergent laboratory abnormalities, vital signs, safety ECGs) and PK findings from non-smoking subjects and healthy, matched cotrols in Cohort 1. Cohort 3 will be enrolled if a clinically meaningful change (≥ 2-fold mean difference from matched healthy controls) in the exposures of ENTO and/or metabolite (if applicable) exposure is identified in non-smoking hepatic impairment subjects in Cohort 1..

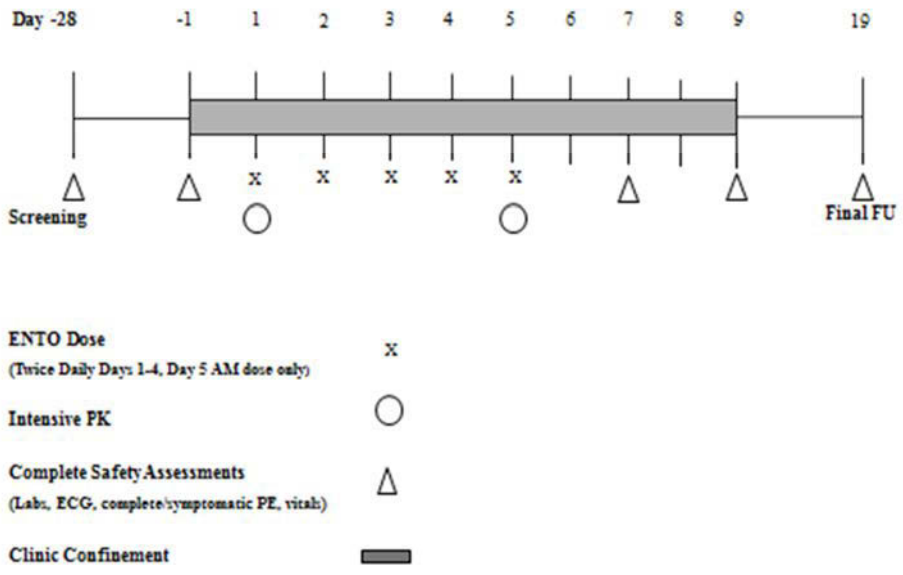
An overview of the study design is shown below in Figure 3-1

Figure 3-1. High Level Study Schema



The study schema for all subjects is shown in Figure 3-2

Figure 3-2. Study Schema – All Cohorts



3.2. Study Drug Administration

Following completion of Screening and Day -1 assessments, eligible subjects will be enrolled in 1 of 3 cohorts and receive multiple doses of 100 mg twice a day (BID) ENTO (1 × 100 mg tablet) in the fasted state starting on Day 1 for 5 days.

Please refer to Section 5.3 for additional information for study drug dosage and administration.

3.3. Clinic Confinement

Following completion of Screening and Day -1 assessments, eligible subjects will be confined to the study center starting on Day -1 until completion of assessments on Day 9. Subjects will be required to return for an in-clinic follow-up visit 14 (±1) days after the last dose of study drug (ie, Day 19).

3.4. Pharmacokinetic Assessments

Pharmacokinetic assessments will occur on assigned study days as outlined in Table 6-1 and Section 6.7.

3.4.1. Plasma Pharmacokinetic Collection

Plasma concentrations of Entospletinib and/or its major metabolite (if applicable) will be determined and PK parameters estimated. PK of other metabolites (if applicable) of Entospletinib may be explored.

3.5. Safety Assessments

Safety assessments will be performed through the study as outlined in Table 6-1 Section 6.9.

3.6. Genetic Testing

A blood sample for genetic sampling will be taken in the study as outlined in Table 6-1 Section 6.10.

A separate, mandatory blood specimen will be collected for the extraction of DNA for genotyping to identify polymorphisms of drug metabolizing enzymes (such as CYP2C9, CYP3A4/5, CYP1A2 and UGT1A1) and transporters (such as OATP 1B1/3, P-gp, BCRP and MATE1) to optimize the therapeutic strategy for ENTO. This sample should be collected on Day -1, before administration of the first dose of study drug, but may be collected at any time during clinic confinement.

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

A minimum of 20 and a maximum of 80 unique subjects will be enrolled in the study, with an approximate even distribution of male and nonpregnant, nonlactating female subjects 18 years of age or older, with varying degrees of hepatic impairment and matched healthy controls will be enrolled. Replacement subjects may be enrolled if fewer than 16 evaluable subjects (8 per group) complete the study in any cohort. Replacement subjects will not be enrolled for subjects who discontinue the study due to treatment-related toxicity.

Cohort 1 enrollment of hepatic impairment subjects will be an approximate even distribution of subjects who are active cigarette smokers (at least 10 cigarettes/day) and subjects who are current non-smokers (no use of tobacco, nicotine-containing or THC-containing products within at least 14 days prior to study drug dosing). Hepatic impairment subjects enrolled in adaptive Cohorts 2 and 3 will be current non-smokers (no use of tobacco, nicotine-containing or THC-containing products within at least 14 days prior to study drug dosing).

All subjects will be categorized by the Child-Pugh-Turcotte (CPT) classification system (Appendix 5) for hepatic impairment as recommended by the United States Food and Drug Administration (FDA) and international guidance documents. Within the CPT system, subjects will be assigned to Class A, B, or C (CPT Class A, B, or C) based on a cumulative score evaluating the presence and severity of hyperbilirubinemia, hypoalbuminemia, prolongation of internationalized normalized ratio (INR) for coagulation time, ascites, and hepatic encephalopathy. Designations of hepatic impairment will be assigned as follows:

- Class A (mild): CPT score 5-6
- Class B (moderate): CPT score 7-9
- Class C (severe): CPT score 10-15

Based on CPT classification, subjects with hepatic impairment and healthy matched controls will be enrolled as described in Section 6.1. The control group will consist of matched healthy subjects with normal hepatic function. Each subject in the control group will be matched to a subject with impaired hepatic function by age (± 10 years), gender, and body mass index (± 20%).

4.2. Inclusion Criteria

4.2.1. All Subjects (Healthy Control Subjects and Subjects with Hepatic Impairment)

All subjects must meet *all* of the following inclusion criteria to be eligible for participation in this study.

1) Have the ability to understand and sign a written informed consent form (ICF), which must be obtained prior to initiation of study procedures

2) Must be ≥ 18 years of age at Screening

3) Have a calculated body mass index (BMI) from 18 to 40 kg/m^2, inclusive, at study Screening.

4) Have a creatinine clearance (Cr_{Cl}) ≥ *50 mL/min* (using the Cockcroft-Gault method {Cockcroft et al 1976}) based on serum creatinine and actual body weight as measured at Screening ie.,

Male: $$\frac{(140 - \text{age in years}) \times (\text{wt in kg})}{72 \times (\text{serum creatinine in mg/dL})} = \text{CrCl (mL/min)}$$

Female: $$\frac{(140 - \text{age in years}) \times (\text{wt in kg})}{72 \times (\text{serum creatinine in mg/dL})} \times 0.85 = \text{CrCl (mL/min)}$$

5) Females of childbearing potential (as defined in Appendix 3) must have a negative serum pregnancy test at Screening and clinic admission.

6) **Male subjects and female subjects of childbearing potential who engage in** heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 3.

7) Male subjects must refrain from sperm donation from clinic admission, throughout the study period, and continuing for at least 90 days following the last dose of study drug.

8) Subjects must refrain from blood donation from clinic admission, throughout the study period, and continuing for at least 30 days following the last dose of study drug.

9) Have either a normal 12-lead electrocardiogram (ECG) or one with abnormalities that are considered clinically insignificant by the investigator.

10) Must be willing and able to comply with all study requirements.

4.2.2. Subjects with Impaired Hepatic Function

Subjects with mild, moderate, or severe hepatic impairment must also meet the following additional inclusion criteria to be eligible for participation in this study:

1) Aside from hepatic insufficiency, the subject must, in the opinion of the Investigator, be sufficiently healthy for study participation based upon medical history, physical examination, vital signs, and screening laboratory evaluations.

2) Must have diagnosis of chronic (> 6 months), stable hepatic impairment with no clinically significant changes within 3 months (90 days) prior to study drug administration (Day 1).

3) Must meet all of the following laboratory parameters at Screening:

- ALT value ≤ 10 × ULN
- AST value ≤ 10 × ULN

- Absolute neutrophil count ≥ 1,000/mm^3
- Platelets ≥ 25,000/mm^3
- Hemoglobin ≥ 8 g/dL
- α-fetoprotein ≤ 50 ng/mL

4) Subjects with ***severe*** hepatic impairment must have a score on the Child-Pugh-Turcotte scale of 10-15 at Screening. If a subject's score changes during the course of the study, the score at Screening will be used for classification.

5) Subjects with ***moderate*** hepatic impairment must have a score on the Child-Pugh-Turcotte scale of 7-9 at Screening. If a subject's score changes during the course of the study, the score at Screening will be used for classification.

6) Subjects with ***mild*** hepatic impairment must have a score on the Child-Pugh-Turcotte scale of 5-6 at Screening. If a subject's score changes during the course of the study, the score at Screening will be used for classification.

7) Subjects in Cohort 1: Non-smoking hepatic impairment subjects must have no use of tobacco, nicotine-containing, or THC-containing products within at least 14 days prior to study drug dosing, and cannot smoke or use these products during the study. Smoking hepatic impairment subjects must have smoked ≥10 cigarettes/day for at least 30 days and plan to continue smoking ≥10 cigarettes/day during the study.

8) Subjects in adaptive Cohorts 2 and 3: Must be current non-smokers (no use of tobacco, nicotine-containing, or THC-containing products within the last 14 days prior to study drug dosing, and cannot smoke or use these products during the study).

4.2.3. Healthy Matched Controlled Subjects

Healthy matched control subjects must also meet the following additional inclusion criteria to be eligible for participation in this study:

1) Must, in the opinion of the Investigator, be in good health based upon medical history, physical examination, vital signs, and screening laboratory evaluations.

2) Must meet all of the following laboratory parameters at Screening:

- INR ≤ 1 × ULN
- Albumin ≥ 1 × LLN
- Total bilirubin < 1 × ULN
- AST value ≤ 1 × ULN

- ALT value ≤ 1 × ULN
- Alkaline phosphatase ≤ 1 × ULN
- α-fetoprotein ≤ 1 × ULN
- Negative Hepatitis B surface antigen (HBsAg)
- Negative Hepatitis B core (HBc) antibody
- Negative HCV antibody
- Screening laboratory evaluations (hematology, fasting lipids, chemistry, and urinalysis) must be within the normal range unless the results have been determined by the investigator to have no clinical significance.

4.3. Exclusion Criteria

4.3.1. All Subjects

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

1) Pregnant or lactating subjects
2) Have received any investigational compound within 30 days prior to study dosing
3) Concurrent participation in another therapeutic clinical trial
4) Current alcohol or substance abuse judged by the investigator to potentially interfere with subject compliance or subject safety
5) A positive test result for human immunodeficiency virus (HIV-1/HIV-2) antibody, hepatitis B (HBV) surface antigen or current HCV infection (exclude all subjects who test positive (reactive) for HCV antibody with repeat test HCV RNA detected)
6) Have poor venous access that limits phlebotomy
7) History of having donated blood within 56 days prior to check in (Day-1).
8) History of having donated plasma within 7 days prior to check in (Day -1).
9) History of prior allogeneic bone marrow progenitor cell or solid organ transplantation.
10) Currently registered on an organ transplantation list.
11) History of bleeding from esophageal varices within 90 days prior to check in (Day-1).

12) Have been treated with systemic steroids, immunosuppressant therapies, or chemotherapeutic agents within 3 months prior to Screening or expected to receive these agents during the study (eg., corticosteroids, immunoglobulins, and other immune- or cytokine-based therapies)

13) Significant serious skin disease, such as but not limited to rash, food allergy, eczema, psoriasis, or urticaria

14) Significant drug sensitivity or drug allergy (such as anaphylaxis or hepatotoxicity)

15) Known hypersensitivity to the study drugs, their metabolites (if applicable), or to formulation excipients (see Section 5.2.1)

16) Significant cardiac disease (including history of myocardial infarction based on ECG and/or clinical history, any history of ventricular tachycardia, congestive heart failure, or dilated cardiomyopathy with left ventricular ejection fraction <40%), a family history of Long QT Syndrome, or unexplained death in an otherwise healthy individual between the ages of 1 and 30 years.

17) Presence or history of cardiovascular disease, cardiomyopathy, and/or clinically significant cardiac conduction abnormalities.

18) Syncope, palpitations, or unexplained dizziness

19) Implanted defibrillator or pacemaker.

20) Severe peptic ulcer disease, gastroesophageal reflux disease, or other gastric acid hypersecretory conditions requiring prolonged (>6 months) medical treatment.

21) Medical or surgical treatment that permanently alters gastric absorption (eg, gastric or intestinal surgery). A history of cholecystectomy is not exclusionary.

22) Subjects with use of moderate or strong CYP3A or CYP2C9 inducers, or strong CYP2C9 inhibitors within 2 weeks prior to study drug administration will be excluded. Subjects with use of proton pump inhibitors within 1 week prior to study drug administration will be excluded. (Please see Section 5.6.1 for excluded Concomitant Medications)

23) Are unable to comply with study requirements or are otherwise believed, by the study investigator, to be inappropriate for study participation for any reason.

4.3.2. Subjects with Impaired Hepatic Function

Subjects with mild, moderate, or severe hepatic impairment meeting *any* of the following additional exclusion criteria are not to be enrolled in this study:

1) Aside from hepatic insufficiency, serious or active medical or psychiatric illness that, in the opinion of the Investigator, would interfere with subject treatment, assessment, or compliance with the protocol. This would include renal, cardiac, hematological, unstable hepatic, pulmonary (including chronic asthma), endocrine (eg, diabetes), central nervous, gastrointestinal (including an ulcer), vascular, metabolic (thyroid disorders, adrenal disease), immunodeficiency disorders, active infection, or malignancy that are clinically significant or requiring treatment.

2) Requires paracentesis > 1 time per month.

3) Subjects with hepatic impairment with co-morbid diseases requiring medication(s) must be taking the medication(s) without a clinically significant change in dose of con-meds for co-morbid diseases for > 3 months prior to screening.

4) Smoking Subjects in Cohort 1: Recent significant changes in smoking habits or the use of nicotine or nicotine containing products (ie, initiation, substantial increase or decrease or cessation of use) for at least 14 days prior to study drug dosing, or anticipated significant changes in smoking habits or the use of nicotine or nicotine containing products during the course of the study through the follow-up visit.

5) Positive test for drugs of abuse, including alcohol at Screening or on Day -1/check-in (Positive THC screen allowed for subjects in states/countries that have legalized THC containing substances)

All concomitant medications including over-the-counter and herbal products must be approved by the Investigator and Medical Monitor prior to study enrollment and study drug administration.

4.3.3. Healthy Matched Controlled Subjects

Healthy matched controlled subjects meeting *any* of the following additional exclusion criteria are not to be enrolled in this study:

1) Serious or active medical or psychiatric illness that, in the opinion of the Investigator, would interfere with subject treatment, assessment, or compliance with the protocol. This would include renal, cardiac, hematological, hepatic, pulmonary (including chronic asthma), endocrine (eg, diabetes), central nervous, gastrointestinal (including an ulcer), vascular, metabolic (thyroid disorders, adrenal disease), immunodeficiency disorders, active infection, or malignancy that are clinically significant or requiring treatment.

2) History of liver disease.

3) Have taken any prescription medications or over-the-counter medications, including herbal products, within 28 days prior to start of study drug dosing, with the exception of vitamins and/or acetaminophen and/or ibuprofen

4) Positive test for drugs of abuse, including alcohol at Screening or on Day -1/check-in

5) Subjects will be required to refrain from the use of nicotine, nicotine-containing products (including cigarette smoking) or THC-containing products for at least 14 days prior to first dose of study drug, and during the course of the study through the follow-up visit

5. STUDY DRUGS

5.1. Randomization and Blinding

This is an open-label, non-randomized study.

It is the responsibility of the Investigator to ensure that the subject is eligible for the study prior to enrollment. Subjects will be assigned a Screening number at the time of consent.

A minimum of 40 and a maximum of 80 male and non-pregnant, non-lactating female subjects with either impaired hepatic function of CPT classification A, B, or C or with normal hepatic function will be enrolled to 1 of the 3 cohorts as described in Section 6.1.

Study drug will be dispensed by the study pharmacist in an open-label fashion to the subjects.

All Screening and check-in (Day -1) tests and procedures must be completed prior to the administration of the first dose of study drug on Day 1. Once a subject number has been assigned to a subject, it will not be reassigned to another subject. If necessary, replacement subjects may be enrolled after discussion and approval from Sponsor. A new unique subject number will be assigned to the replacement subject.

A subject number schema will be provided to the study center by the Sponsor. Once eligibility is confirmed in consultation with the Sponsor, a subject number will be assigned by the Sponsor.

5.2. Description and Handling of Entospletinib

5.2.1. Formulation

Study drug entospletinib (ENTO, GS-9973) is available as 100 mg strength tablets. The tablets contain ENTO spray-dried dispersion (SDD) and commonly used excipients including mannitol, poloxamer 188, crospovidone, silicon dioxide, microcrystalline cellulose, magnesium stearate, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and FD&C blue #2 aluminum lake. ENTO SDD consists of ENTO, methanesulfonic acid, and hypromellose. The 100 mg ENTO tablets are blue, capsule-shaped, plain-faced, film-coated blue tablets.

5.2.2. Packaging and Labeling

ENTO 100 mg tablets are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 60 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 US and other participating countries shall be labeled to meet applicable requirements of the United States Food and Drug Administration (FDA), EU Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.2.3. Storage and Handling

ENTO should be stored at a controlled room temperature of 25°C (77°F); excursions are permitted from 15°C to 30°C (59°F to 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. 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 through inhalation when handling.

5.3. Dosage and Administration of Study Drug

Following completion of Screening and Day -1 assessments, eligible subjects will be enrolled in 1 of 3 cohorts and receive multiple doses of 100 mg twice a day (BID) ENTO (1 x 100 mg tablet) starting on Day 1 in the fasted state.

When feasible, dosing in a control subject with normal hepatic function will occur after the matched subject with impaired hepatic function has completed the PK assessments, except for control subjects that were already matched to a subject with impaired hepatic function in a previous cohort, as permitted in adaptive Cohorts 2 and 3.

Subjects in adaptive Cohort 2 (Severe Hepatic Impairment) and/or adaptive Cohort 3 (Mild Hepatic Impairment) will be enrolled as determined by safety and/or PK data non-smoking subjects and healthy, matching controls in Cohort 1 (Moderate Hepatic Impairment). Specifically, Cohort 2 will be initiated if supported by safety and PK **findings from non-smoking hepatic impairment subjects and matching, healthy control subjects in Cohort 1**.. Cohort 3 will be enrolled if a clinically meaningful change (≥ 2-fold mean difference from matched healthy controls) in the exposures of ENTO and/or metabolite (if applicable) exposure is identified in non-smoking hepatic impairment subjects in Cohort 1.

5.4. Fasting and Meals

All study treatments will be administered at approximately the same time each day with 240 mL of water following an overnight fast (no food or drinks except water, for at least 8 hours).

When ENTO is administered twice a day, the evening dose of ENTO will be administered approximately 12 hours after the AM dose. Subjects should continue fasting for 2 hours post AM dose and 2 hours before and 2 hours after the PM dose. Only the AM dose of ENTO will be given on Day 5.

On the days of intensive pharmacokinetic sampling, study treatments will be administered in the morning following an overnight fast (no food or drinks except water, for at least 8 hours). Subjects will continue to fast until after collection of the 4-hour pharmacokinetic samples,

relative to study drug dosing. Additionally, subjects will be restricted from water consumption 1 hour before until 2 hours after dosing, except for the 240 mL given with the study treatment.

All meals and/or snacks given to subjects during their stay in the clinical study facility will be standardized for all subjects and should be similar in calorie and fat content and taken at approximately the same time each day. All meals provided must be approved by the Sponsor. Components of meals (eg, margarine, jelly, bread) should be given to subjects in individual portions (eg, 1 tablespoon) per the approved meal schedule. The provision of meal components in bulk (eg, a jar of jelly for subjects to share) should not be practiced. All meals should be given at approximately the same time each day (eg, 07:30, 12:00, and 18:00).

5.5. Dispensing, Accountability, and Disposal or Return of Study Drug

The Investigator (or designee, eg, study center pharmacist) will acknowledge receipt of the study drug (after reviewing the shipment's content and condition) from Gilead (or designee). The Investigator will maintain an accurate inventory of all study drug(s). Each dose of the study drug(s) administered at the study center will be administered by qualified study center staff. The dose of study drug(s) administered to subjects in the clinic under the supervision of staff will be accurately recorded on the Study Drug Accountability Form provided by Gilead (or on equivalent documentation maintained by the study center), which indicates the date and quantity of each dosage formulation dispensed to individual subjects.

Gilead recommends that used and unused study drug supplies, including empty containers, be returned to the shipping facility from which it came or Gilead Sciences for destruction following drug accountability and drug inventory reconciliation.

If returning drug supplies to the shipping facility from which it came or to Gilead Sciences is not possible, the monitor will evaluate the site's SOP for study drug disposal/destruction in order to ensure that it complies with Gilead's requirements. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures.

5.6. Concomitant Medications and Other Protocol Restrictions

5.6.1. Concomitant Medications

The following medications are excluded while subjects are participating in the study:

For subjects with normal hepatic function:

- Any prescription medications and over-the-counter medications including herbal products and antacids with the exception of vitamins, and/or acetaminophen and/or ibuprofen. However, the short term use of topical hydrocortisone cream or A&D ointment to treat minor skin irritation due to ECG leads will be allowed. If a subject requires use of a disallowed medication, a request for such use must be reviewed by the Sponsor and if approved, subjects may continue to participate in the study.

For all subjects:

- Any and all illegal or illicit drug use, including use of prescription drugs outside the care of the prescribing physician.
- Subjects may not be taking rifaximin within 7 days prior to baseline (Day -1) or during the study. Rifaximin is a substrate of P-gp, OATP1B1 and OATP1B3; in a clinical DDI study with cyclosporine (an inhibitor of these transporters), a 124-fold increase in rifaximin exposure was observed. ENTO is an inhibitor of P-gp, OATP1B1 and OATP1B3 and a similar DDI with rifaximin may occur. Rifaximin exposures are also significantly increased in subjects with mild, moderate and severe hepatic impairment. Further, rifaximin activates PXR at higher exposures leading to induction of drug metabolizing enzymes, therefore the use of rifaximin in this study may significantly confound the evaluation of the effect of hepatic impairment on ENTO PK.

Subjects with hepatic impairment:

- Subjects with hepatic impairment with co-morbid diseases requiring medication(s) must be taking the medication(s) without a clinically significant change in dose for > 3 months prior to screening.
- The use of moderate or strong CYP3A or CYP2C9 inducers, or strong CYP2C9 inhibitors within 2 weeks prior to study drug administration and during the study is prohibited. The use of proton pump inhibitors within 1 week prior to study drug administration and during the study is prohibited.
- All concomitant medications must be approved by the medical monitor (or the clinical pharmacologist) prior to enrollment.

5.6.2. Other Protocol Restrictions

- Subjects will be required to refrain from the consumption of food and beverages containing alcohol products 72 hours prior to the first dose of study drug and during the course of the study through the follow-up visit.
- Subjects will be required to refrain from the use of nicotine or nicotine-containing products and THC-containing products for at least 14 days prior to first dose of study drug, and during the course of the study through the follow-up visit. This restriction does not apply to smoking hepatic impairment subjects enrolled in Cohort 1.
- Subjects will be required to refrain from consumption of grapefruit juice, grapefruits, and Seville orange juice 72 hours prior to the first dose of study drug and during the course of the study through the follow-up visit.
- While confined at the study center, tea, coffee, chocolate, and other foods and beverages containing caffeine and other methyl xanthines will be prohibited on each dosing day. At all

other times, caffeine-containing beverages and foodstuffs may be served or withheld in accordance with normal study center practice. Caffeine-containing beverages and foodstuffs will not be restricted while subjects are outside of the clinic.

- Subjects will be encouraged to avoid strenuous or prolonged exercise, as well as saunas, steambaths, and sunbathing or other prolonged UV exposure, eg, in a tanning salon, from the Screening evaluation until completion of the follow-up visit, as these activities are known to affect certain clinical laboratory test parameters, (eg, creatine kinase (CPK)) and will provide false indicators of a potentially treatment-related toxicity.

Upon every admission to the clinic, each subject will be questioned as to their compliance with the above protocol restrictions**.** If a subject is unable to comply with any of the restrictions described above, the subject's continued participation in the study will be reevaluated by the Investigator in consultation with the Sponsor.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are detailed below.

Any deviation from protocol procedures should be noted in the subject's clinical chart and appropriate CRFs / eCRFs. In addition, the Sponsor should be promptly notified of any protocol deviations.

The study center will not initiate dosing until:

- The Institutional Review Board (IRB)/Ethics Committee (EC)/other applicable regulatory agencies have reviewed and approved the study and the informed consent document;
- All requested regulatory documents have been submitted to and approved by Gilead;
- A Master Services Agreement and/or Study Agreement is executed;
- The study initiation meeting has been conducted by Gilead (or designee).

The initiation meeting will include but is not limited to a review of the protocol, the IB, study drugs, and Investigator responsibilities.

Documentation of the personally signed and dated informed consent of each subject, using the study-specific, IRB/EC-approved Informed Consent Forms (ICF), is required before initiating the screening process.

6.1. Subject Enrollment and Treatment Assignment

It is the responsibility of the Investigator to ensure that subjects are eligible to participate in the study prior to enrollment and continue to remain eligible throughout the study.

Once informed consent has been obtained, all screening and admission tests and procedures have been assessed, and study eligibility has been confirmed, subjects will be enrolled to receive study drug on Day 1.

Subjects will receive the study treatments as described in Section 5.3.

Table 6-1. Schedule of Assessments – All Cohorts

Study Procedure	Screen[a]	Day -1	Days 1 and 5	Days 2 and 4	Day 3	Days 6 and 8	Day 7	Day 9[b]	Day 19 (±1) FU[c]	ET[d]
Written Informed Consent	X									
Medical History	X									
Complete Physical Exam	X								X	X
Symptom-Driven Physical Examination[e]		X			X		X	X		
Height	X									
Weight	X	X								
Vital Signs[f]	X	X			X		X	X	X	X
HIV-1/HIV-2, HBV, and HCV Serology	X									
Hematology[g]	X	X					X	X	X	X
Serum Chemistry[h]	X	X					X	X	X	X
Genotype Testing for Enzymes and Transporters		X[p]								
Urinalysis	X	X					X	X	X	X
Serum Pregnancy Test[i]	X	X		X[n]				X	X	X
FSH testing[i]	X									
Urine and Alcohol Drug Screen	X	X	X[o]					X	X	X
12-Lead ECG	X	X			X		X	X	X	X
Subject Enrollment[j]		X								

Study Procedure	Screen[a]	Day -1	Days 1 and 5	Days 2 and 4	Day 3	Days 6 and 8	Day 7	Day 9[b]	Day 19 (±1) FU[c]	ET[d]
Study Drug Administration			X	X	X					
Intensive Plasma PK[k]			X			X	X	X		
Trough PK[l]				X[l]					X	
Review Study Restrictions										
Clinic Confinement		X	X	X	X	X	X	X		
Review AEs & Concomitant Medications[m]	X	X	X	X	X	X	X	X	X	X

a Prospective subjects should be screened no more than 28 days prior to administration of the first dose of study drugs.
b Subjects will be discharged from the clinic on *Day 9,* following all morning assessments.
c 14 (±1) days after the last administration of study drug, all subjects will return to the clinic for a follow-up visit.
d Assessments will be performed within 72 hours of early termination from the study.
e Symptom-driven PE's will be performed on Days -1, 3, 7, 9, during confinement as needed, and the follow-up visit.
f Vital signs include blood pressure, pulse rate, respiration rate, and body temperature.
g Hematology: INR, CBC with differential and platelet, neutrophil, and hemoglobin count.
h Fasting serum chemistry: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, α-fetoprotein (at screening only), LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, total cholesterol, HDL, LDL, and triglycerides, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 x ULN).
i Females of child-bearing potential only.
j On Day -1, subjects will be enrolled.
k Intensive PK sampling will occur relative to the morning dosing of *ENTO* at the following time points:
Day 1: 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 (pre-PM dose) hours postdose
Day 5: 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 60, 72, 84, and 96 hours postdose
l Trough PK sample is taken pre-morning dose on Days 2 and 4 at approximately the same time each day. An additional trough PK sample is taken at the Follow Up visit.
m From the time of obtaining informed consent through the first administration of study drug, record all SAEs, as well as any non-serious adverse events related to protocol-mandated procedures on the AE eCRF. All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history CRF. See Section 7 Adverse Events and Toxicity Management for additional details.
n Day 4 only
o Day 5 only
p Day -1, before administration of the first dose of study drug, or at any time during clinic confinement.

6.2. Pretreatment Assessments

6.2.1. Screening Visit

Prospective subjects should be screened no more than 28 days prior to administration of the first dose of study drug. If the subject does not begin the treatment phase within this 28-day window, all screening evaluation procedures must be repeated. Screening labs may be repeated once within 28 days prior to administration of study drug to rule out laboratory error.

Subjects should fast (no food or drink, except water), starting from midnight (00:00) or earlier, as appropriate, on the evening prior to the Screening visit to ensure an approximate 8-hour fast prior to the fasted blood sample collection the next morning.

Written informed consent must be obtained from each subject before initiation of any screening procedure. After a subject has provided informed consent, the Investigator and other study personnel will determine if the subject is eligible for participation in the study. This assessment will include a review of the inclusion/exclusion criteria and completion of all screening procedures as outlined in Table 6-1 and described in the following text.

Eligible subjects meeting all of the inclusion criteria and none of the exclusion criteria will be instructed on all protocol requirements, including the restrictions on concomitant medication usage and other substances as well as consumption of food or beverages containing alcohol, caffeine, or xanthine. Subjects will be asked to arrive at the study center on Day -1 for admission assessments.

From the time of obtaining informed consent through the first administration of study drug, record all SAEs, as well as any AE related to protocol-mandated procedures on the AE eCRF. All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history eCRF. See Section 7 Adverse Events and Toxicity Management for additional details.

6.2.2. Admission Assessments

6.2.2.1. Admission

Subjects meeting all eligibility criteria following the screening evaluation will return to the clinic for admission assessments on Day -1. The admission evaluations and/or procedures are outlined in Table 6-1.

Prior to dosing on Day 1, the results of the clinical and laboratory evaluations (as described in Table 6-1) must be reviewed by the Investigator to confirm the continued eligibility of each subject to participate in the study. At the time of randomization, subjects will be assigned a sequential subject number as described in Section 5.1. Subjects will remain confined to the study clinic for the duration as described in Section 6.2.2.2 and Table 6-1.

6.2.2.2. Clinic Confinement

Eligible subjects will be confined to the study center beginning Day -1 until the completion of assessments on Day 9. Subjects will return for an in-clinic follow-up visit 14 (±1) days after the last dose of study drug (i.e., Day 19).

6.3. Check-In Assessments

Subjects meeting all eligibility criteria following the screening evaluation will return to the clinic for admission assessments. The admission evaluations and/or procedures are outlined in Table 6-1. Subjects should be instructed to fast (no food or drink, except water) for 8 hours prior to admission on Day -1, to ensure an approximate 8-hour fast prior to the fasted blood sample collection.

Prior to dosing on Day 1, the results of the clinical and laboratory evaluations (as described in Section 4.1) must be reviewed by the Investigator to confirm the continued eligibility of each subject to participate in the study. **The decision to exclude a subject following that review will be made by the Investigator, in consultation with the Sponsor.**

Upon confirmation of eligibility, subjects will be assigned a sequential subject number as described in Section 5.1. Subjects will remain confined to the clinic for the study as described in Section 3.3 and Table 6-1.

6.4. Treatment Assessments

Study procedures and assessments are outlined in Table 6-1.

6.5. Posttreatment Assessments

All subjects will be instructed to return to the clinic within 14 (± 1) days after the last dose of study drug for follow-up assessments as outlined in Table 6-1.

6.6. Assessments for Premature Discontinuation from Study

If a subject discontinues study treatment dosing (see Section 6.7), for example as a result of an AE, every attempt should be made to keep the subject in the study and continue to perform the required study-related follow-up procedures. If this is not possible or acceptable to the subject or Investigator, the subject may be withdrawn from the study. Evaluations indicating abnormal results believed to be possibly or probably related to study treatment at the ET visit should be repeated weekly or as often as deemed appropriate by the Investigator until the abnormality resolves, returns to baseline visit levels, or is otherwise explained.

If the subject discontinues prematurely from the study, the ET evaluations and/or procedures outlined in Table 6-1 should be performed within 72 hours of permanently discontinuing the study drug.

6.7. Criteria for Discontinuation of Study Drug

Study medication may be discontinued in the following instances:

- Intercurrent illness that would, in the judgment of the Investigator, affect assessments of clinical status to a significant degree
- Unacceptable toxicity, as defined in the toxicity management section of the protocol, or toxicity that, in the judgment of the Investigator, compromises the ability to continue study-specific procedures or is considered not to be in the subject's best interest
- Subject request to discontinue for any reason
- Subject noncompliance
- Pregnancy during the study (Refer to Appendix 4)
- Investigator discretion
- Discontinuation of the study at the request of Gilead, regulatory agency, or an IRB/EC

6.8. Pharmacokinetic Assessments

6.8.1. Plasma PK Collection

Plasma concentrations for ENTO and/or its metabolites (if applicable) will be determined and PK parameters evaluated. Protein binding of ENTO and/or its metabolites (if applicable), may be assessed at their T_{max} time point(s) as well as another later time point.

Intensive PK sampling will occur relative to the morning dose of ENTO at the following time points:

Day 1: 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 (pre-PM dose) hours postdose

Day 5: 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 60, 72, 84, and 96 hours postdose

Trough Sampling: Days 2 and 4: 0 (pre-AM dose, at approximately the same time each day)

An additional PK sample will be collected at the Day 19 Follow-Up visit.

6.9. Safety Assessments

Safety will be evaluated throughout the study. Refer to Table 6-1 for a schedule of assessments.

6.9.1. Electrocardiogram Assessment

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

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

The Investigator or other qualified individuals at the study center will review ECGs to assess for changes in ECG intervals and morphology as compared to pretreatment ECGs. ECG interval measurements output by the machine will be used for bedside safety monitoring.

Collection of additional ECGs for routine safety monitoring at additional time points or days is at the discretion of the Investigator based on GCP.

6.9.2. Physical Examination

Physical examinations conducted throughout the study will be a complete physical examination or a symptom-directed physical examination, as outlined in Table 6-1. The complete physical examination conducted at Screening will also include the following assessments:

- Review medical history, including history of allergies, and history of prior and current use of nicotine or nicotine-containing products, history of alcohol and illegal drug use; and history of prior (within 30 days, or within 3 months for systemic steroids, immunosuppressant therapies, or chemotherapeutic agents) and current medication use.

6.9.3. Vital Signs

Vital sign measurements include blood pressure, pulse, respiration rate, and temperature and will occur throughout the study and will be recorded as outlined in Table 6-1. Vital signs (systolic blood pressure, diastolic blood pressure, respiration rate, temperature and heart rate) should be taken once subjects have been seated or in the supine position for a minimum of approximately 5 minutes. Subject position for measurement should be kept consistent throughout the study. Vital signs should be assessed prior to study drug administration. Refer to Table 6-1 for vital signs collection time points.

6.9.4. Body Mass Index

Height and weight will be collected at Screening for calculation of BMI for inclusion criteria.

6.9.5. Clinical Laboratory Tests/Assessments

Blood and urine samples for safety evaluations will be collected throughout the study as outlined in Table 6-1.

6.9.5.1. Blood Sampling

Blood samples will be collected for the following laboratory analyses:

- Hematology: INR, CBC with differential and platelet, neutrophil, and hemoglobin count.
- Serum chemistry (fasting): alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, α-fetoprotein (at screening only), LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, total cholesterol, HDL, LDL, and triglycerides, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 x ULN).
- Serum pregnancy test (females of childbearing potential only)
- FSH (females only)
- HIV, HBV, and HCV testing (Screening only)
- Genotyping for drug metabolizing enzymes and transporters (Day -1 only, or any day during clinic confinement)

6.9.5.2. Urine Samples

Urine samples will be collected for urinalysis and urine alcohol and drug screening assessments.

6.9.6. Creatinine Clearance

Weight will be collected at Screening and upon admission to calculate creatinine clearance (using the Cockcroft-Gault method) for inclusion criteria.

6.9.7. Adverse Events/Concomitant Medications/Protocol Restrictions

Evaluation for AEs, review of concomitant medications, and review of protocol restrictions will occur at the times shown in Table 6-1. See Section 7 for more information regarding AEs and Sections 4.3 and Section 5.6.1 for more information about concomitant medications.

6.10. Genetic Testing

A blood sample for genetic sampling will be taken in the study as outlined in Table 6-1.

A separate, mandatory blood specimen will be collected for the extraction of DNA for genotyping to identify polymorphisms of drug metabolizing enzymes (such as CYP2C9,

CYP3A4/5, CYP1A2 and UGT1A1) and transporters (such as OATP 1B1/3, P-gp, BCRP and MATE1) to optimize the therapeutic strategy for ENTO. This sample should be collected on Day -1, before administration of the first dose of study drug, but may be collected at any time during clinic confinement.

6.11. Sample Storage

PPD

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 post treatment 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.
- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the Screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg., hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.7.1.)
- 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 preexisting and should be documented on the medical history CRF.

7.1.2. Serious Adverse Events

A **serious adverse event** (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.

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

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

For specific information on handling of clinical laboratory abnormalities in this study, please refer to Section 7.5.

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study Drugs and Procedures

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

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

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

The relationship to study procedures (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

AE severity should be recorded and graded according to the CTCAE Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 4). For adverse events 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.

The distinction between the seriousness and the severity of an adverse event should be noted. Severe is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events.

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

7.3.1. Requirements for collection prior to study drug initiation:

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

7.3.1.1. Adverse Events

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

7.3.1.2. 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 DSPH 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 study drug, he/she should promptly document and report the event to Gilead DSPH.

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

- At the time of study start, SAEs will be reported using a paper serious AE reporting form. During the study conduct, sites may transition to an electronic SAE (eSAE) system. Gilead will notify sites in writing and provide training and account information prior to implementing an eSAE system.

7.3.1.3. Serious Adverse Event Paper Reporting Process

- All SAEs will be recorded on the SAE report form and submitted by faxing or emailing the report form within 24 hours of the investigator's knowledge of the event to the attention of Gilead DSPH or to the designated CRO.

Gilead DSPH: Fax PPD
Email: PPD

7.3.1.4. 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 DSPH 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: Email: PPD and Fax: 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 suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

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

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

7.5. 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) 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, electrocardiogram, X-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2 respectively. 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 GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 4).

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

Treatment-emergent toxicities will be noted by the investigator and brought to the attention of the Gilead Sciences Medical Monitor or designee. Whether or not considered treatment-related, all subjects experiencing AEs must be monitored periodically until symptoms subside, any abnormal laboratory values have resolved or returned to baseline levels or they are considered irreversible, or until there is a satisfactory explanation for the changes observed.

Clinical events and clinically significant laboratory abnormalities will be graded according to the GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 4). Grade 3 and 4 clinically significant laboratory abnormalities should be confirmed by repeat testing as soon as practical to do so, and preferably within 3 calendar days after receipt of the original test results.

- Any questions regarding toxicity management should be directed to the Gilead 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 labelling (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 Gilead DSPH 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 Section 7.3. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead DSPH.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead DSPH 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 DSPH. Gilead DSPH 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 or Gilead DSPH using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the subject should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH,
fax number PPD or email PPD

Refer to Appendix 3 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 DSPH within 24 hours of the investigator becoming aware of the situation.

These reports must consist of situations that involve study drug and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

Special situations involving non-Gilead concomitant medications does not need to be reported on the 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.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary analysis objective of this study is to evaluate the PK of ENTO and/or its metabolites (if applicable) in subjects with impaired hepatic function (stratified by smoking status, as appropriate) relative to matched, healthy controls

The secondary objectives of this study are as follows:

- To evaluate the safety and tolerability of administration of ENTO in subjects with normal and impaired hepatic function
- To evaluate the potential impact of smoking on the PK of ENTO in subjects with moderate hepatic impairment

8.1.2. Primary Endpoint

The primary endpoints are the PK parameters AUC and C_{max} of ENTO and/or its metabolites (if applicable).

8.1.3. Secondary Endpoint

The secondary endpoints are the incidences of adverse events and laboratory abnormalities.

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. PK Analysis Set

The PK analysis set will include all enrolled/randomized subjects who received at least 1 dose of study drug (ENTO) and had at least 1 non-missing PK concentration data reported by PK lab for each respective analyte. This is the primary analysis set for PK summaries.

8.2.1.2. Safety Analysis Set

The safety analysis set will include all enrolled subjects who received at least 1 dose of study drug. This is the primary analysis set for safety summaries.

8.2.1.3. All Enrolled Analysis Set

The all enrolled analysis set will include all subjects who were enrolled into the study. This is the primary analysis set for safety listings.

8.3. Data Handling Conventions

For summary statistics, PK concentration values below the limit of quantitation (BLQ) will be treated as zero at predose and one-half of the lower limit of quantitation (LLOQ) for postdose timepoints, where LLOQ is corrected for the dilution factor (ie, reported dilution/dilution factor).

Laboratory data that are continuous in nature but are less than the lower limit of quantitation or above the upper limit of quantitation will be imputed to the value of the lower or upper limit minus or plus one significant digit, respectively (eg, if the result of a continuous laboratory test is < 20, a value of 19 will be assigned; if the result of a continuous laboratory test is < 20.0, a value of 19.9 will be assigned).

Missing data can have an impact upon the interpretation of the trial data. As this study is of short duration, it is anticipated that missing data will be minimal. In general, values for missing data will not be imputed. However, a missing pretreatment laboratory result would be treated as normal (ie., no toxicity grade) for the laboratory abnormality summary.

8.4. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized and descriptive statistics will be provided.

8.5. Safety Analysis

All safety data collected on or after the date that study drug was first administered up to the date of last dose of study drug plus 30 days will be listed and summarized using safety analysis set.

8.5.1. Extent of Exposure

A subject's extent of exposure to study drug data will be generated from the study drug administration page in eCRF. Exposure data will be listed.

8.5.2. 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.

Adverse event data will be listed by subject. Treatment-emergent AE (TEAE) and Serious TEAE will be summarized by system organ class and preferred term using the current version the Medical Dictionary for Regulatory Activities (MedDRA).

8.5.3. Laboratory Evaluations

Selected laboratory data (clinical chemistry and hematology) will be summarized using only observed data. Absolute values and change from predose at all scheduled time points will be summarized.

Laboratory abnormalities will be graded using GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 4) for analysis purposes.

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least one toxicity grade from predose at any time postdose up to the completion of study follow-up, will be summarized. If predose data are missing, then any graded abnormality (ie, at least a Grade 1) will be considered treatment emergent.

Laboratory abnormalities that occur before the first dose of investigational medicinal product or after the completion of study follow-up will be included in a data listing.

8.5.4. Other Safety Evaluations

ECG data will be summarized over time and presented in a listing.

Individual data for vital signs measurements will be listed by subject and summarized using incidence (frequencies) of events/ abnormalities or descriptive statistical summaries (eg, n, mean, SD, median, and range), as appropriate.

8.6. Pharmacokinetic Analysis

Plasma concentrations of ENTO and/or its metabolites (if applicable) over sampling time will be listed and summarized by hepatic function group and smoking status (Cohort 1 only).

Plasma concentrations of ENTO and/or its metabolites (if applicable) over time will be plotted in semi-logarithmic and linear formats as mean ± SD and as median (Q1, Q3).

The PK parameters will be listed and summarized for ENTO and/or its metabolites (if applicable) using descriptive statistics (e.g., sample size, arithmetic mean, geometric mean, % CV, SD, median, minimum, and maximum) by hepatic function group (normal or CPT Class A, B, or C) and smoking status (Cohort 1 only).

A parametric (normal theory) ANOVA model appropriate for a parallel design will be fitted to the natural logarithmic transformation of PK parameters (AUC_{tau} and C_{max}) for ENTO and/or its metabolites (if applicable). The 90% CIs will be constructed for the GLSM ratios of PK parameters for ENTO and/or its metabolites (if applicable) in each hepatic impairment group versus the matched control (normal hepatic function) group (and for Cohort 1, stratified by smoking status). The 90% CIs will be examined to determine if the GLSM ratio is within limits of 50% to 200%.

ENTO percent protein binding will be summarized by hepatic function group and smoking status (Cohort 1 only), and data for individual subjects will be presented in a listing (if applicable).

8.7. Sample Size

A sample size of 8 evaluable subjects per hepatic function group (for Cohort 1, it is 8 evaluable subjects per hepatic function group within each smoking status group) will provide a

≥ 89% probability for the 90% CI for the GLSM ratio of pharmacokinetic parameters (AUC or C_{max}) for ENTO in the hepatic impairment/dysfunction group(s) versus the appropriate group of matched controls, to be within limits of 50% to 200%. The calculation assumes an expected ratio of geometric means of 1.0 in pharmacokinetic parameters and inter-subject standard deviation of 0.455 for the natural logarithm-transformed pharmacokinetic parameters for ENTO. The assumption is based on the data obtained from a prior clinical study of ENTO (Study GS-US-339-0111).

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. These standards are consistent with the European Union Clinical Trials Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC.

The investigator will ensure adherence to the basic principles of Good Clinical Practice, as outlined in 21 CFR 312, subpart D, “Responsibilities of Sponsors and Investigators,” 21 CFR, part 50, "Protection of Human Subjects", and 21 CFR, part 56, "Institutional Review Boards".

The investigator and all applicable subinvestigators will comply with 21 CFR, Part 54, "Financial Disclosure by Clinical Investigators", providing documentation of their financial interest or arrangements with Gilead, or proprietary interests in the study 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.

9.1.2. Institutional Review Board (IRB)/Independent Ethics Committee (EC) 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/EC. 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/EC any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB/EC approval, with the exception of those necessary to reduce immediate risk to study subjects.

9.1.3. 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 EC-approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB or EC or local requirements.

9.1.4. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, another unique identifier (as allowed by local law) and an identification code will be recorded on any form or biological sample submitted to the Sponsor, IRB/EC, 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 or in accordance with local regulations. 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 investigator brochure, this protocol, CRF/eCRF, the study drug, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.5. 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 two 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/EC 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, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Documentation of the reason(s) a consented subject is not enrolled

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

All clinical study documents must be retained by the investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, 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.

9.1.6. 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 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 (e.g. 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 9.1.5.

9.1.7. Study Drug Accountability and Return

Gilead recommends that used and unused study drug supplies be returned to the shipping facility from which it came for eventual destruction. The study monitor will provide instructions for return. If return is not possible, the study monitor will evaluate each study center's study drug disposal procedures and provide appropriate instruction for destruction of unused study drug supplies. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead QA, the site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files.

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

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

9.1.8. Inspections

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

9.1.9. Protocol Compliance

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

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB/EC in

accordance with local requirements and receive documented IRB/EC approval before modifications can be implemented.

9.2.2. Study Report

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.

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 ECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects’ interests.

10. REFERENCES

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.

Friedberg JW, Sharman J, Sweetenham J, Johnston PB, Vose JM, Lacasce A, et al. Inhibition of Syk with fostamatinib disodium has significant clinical activity in non-Hodgkin lymphoma and chronic lymphocytic leukemia. Blood 2010;115 (13):2578-85.

Morris DL, O'Neil SP, Devraj RV, Portanova JP, Gilles RW, Gross CJ, et al. Acute lymphoid and gastrointestinal toxicity induced by selective p38alpha map kinase and map kinase-activated protein kinase-2 (MK2) inhibitors in the dog. Toxicol Pathol 2010;38 (4):606-18.

Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60 (8):646-9.

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Zhang D, Chando TJ, Everett DW, Patten CJ, Dehal SS, Humphreys WG. In vitro inhibition of UDP glucuronosyltransferases by atazanavir and other HIV protease inhibitors and the relationship of this property to in vivo bilirubin glucuronidation. Drug Metab Dispos 2005;33 (11):1729-39.

11. APPENDICES

Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGEMENT

A Phase 1, Open-Label, Multiple Dose Study to Evaluate the Pharmacokinetics of Entospletinib in Subjects with Normal and Impaired Hepatic Function

GS-US-339-1631 Protocol Amendment 2, 01 July 2016

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

PPD

Author

PPD

1 July 2016
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.

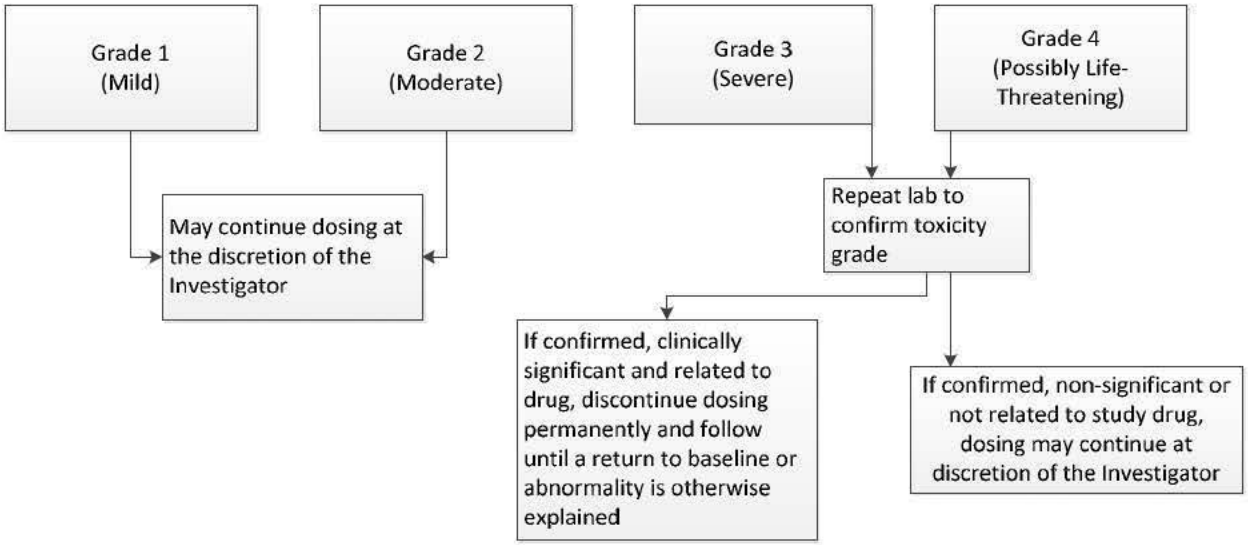
Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Management of Clinical and Laboratory Adverse Events



Appendix 3. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

ENTO is contraindicated in pregnancy as animal studies in rats and rabbits have shown that study drug is teratogenic. Pregnancy must be excluded before the start of treatment with study drug and prevented thereafter by reliable contraceptive methods. Pregnancy tests will be performed regularly throughout this study per Table 6-1. Please refer to the latest version of the investigator's brochure for additional information.

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

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

b) Definition of Male Fertility

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

2) Contraception Requirements for Female Subjects

a) Study Drug Effects on Pregnancy and Hormonal Contraception

ENTO is contraindicated in pregnancy as there is a strong suspicion of human teratogenicity/fetotoxicity in early pregnancy based on non-clinical data. In addition, ENTO has insufficient data to exclude the possibility of a clinically relevant interaction with hormonal contraception that results in reduced contraception efficacy; therefore, contraceptive steroids are not recommended as a contraceptive method either solely or as a part of a contraceptive regimen. Please refer to the latest version of the investigator's brochure for additional information.

b) Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of highly effective contraceptive measures. They must also not rely on hormone-containing contraceptives as a form of birth control during the study. They must have a negative serum pregnancy test at Screening and a negative pregnancy test on the Baseline/Day -1 visit. Pregnancy tests will be performed on the protocol-specified schedule thereafter. Female subjects must agree to one of

the following methods to avoid pregnancy from Screening until 30 days from the last dose of ENTO:

- 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
  - Tubal sterilization
  - Essure micro-insert system (provided confirmation of success 3 months after procedure)
  - Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until at least 30 days from the last dose of ENTO.

3) Contraception Requirements for Male Subjects

It is theoretically possible that a relevant systemic concentration may be achieved in a female partner from exposure of the male subject's seminal fluid. Therefore, male subjects with female partners of childbearing potential must use condoms during treatment and until 90 days from the last dose of ENTO. Additional contraception recommendations should also be considered if the female partner is not pregnant.

Male subjects must also refrain from sperm donation during treatment and until at least 90 days from the last dose of ENTO.

4) Unacceptable Birth Control Methods

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

5) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 30 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. Subjects whose partner has become pregnant or suspects she is pregnant during the study must report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.7.2.1.

Appendix 4. GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

Version: 18 June 2012

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin HIV POSITIVE **Adult and Pediatric ≥ 57 Days**	8.5 to 10.0 g/dL 85 to 100 g/L	7.5 to < 8.5 g/dL 75 to < 85 g/L	6.5 to < 7.5 g/dL 65 to < 75 g/L	< 6.5 g/dL < 65 g/L
HIV NEGATIVE **Adult and Pediatric ≥ 57 Days**	10.0 to 10.9 g/dL 100 to 109 g/L OR Any decrease from Baseline 2.5 to < 3.5 g/dL 25 to < 35 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L OR Any decrease from Baseline 3.5 to < 4.5 g/dL 35 to < 45 g/L	7.0 to < 9.0 g/dL 70 to < 90 g/L OR Any decrease from Baseline ≥ 4.5 g/dL ≥ 45 g/L	< 7.0 g/dL < 70 g/L
Infant, 36–56 Days (HIV POSITIVE OR NEGATIVE)	8.5 to 9.4 g/dL 85 to 94 g/L	7.0 to < 8.5 g/dL 70 to < 85 g/L	6.0 to < 7.0 g/dL 60 to < 70 g/L	< 6.0 g/dL < 60 g/L
Infant, 22–35 Days (HIV POSITIVE OR NEGATIVE)	9.5 to 10.5 g/dL 95 to 105 g/L	8.0 to < 9.5 g/dL 80 to < 95 g/L	7.0 to < 8.0 g/dL 70 to < 80 g/L	< 7.0 g/dL < 70 g/L
Infant, 1–21 Days (HIV POSITIVE OR NEGATIVE)	12.0 to 13.0 g/dL 120 to 130 g/L	10.0 to < 12.0 g/dL 100 to < 120 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L	< 9.0 g/dL < 90 g/L
Absolute Neutrophil Count (ANC) **Adult and Pediatric, > 7 Days**	1000 to 1300/mm^3 1.00 to 1.30 GI/L	750 to < 1000/mm^3 0.75 to < 1.00 GI/L	500 to < 750/mm^3 0.50 to < 0.75 GI/L	< 500/mm^3 < 0.50 GI/L
Infant, 2 – ≤ 7 Days	1250 to 1500/mm^3 1.25 to 1.50 GI/L	1000 to < 1250/mm^3 1.00 to < 1.25 GI/L	750 to < 1000/mm^3 0.75 to < 1.00 GI/L	< 750/mm^3 < 0.75 GI/L
Infant, 1 Day	4000 to 5000/mm^3 4.00 to 5.00 GI/L	3000 to < 4000/mm^3 3.00 to < 4.00 GI/L	1500 to < 3000/mm^3 1.50 to < 3.00 GI/L	< 1500/mm^3 < 1.50 GI/L

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Absolute CD4+ Count HIV NEGATIVE ONLY **Adult and Pediatric** **> 13 Years**	300 to 400/mm^3 300 to 400/µL	200 to < 300/mm^3 200 to < 300/µL	100 to < 200/mm^3 100 to < 200/µL	< 100/mm^3 < 100/µL
Absolute Lymphocyte Count HIV NEGATIVE ONLY **Adult and Pediatric** **> 13 Years**	600 to 650/mm^3 0.60 to 0.65 GI/L	500 to < 600/mm^3 0.50 to < 0.60 GI/L	350 to < 500/mm^3 0.35 to < 0.50 GI/L	< 350/mm^3 < 0.35 GI/L
Platelets	100,000 to < 125,000/mm^3 100 to < 125 GI/L	50,000 to < 100,000/mm^3 50 to < 100 GI/L	25,000 to < 50,000/mm^3 25 to < 50 GI/L	< 25,000/mm^3 < 25 GI/L
WBCs	2000/mm^3 to 2500/mm^3 2.00 GI/L to 2.50 GI/L	1,500 to < 2,000/mm^3 1.50 to < 2.00 GI/L	1000 to < 1,500/mm^3 1.00 to < 1.50 GI/L	< 1000/mm^3 < 1.00 GI/L
Hypofibrinogenemia	100 to 200 mg/dL 1.00 to 2.00 g/L	75 to < 100 mg/dL 0.75 to < 1.00 g/L	50 to < 75 mg/dL 0.50 to < 0.75 g/L	< 50 mg/dL < 0.50 g/L
Hyperfibrinogenemia	> ULN to 600 mg/dL > ULN to 6.0 g/L	> 600 mg/dL > 6.0 g/L	— —	— —
Fibrin Split Product	20 to 40 µg/mL 20 to 40 mg/L	> 40 to 50 µg/mL > 40 to 50 mg/L	> 50 to 60 µg/mL > 50 to 60 mg/L	> 60 µg/mL > 60 mg/L
Prothrombin Time (PT)	> 1.00 to 1.25 × ULN	> 1.25 to 1.50 × ULN	> 1.50 to 3.00 × ULN	> 3.00 × ULN
International Normalized Ratio of prothrombin time (INR)	1.1 to 1.5 x ULN	>1.5 to 2.0 x ULN	>2.0 to 3.0 x ULN	>3.0 x ULN
Activated Partial Thromboplastin Time (APTT)	> 1.00 to 1.66 × ULN	> 1.66 to 2.33 × ULN	> 2.33 to 3.00 × ULN	> 3.00 × ULN
Methemoglobin	5.0 to 10.0%	> 10.0 to 15.0%	> 15.0 to 20.0%	> 20.0%

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130 to <LLN mEq/L 130 to <LLN mmol/L	125 to < 130 mEq/L 125 to < 130 mmol/L	121 to < 125 mEq/L 121 to < 125 mmol/L	< 121 mEq/L < 121 mmol/L
Hypernatremia	146 to 150 mEq/L 146 to 150 mmol/L	> 150 to 154 mEq/L > 150 to 154 mmol/L	> 154 to 159 mEq/L > 154 to 159 mmol/L	> 159 mEq/L > 159 mmol/L
Hypokalemia	3.0 to 3.4 mEq/L 3.0 to 3.4 mmol/L	2.5 to < 3.0 mEq/L 2.5 to < 3.0 mmol/L	2.0 to < 2.5 mEq/L 2.0 to < 2.5 mmol/L	< 2.0 mEq/L < 2.0 mmol/L
Hyperkalemia	5.6 to 6.0 mEq/L 5.6 to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
Hypoglycemia **Adult and Pediatric** **≥ 1 Month** **Infant, < 1 Month**	55 to 64 mg/dL 3.03 to 3.58 mmol/L 50 to 54 mg/dL 2.8 to 3.0 mmol/L	40 to < 55 mg/dL 2.20 to < 3.03 mmol/L 40 to < 50 mg/dL 2.2 to < 2.8 mmol/L	30 to < 40 mg/dL 1.64 to < 2.20 mmol/L 30 to < 40 mg/dL 1.7 to < 2.2 mmol/L	< 30 mg/dL < 1.64 mmol/L < 30 mg/dL < 1.7 mmol/L
Hyperglycemia, Nonfasting	116 to 160 mg/dL 6.42 to 8.91 mmol/L	> 160 to 250 mg/dL > 8.91 to 13.90 mmol/L	> 250 to 500 mg/dL > 13.90 to 27.79 mmol/L	> 500 mg/dL > 27.79 mmol/L
Hyperglycemia, Fasting	110 to 125 mg/dL 6.08 to 6.96 mmol/L	>125 to 250 mg/dL >6.96 to 13.90 mmol/L	>250 to 500 mg/dL >13.90 to 27.79 mmol/L	>500 mg/dL >27.79 mmol/L
Hypocalcemia (corrected for albumin if appropriate*) **Adult and Pediatric** **≥ 7 Days** **Infant, < 7 Days**	7.8 to 8.4 mg/dL 1.94 to 2.10 mmol/L 6.5 to 7.5 mg/dL 1.61 to 1.88 mmol/L	7.0 to < 7.8 mg/dL 1.74 to < 1.94 mmol/L 6.0 to < 6.5 mg/dL 1.49 to < 1.61 mmol/L	6.1 to < 7.0 mg/dL 1.51 to < 1.74 mmol/L 5.5 to < 6.0 mg/dL 1.36 to < 1.49 mmol/L	< 6.1 mg/dL < 1.51 mmol/L < 5.5 mg/dL < 1.36 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypercalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥ 7 Days** **Infant, < 7 Days**	>ULN to 11.5 mg/dL >ULN to 2.88 mmol/L 11.5 to 12.4 mg/dL 2.86 to 3.10 mmol/L	> 11.5 to 12.5 mg/dL > 2.88 to 3.13 mmol/L > 12.4 to 12.9 mg/dL > 3.10 to 3.23 mmol/L	> 12.5 to 13.5 mg/dL > 3.13 to 3.38 mmol/L > 12.9 to 13.5 mg/dL > 3.23 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L > 13.5 mg/dL > 3.38 mmol/L
Hypocalcemia (ionized)	3.0 mg/dL to < LLN 0.74 mmol/L to < LLN	2.5 to < 3.0 mg/dL 0.62 to < 0.74 mmol/L	2.0 to < 2.5 mg/dL 0.49 to < 0.62 mmol/L	< 2.0 mg/dL < 0.49 mmol/L
Hypercalcemia (ionized)	> ULN to 6.0 mg/dL > ULN to 1.50 mmol/L	> 6.0 to 6.5 mg/dL > 1.50 to 1.63 mmol/L	> 6.5 to 7.0 mg/dL > 1.63 to 1.75 mmol/L	> 7.0 mg/dL > 1.75 mmol/L
Hypomagnesemia	1.40 to <LLN mg/dL 1.2 to <LLN mEq/L 0.58 to <LLN mmol/L	1.04 to < 1.40 mg/dL 0.9 to < 1.2 mEq/L 0.43 to < 0.58 mmol/L	0.67 to < 1.04 mg/dL 0.6 to < 0.9 mEq/L 0.28 to < 0.43 mmol/L	< 0.67 mg/dL < 0.6 mEq/L < 0.28 mmol/L
Hypophosphatemia **Adult and Pediatric > 14 Years** **Pediatric 1 Year–14 Years** **Pediatric < 1 Year**	2.0 to < LLN mg/dL 0.63 to < LLN mmol/L 3.0 to 3.5 mg/dL 0.96 to 1.14 mmol/L 3.5 to 4.5 mg/dL 1.12 to 1.46 mmol/L	1.5 to < 2.0 mg/dL 0.47 to < 0.63 mmol/L 2.5 to < 3.0 mg/dL 0.80 to < 0.96 mmol/L 2.5 to < 3.5 mg/dL 0.80 to < 1.12 mmol/L	1.0 to < 1.5 mg/dL 0.31 to < 0.47 mmol/L 1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L 1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.0 mg/dL < 0.31 mmol/L < 1.5 mg/dL < 0.47 mmol/L < 1.5 mg/dL < 0.47 mmol/L
Hyperbilirubinemia **Adult and Pediatric > 14 Days** **Infant, ≤ 14 Days** (non-hemolytic) **Infant, ≤ 14 Days** (hemolytic)	> 1.0 to 1.5 × ULN NA NA	> 1.5 to 2.5 × ULN 20.0 to 25.0 mg/dL 342 to 428 µmol/L NA	> 2.5 to 5.0 × ULN > 25.0 to 30.0 mg/dL > 428 to 513 µmol/L 20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 5.0 × ULN > 30.0 mg/dL > 513 µmol/L > 25.0 mg/dL > 428 µmol/L
Blood Urea Nitrogen	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyperuricemia	>ULN to 10.0 mg/dL >ULN to 597 µmol/L	> 10.0 to 12.0 mg/dL > 597 to 716 µmol/L	> 12.0 to 15.0 mg/dL > 716 to 895 µmol/L	> 15.0 mg/dL > 895 µmol/L
Hypouricemia	1.5 mg/dL to < LLN 87 µmol/L to < LLN	1.0 to < 1.5 mg/dL 57 to < 87 µmol/L	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L
Creatinine	> 1.50 to 2.00 mg/dL > 133 to 177 µmol/L	> 2.00 to 3.00 mg/dL > 177 to 265 µmol/L	> 3.00 to 6.00 mg/dL > 265 to 530 µmol/L	> 6.00 mg/dL > 530 µmol/L
Bicarbonate	16.0 mEq/L to < LLN 16.0 mmol/L to < LLN	11.0 to < 16.0 mEq/L 11.0 to < 16.0 mmol/L	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L
Triglycerides (Fasting)	NA	500 to 750 mg/dL 5.64–8.47 mmol/L	> 750 to 1200 mg/dL > 8.47–13.55 mmol/L	> 1200 mg/dL > 13.55 mmol/L
LDL (Fasting)	130 to 160 mg/dL 3.35 to 4.15 mmol/L	>160 to 190 mg/dL >4.15 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L	NA
Pediatric >2 to <18 years	110 to 130 mg/dL 2.84 to 3.37 mmol/L	>130 to 190 mg/dL >3.37 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L	NA
Hypercholesterolemia (Fasting)	200 to 239 mg/dL 5.16 to 6.19 mmol/L	> 239 to 300 mg/dL > 6.19 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
Pediatric < 18 Years	170 to 199 mg/dL 4.39 to 5.15 mmol/L	> 199 to 300 mg/dL > 5.15 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
Creatine Kinase	3.0 to < 6.0 × ULN	6.0 to < 10.0 × ULN	10.0 to < 20.0 × ULN	≥ 20.0 × ULN

* Calcium should be corrected for albumin if albumin is < 4.0 g/dL

ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT)	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
ALT (SGPT)	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
GGT	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Alkaline Phosphatase	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Total Amylase	> 1.0 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 5.0 × ULN	> 5.0 × ULN
Pancreatic Amylase	> 1.0 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 5.0 × ULN	> 5.0 × ULN
Lipase	> 1.0 to 1.5 × ULN	> 1.5 to 3.0 × ULN	> 3.0 to 5.0 × ULN	> 5.0 × ULN
Albumin	3.0 g/dL to < LLN 30 g/L to < LLN	2.0 to < 3.0 g/d 20 to < 30 g/L	< 2.0 g/dL < 20 g/L	NA

URINALYSIS				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hematuria (Dipstick)	1+	2+	3-4+	NA
Hematuria (Quantitative) See Note below Females	>ULN - 10 RBC/HPF	> 10-75 RBC/HPF	> 75 RBC/HPF	NA
Males	6-10 RBC/HPF	> 10-75 RBC/HPF	> 75 RBC/HPF	NA
Proteinuria (Dipstick)	1+	2–3+	4+	NA
Proteinuria, 24 Hour Collection **Adult and Pediatric ≥ 10 Years**	200 to 999 mg/24 h	>999 to 1999 mg/24 h	>1999 to 3500 mg/24 h	> 3500 mg/24 h
Pediatric > 3 Mo to < 10 Years	201 to 499 mg/m^2/24 h	>499 to 799 mg/m^2/24 h	>799 to 1000 mg/m^2/24 h	> 1000 mg/ m^2/24 h
Glycosuria (Dipstick)	1+	2-3+	4+	NA

Notes:

- Toxicity grades for Quantitative and Dipstick Hematuria will be assigned by Covance Laboratory, however for other laboratories, toxicity grades will only be assigned to Dipstick Hematuria.
- With the exception of lipid tests, any graded laboratory test with a result that is between the LLN and ULN should be assigned Grade 0.
- If the severity of a clinical AE could fall under either one of two grades (e.g., the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE.

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cardiac Arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/ Infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs indicated (for children ≤ 10 cc/kg) indicated
Hypertension (with repeat testing at same visit)	140–159 mmHg systolic OR 90–99 mmHg diastolic	> 159–179 mmHg systolic OR > 99–109 mmHg diastolic	> 179 mmHg systolic OR > 109 mmHg diastolic	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization (other than ER visit) indicated
Pediatric ≤ 17 Years (with repeat testing at same visit)	NA	91st–94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial Effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life-threatening physiologic consequences OR Effusion with nonurgent intervention indicated	Life-threatening consequences (eg, tamponade) OR Urgent intervention indicated

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Prolonged PR Interval	PR interval 0.21 to 0.25 sec	PR interval > 0.25 sec	Type II 2nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
Pediatric ≤ 16 Years	1st degree AV block (PR > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block
Prolonged QTc	Asymptomatic, QTc interval 0.45 to 0.47 sec OR Increase interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 to 0.49 sec OR Increase in interval 0.03 to 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia
Pediatric ≤ 16 Years	Asymptomatic, QTc interval 0.450 to 0.464 sec	Asymptomatic, QTc interval 0.465 to 0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/Embolism	NA	Deep vein thrombosis AND No intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Embolic event (eg, pulmonary embolism, life-threatening thrombus)
Vasovagal Episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular Dysfunction (congestive heart failure, CHF)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic CHF	Life-threatening CHF

RESPIRATORY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Bronchospasm (acute)	FEV1 or peak flow reduced to 70% to 80%	FEV1 or peak flow 50% to 69%	FEV1 or peak flow 25% to 49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or Respiratory Distress	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated
Pediatric < 14 Years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90% to 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated

OCULAR/VISUAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual Changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

SKIN				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alopecia	Thinning detectable by study participant or caregiver (for disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous Reaction – Rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [eg, tube feeding or total parenteral nutrition]
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (eg, diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (eg, sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (eg, obstruction)
Diarrhea **Adult and Pediatric ≥ 1 Year**	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline/24 hr	Persistent episodes of unformed to watery stools OR Increase of 4–6 stools over baseline per 24 hrs.	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (eg, hypotensive shock)
Pediatric < 1 Year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Mucositis/Stomatitis (clinical exam) See also Proctitis, Dysphagia-Odynophagia	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (eg, aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24–48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than ER visit)	Symptomatic AND Hospitalization indicated (other than ER visit)	Life-threatening consequences (eg, sepsis, circulatory failure, hemorrhage)
Proctitis (functional-symptomatic) Also see Mucositis/ Stomatitis for Clinical Exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social/ functional activities OR Operative intervention indicated	Life-threatening consequences (eg, perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated	Life-threatening consequences (eg, hypotensive shock)

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alteration in Personality-Behavior or in Mood (eg, agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (eg, suicidal/homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and Behavioral/Attentional Disturbance (including dementia and ADD)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions
Cognitive and Behavioral/Attentional Disturbance (including dementia and Attention Deficit Disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
CNS Ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Developmental delay – **Pediatric ≤ 16 Years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than ER visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social/functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular Weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Seizure: (new onset)	NA	1 seizure	2–4 seizures	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)
Seizure: (pre-existing) For Worsening of Existing Epilepsy the Grades Should Be Based on an Increase from Previous Level of Control to Any of These Levels	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR infrequent breakthrough seizures while on stable meds in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (eg, severity or focality)	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)
Seizure **– Pediatric < 18 Years**	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5-20 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting > 20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions

MUSCULOSKELETAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss	BMD t-score or z-score –2.5 to –1.0	BMD t-score or z-score < –2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Pediatric < 21 Years	BMD z-score –2.5 to –1.0	BMD z-score < –2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions

SYSTEMIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Acute Systemic Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7°C to 38.6°C 99.8°F to 101.5°F	38.7°C to 39.3°C 101.6°F to 102.8°F	39.4°C to 40.5°C 102.9°F to 104.9°F	> 40.5°C > 104.9°F
Pain- Indicate Body Site See also Injection Site Pain, Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than ER visit) indicated
Unintentional Weight Loss	NA	5% to 9% loss in body weight from baseline	10% to 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [eg, tube feeding or total parenteral nutrition]

INJECTION SITE REACTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Injection Site Pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than ER visit) indicated for management of pain/tenderness
Injection Site Reaction (Localized), > 15 Years **Pediatric ≤ 15 Years**	Erythema OR Induration of 5 × 5 cm to 9 × 9 cm (or 25–81 × cm^2) **Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter**	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2) **Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (eg, upper arm/thigh)**	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage **Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (eg, upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage**	Necrosis (involving dermis and deeper tissue) **Necrosis (involving dermis and deeper tissue)**
Pruritis Associated with Injection See also Skin: Pruritis (itching—no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 h treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 h treatment	Generalized itching causing inability to perform usual social & functional activities	NA

ENDOCRINE/METABOLIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Lipodystrophy (eg, back of neck, breasts, abdomen)	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes Mellitus	NA	New onset without need to initiate medication OR Modification of current meds to regain glucose control	New onset with initiation of indicated med OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (eg, ketoacidosis, hyperosmolar non-ketotic coma)
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, myxedema coma)
Lipoatrophy (eg, fat loss from the face, extremities, buttocks)	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

GENITOURINARY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Intermenstrual Bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic exam	Intermenstrual bleeding not greater in duration or amount than usual menstrual cycle	Intermenstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary Tract obstruction (eg, stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

INFECTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Infection (any other than HIV infection)	Localized, no systemic antiμbial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antiμbial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antiμbial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (eg, septic shock)

Basic Self-care Functions: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.
Usual Social & Functional Activities: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Appendix 5. Child -Pugh-Turcotte Score

Child-Pugh classification of severity of liver disease

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin	<2 mg/dL (<34.2 micromol/liter)	2-3 mg/dL (34.2 to 51.3 micromol/liter)	>3 mg/dL (>51.3 micromol/liter)
Albumin	>3.5 g/dL (35 g/liter)	2.8-3.5 g/dL (28 to 35 g/liter)	<2.8 g/dL (<28 g/liter)
Prothrombin time			
Seconds over control	<4	4-6	>6
INR	<1.7	1.7-2.3	>2.3
Encephalopathy	None	Grade 1-2	Grade 3-4

Modified Child-Pugh classification of the severity of liver disease according to the degree of ascites, the plasma concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy. A total score of 5-6 is considered grade A (well-compensated disease); 7-9 is grade B (significant functional compromise); and 10-15 is grade C (decompensated disease). These grades correlate with one- and two-year patient survival: grade A - 100 and 85 percent; grade B - 80 and 60 percent; and grade C - 45 and 35 percent.