CLINICAL STUDY PROTOCOL

Study Title:	A Randomized Open-Label Phase III Study of Sacituzumab Govitecan Versus Treatment of Physician's Choice in Subjects with Metastatic or Locally Advanced Unresectable Urothelial Cancer
Plain Language Short Title:	Study of Sacituzumab Govitecan Versus Physician's Choice of Treatment in Participants With Urothelial Cancer That Cannot Be Removed or Has Spread
Sponsor:	Gilead Sciences, Inc. (Immunomedics, Inc. is now part of the Gilead group of companies) 333 Lakeside Drive Foster City, CA 94404
IND Number: **EU CT Number:** **Clinical Trials.gov Identifier:**	140084 2024-513870-23 NCT04527991
Indication:	Unresectable locally advanced or metastatic urothelial cancer
Protocol ID:	IMMU-132-13
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Original: 09 June 2020 Amendment 1: 11 November 2020 Amendment 2: 21 December 2020 Amendment 3: 14 July 2021 Amendment 4: 16 August 2021 Amendment 4.1 China: 15 December 2021 Amendment 5: 08 June 2022 Amendment 6: 30 August 2024 A high-level summary of the changes in each amendment is provided in Appendix 18.11.
Country-specific Requirements:	Country-specific requirements, as applicable, are listed in Appendix 18.10

This study will be conducted under United States Food and Drug Administration investigational new drug application regulations (21 Code of Federal Regulations Part 312); however, all sites outside the US are not included under the investigational new drug (IND) application and are not considered to be IND application sites.

PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
(Immunomedics, Inc. is now part of the Gilead group of companies)
333 Lakeside Drive
Foster City, CA 94404

Name of Sponsor/Company: Gilead Sciences, Inc. (Immunomedics, Inc. is now part of the Gilead group of companies)		
Name of Investigational Product: sacituzumab govitecan		
Name of Active Ingredient: sacituzumab govitecan is an antibody-drug conjugate (ADC) composed of hRS7, a humanized IgG1κ monoclonal antibody (mAb) which binds to trophoblast cell surface antigen-2 (Trop-2), SN-38, a camptothecin analog, which is an inhibitor of topoisomerase I, and CL2A, a pH-sensitive linker which couples SN-38 to hRS7.		
Protocol Number: IMMU-132-13	**Phase:** III	**Country:** Global
Title of Study: A Randomized Open-Label Phase III Study of Sacituzumab Govitecan Versus Treatment of Physician's Choice in Subjects with Metastatic or Locally Advanced Unresectable Urothelial Cancer		
Plain Language Short Title: Study of Sacituzumab Govitecan Versus Physician's Choice of Treatment in Participants With Urothelial Cancer That Cannot Be Removed or Has Spread		
Study Period (years): 3.5 years (approximately)	**Phase of Development:** III	

Study Objectives

Primary Objective:

To assess overall survival (OS) with sacituzumab govitecan in comparison with treatment of physician's choice (TPC) in subjects with metastatic or locally advanced unresectable urothelial cancer (UC)

Secondary Objectives:

1) To assess progression-free survival (PFS) of sacituzumab govitecan in comparison with TPC by investigator assessment and blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
2) To assess objective response rate (ORR), clinical benefit rate (CBR), and duration of objective tumor response (DOR) with sacituzumab govitecan in comparison with TPC by investigator assessment and BICR using RECIST v1.1
3) To assess safety and tolerability of sacituzumab govitecan in comparison with TPC
4) To assess Quality of Life (QOL) based on European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) with sacituzumab govitecan in comparison with TPC

Exploratory Objectives:

1) To assess and compare efficacy in a subset defined by tumor expression of Trop-2 and ascertain the role of expression of Trop-2 as a biomarker for response
2) To investigate potential blood and tumor biomarkers of response
3) To investigate potential correlation between serum sacituzumab govitecan pharmacokinetics (PK) and the development of immunogenicity (ADA)
4) To characterize the PK of sacituzumab govitecan in metastatic UC subjects
5) To assess additional QOL endpoints of sacituzumab govitecan in comparison with TPC.

Study Design

This is a Phase III, global, multicenter, open-label randomized controlled trial in which approximately 696 subjects with metastatic or locally advanced unresectable (UC) who have progressed after prior therapy with platinum-based regimen and anti-programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) therapy will be randomized in a 1:1 ratio to either sacituzumab govitecan arm or TPC arm.

Subjects in the TPC arm will have 1 of 3 standard of care (SOC) chemotherapeutic options including paclitaxel, docetaxel, and vinflunine. Subjects will be stratified by their type of prior platinum (cisplatin or carboplatin), Bellmunt risk factors (0-1, 2-3), and prior type of therapy in which platinum was administered (neo-adjuvant/adjuvant, locally advanced unresectable/metastatic). The most recent line of platinum therapy should be used for the stratification factor. Subjects randomized to the sacituzumab govitecan arm will receive 10 mg/kg of sacituzumab govitecan intravenously (IV) on Day 1 and Day 8 of 21-day cycles. Those randomized to the TPC arm will have the choice of receiving paclitaxel, docetaxel, and vinflunine (in countries where vinflunine is approved and is commercially available) administered IV at SOC doses of 175, 75, and 320 mg/m^2, respectively, on Day 1 of 21-day cycles, and the determined dosing schedule for these treatments should be adhered to. After a subject is randomized to a TPC, the subject must continue with the same treatment for the duration of the study.

All subjects will be treated until disease progression (PD), unacceptable toxicity, withdrawal of consent or until another treatment discontinuation criterion is met (See Section 5.3 Criteria for Treatment Discontinuation). All subjects will be followed for survival every 8 weeks after study drug discontinuation. Treatment beyond PD may be permitted in subjects deemed to be receiving clinical benefit as per investigator's assessment. Response will be assessed in all subjects by RECIST v1.1 every 6 weeks for the first 12 months and every 9 weeks thereafter until there is evidence of PD, including subjects who discontinue prematurely due to toxicity.

The primary endpoint is OS. Secondary endpoints include PFS, ORR, CBR and DOR evaluated by investigator assessment and BICR using RECIST v1.1, assessment of safety and tolerability, and QOL assessment measured by EORTC QLQ-C30 scores.

An independent Data Monitoring Committee (DMC) will be convened at regular intervals to assess the progress of this study and review safety per an approved DMC charter.

The DMC will meet at the time of interim analysis when at least 65% of total OS events have been accrued to independently review this data.

Study modifications after the final OS analysis and implementation of Protocol Amendment 6 (PA6):

After the final OS analysis and following implementation of PA6, subjects in the sacituzumab govitecan arm who are still receiving treatment may continue treatment as part of the study for as long as they are deriving clinical benefit. Radiographic tumor assessments per protocol will be discontinued; however, treatment response should continue to be evaluated per standard of care. Information on drug administration and safety assessments will continue to be collected. Subjects in the TPC arm will be discontinued from the study; however, they may receive commercially available TPC treatment outside of the study, if deriving continued clinical benefit. Subjects in either treatment arm, who were being followed for survival and subsequent therapy at the time of PA6 implementation, will be discontinued from the study and survival follow-up with subsequent therapy information will no longer be collected.

Methodology

Screening and Baseline Evaluations:

The screening evaluations that must be performed within 28 days prior to Cycle 1 Day 1 (C1D1) include subject's medical and surgical history, complete physical examination, imaging including brain magnetic resonance imaging (MRI) if brain metastases are known/suspected, urinalysis, hematology, blood chemistry, coagulation, LDH, uric acid, and hepatitis B and C testing. The rationale for cisplatin ineligibility for each ineligible subject will also be documented during screening.

Baseline evaluations that must be performed within 3 days or on C1D1 prior to dosing include routine serum chemistries, complete blood count (CBC) with differential, Eastern Cooperative Oncology Group (ECOG) performance score, QOL assessments with EORTC QLQ-C30 and EuroQOL EQ-5D-5L questionnaires. Blood samples for biomarker analysis will be collected at baseline, pre-dose on Cycle 2, Day 1 (C2D1), and at the time of PD, if clinically feasible. In females of childbearing potential, a negative serum pregnancy test is required during screening. A negative urine pregnancy test is required at baseline prior to study treatment administration on C1D1 (unless the screening serum pregnancy test was performed within 72 hours prior to study treatment administration on C1D1).

Twelve-lead electrocardiogram (ECG) will be obtained at baseline, and/or prior to the C1D1 infusion. For subjects receiving vinflunine, ECGs will also be obtained prior to infusion on C2D1 and C3D1. As per the summary of product characteristics for certain TPC agents, additional cardiac monitoring, including echocardiography, may be required. Abnormal findings should be evaluated as clinically indicated, including repeated ECGs. ECGs may be done at other time points during the study if clinically indicated.

Evaluations During Course of Study:

Serum samples for PK and immunogenicity (anti-drug antibody [ADA]) analysis will be collected only for subjects receiving sacituzumab govitecan. Collection times for ADA samples are at pre-dose on Day 1 of Cycles 1, 3, 5, 7, 9, 11 and every 3 cycles thereafter (eg, Cycles 14, 17, etc.), and at end-of-treatment (EOT) visit. The collection window for ADA samples is -30 minutes. Collection times for PK samples are Cycle 1 and Cycle 5 (Day 1: pre-dose, 30 and 60 minutes post end of infusion; Day 8: pre-dose only); Cycle 2–Cycle 4 (Day 1: pre-dose only).

The collection window for PK sample is -30 minutes for pre-dose and +10 minutes for post dose samples.

In female subjects of childbearing potential, urine pregnancy testing will continue on Day 1 of each treatment cycle starting from Cycle 2 through last cycle and every 28 days after the last dose of study drug up to 6 months after the last dose of study drug.

Adverse events (AEs), concomitant medications (continued, changed, and new), hematology and chemistry blood work will be obtained during every study visit with appropriate follow-up of clinically significant abnormal laboratory assessments or AEs. National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0 toxicity grades will be used to classify safety evaluations and AEs, including serious adverse events (SAEs).

SAEs must be reported to the Sponsor's designee within 24 hours of knowledge of the event. Treatment-related AEs and SAEs will be followed until recovery or stabilization in the event of residual effects. Abnormal laboratory values that are clinically significant must be repeated within 48 hours or as per the Principal Investigator discretion and followed until resolution.

Response assessments by computed tomography (CT)/MRI with IV contrast (chest, abdomen, pelvis, other areas of known/suspected involvement), unless known history of anaphylaxis to contrast or any other conditions that would preclude a subject from receiving contrast, will be performed every 6 weeks for the first 12 months from C1D1 and then every 9 weeks thereafter until the occurrence of PD. Scans may be performed within ±5 days of the scheduled visits. Brain MRI is only needed in subjects with known or suspected brain metastases at the study entry. Subjects who discontinue treatment for reasons other than PD will continue with radiologic response assessments per protocol-required schedule, if clinically feasible, until PD, or initiation of new therapy. The reason for treatment discontinuation will be documented and any treatment-related AEs or clinically significant abnormal laboratory values at that time will be followed until resolution or stabilization.

QOL assessments with EORTC QLQ-C30 and EuroQOL EQ-5D-5L questionnaires will be obtained (per RECIST schedule) at: baseline, prior to dosing on Day 1 of every cycle starting from C2D1, and at the EOT visit. EQ-5D-5L will also be assessed at initial determination of PD.

For evaluation of expression of Trop-2 and other biomarkers, archival tissue can be submitted. If a biopsy is obtained as part of SOC, a sample of this may be submitted if archival tissue is not available. Fine needle aspiration and bone biopsies are not suitable samples. This testing is optional and not required for study eligibility.

Biological specimens will be collected from all subjects who provide consent to participate in this study and consent to the optional biomarker collection and may be used to evaluate the association of systemic (blood) and/or tissue-based biomarkers with study drug response (including efficacy and/or AEs) and dose. Biomarker samples may also be used to better understand the mechanism of action of sacituzumab govitecan, disease biology, and relevant biological pathways in metastatic solid tumor diseases. Samples to measure biomarkers may include but will not be limited to the following:

- Archival tissue; a new baseline biopsy may be obtained, if archival tissue is not available.
- Blood samples for biomarker analysis will be collected from all subjects.

- Optional blood collection for germline sequencing. These samples should be collected at the baseline/C1D1 visit. If the optional sample is not collected at C1D1, it can be collected at any other visit. These samples may be used as a control sample for the molecular profiling of the tumor tissues as described above.

In addition to the study-specific informed consent form (ICF) to be signed by each subject participating in the study, subjects will be required to document agreement to provide additional samples for optional genomic research. Additional samples will be obtained from subjects who agree to participate and provide their additional specific consent. These samples should be collected at the baseline/C1D1 visit but may be collected at any time during the study or at a separate post study visit, if necessary.

In addition to the study-specific ICF to be signed by each subject participating in the study, subjects will be required to document agreement to provide additional samples or to allow the use of the remainder of their already-collected tissue, biomarker, PK, immunogenicity, and *UGT1A1* specimens for optional future research, including genomics, in accordance with applicable regulations.

Subjects will be treated until PD, unacceptable toxicity, withdrawal of consent, or until another treatment discontinuation criterion is met (see Section 5.3 Criteria for Treatment Discontinuation). However, treatment may be continued beyond PD if there is evidence of clinical benefit. All subjects will be followed for survival every 8 weeks after study drug discontinuation.

After completion of the final OS analysis and following implementation of PA6, subjects who previously discontinued treatment will no longer be followed for survival follow-up and subsequent therapy and will discontinue the study.

The EOT visit will be conducted within 30 days of last dose of the study drug.

End of study for a subject occurs when there is a death event, withdrawal of consent, documentation of loss to follow-up, or completion of the study by the sponsor.

After completion of the final OS analysis and following implementation of PA6:

- Subjects in the TPC arm will have an EOT visit and will discontinue the study. There will be no additional assessments including survival follow-up and subsequent therapy collection. Subjects in the TPC arm who are still deriving clinical benefit should be transitioned to commercially available therapy, per local regulations.
- Subjects in the sacituzumab govitecan arm may continue treatment as part of the study, for as long as they are deriving clinical benefit. After they meet one of the criteria for treatment discontinuation, they will have an EOT visit. There will be no additional assessments including survival follow-up and subsequent therapy collection.
- Subjects in either treatment arm will have the end of study at the same time as the EOT visit. However, if at the time of an EOT visit, subjects have unresolved AEs, the end of study may be delayed until all AEs have been resolved or stabilized.

Number of Subjects (planned): Approximately 696

Target Population

Subjects with metastatic or locally advanced unresectable UC who have progressed after prior platinum-containing chemotherapy and anti-PD-1/PD-L1 therapy will be enrolled.

Subjects who relapse within 12 months of receiving cisplatin therapy in the neo-adjuvant/adjuvant setting will also be permitted to enroll once they have received subsequent checkpoint inhibitor (CPI) therapy in the metastatic or locally advanced unresectable setting. The 12-month period is counted from completion of surgical intervention or cisplatin therapy, respectively.

Subjects who received either carboplatin or anti-PD-1/PD-L1 therapy in neo-adjuvant/adjuvant setting will not be able to count that line of therapy towards eligibility.

Subjects who have only received carboplatin in the metastatic or locally advanced unresectable setting must have been deemed cisplatin-ineligible per criteria outlined in the inclusion criteria to be eligible for this study.

Subjects who received only concurrent chemoradiation for bladder preservation without further systemic therapy are not eligible to enroll in the study.

Criteria for Inclusion:

Subjects meeting all of the following inclusion criteria at Screening/Baseline will be eligible for participation in the study:

1) Female or male subjects, ≥18 years of age, able to understand and give written informed consent.
2) Subjects with histologically documented UC that is metastatic or locally advanced unresectable defined as
   - Tumor (T) 4b, any node (N) or
   - Any T, N 2-3
3) Tumors of upper and lower urinary tract are permitted. Mixed histologic types are allowed if urothelial is the predominant histology.
4) ECOG performance status (PS) score of 0 or 1.
5) Subjects with progression or recurrence following receipt of platinum-containing regimen and anti-PD-1/PD-L1 therapy for metastatic or locally advanced unresectable disease will be enrolled.
   a) Subjects with recurrence or progression ≤12 months following completion of cisplatin-containing chemotherapy given in the neo-adjuvant/adjuvant setting may utilize that line of therapy to be eligible for the study. The 12-month period is counted from completion of surgical intervention or cisplatin therapy, respectively. These subjects must receive anti-PD-1/PD-L1 therapy in the metastatic or locally advanced unresectable setting to be eligible.
   b) Subjects who received either carboplatin or anti-PD-1/PD-L1 therapy in the neo-adjuvant/adjuvant setting will not be able to count that line of therapy towards eligibility for the study.

c) Cisplatin-ineligible subjects who meet one of the below criteria and who were treated with carboplatin in the metastatic or locally advanced unresectable settings may count that line of therapy towards eligibility. They must then have received anti-PD-1/PD-L1 therapy in metastatic or locally advanced unresectable setting to be eligible for the study.

Cisplatin ineligibility is defined as meeting one of the following criteria:

i) Creatinine Clearance <60 mL/min

ii) Grade ≥2 Audiometric Hearing Loss

iii) Grade ≥2 Peripheral Neuropathy

iv) New York Heart Association (NYHA) Class III heart failure

v) ECOG PS ≥2

d) Anti-PD-1/PD-L1 therapy administered as part of maintenance therapy may be counted towards eligibility for the study

e) Subjects who have progressed after receiving enfortumab vedotin in prior lines of therapy, and subjects who are either ineligible or unable to tolerate enfortumab vedotin therapy, are eligible to enroll in the study.

f) Subjects who received only concurrent chemoradiation for bladder preservation without further systemic therapy are not eligible to enroll in the study. The substitution of carboplatin for cisplatin does not constitute a new regimen provided no new chemotherapeutic agents were added to the regimen and no progression was noted prior to the change in platinum.

6) Subjects with previously treated brain metastases may participate in the study provided they have stable central nervous system disease for at least 4 weeks prior to the first dose of study drug and stabilization of all neurologic symptoms, have no evidence of new or enlarging brain metastases, and are not using steroids > 20 mg of prednisone (or equivalent) daily for brain metastases for at least 7 days prior to first dose of the study drug.

7) Adequate hematologic counts without transfusion or growth factor support within 2 weeks of study drug initiation (hemoglobin ≥9 g/dL, absolute neutrophil count [ANC] ≥1500/mm^3, and platelets ≥100,000/μL).

8) Adequate hepatic function (bilirubin ≤1.5 x institutional upper limit of normal [IULN], aspartate aminotransferase [AST] and alanine aminotransferase [ALT] ≤2.5 x IULN or ≤5 x IULN if known liver metastases and serum albumin ≥3 g/dL).

Docetaxel will only be an option in TPC arm for subjects with a total bilirubin ≤1 x IULN, and an AST and/or ALT ≤1.5 x IULN if alkaline phosphatase is also >2.5 x IULN.

9) Creatinine clearance ≥30 mL/min as assessed by the Cockcroft-Gault equation or other validated instruments (eg, Modification of Diet in Renal Disease [MDRD] equation).

10) 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 18.7.

Criteria for Exclusion:

Subjects meeting any of the following exclusion criteria at Screening/Baseline will not be enrolled in the study:

1) Women who are pregnant or lactating (see Appendix 18.7).
2) Have had a prior anti-cancer mAb/ADC within 4 weeks prior to C1D1 or have had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to C1D1. Subjects participating in observational studies are eligible.
3) Have received prior chemotherapy for UC with any available SOC therapies in the control arm (ie, either prior paclitaxel and docetaxel in countries where vinflunine is not an approved therapy, or either prior paclitaxel, docetaxel and vinflunine in countries where vinflunine is approved and is commercially available).
4) Have not recovered (ie, ≤Grade 1) from AEs due to previously administered chemotherapeutic agent.
   - Note: Subjects with ≤Grade 2 neuropathy or any grade of alopecia are an exception to this criterion and will qualify for the study.
   - Note: If subjects received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study therapy.
5) Have previously received topoisomerase 1 inhibitors.
6) Have an active second malignancy.
   - Note: Subjects with a history of malignancy that have been completely treated and with no evidence of active cancer for 3 years prior to enrollment, or subjects with surgically cured tumors with low risk of recurrence are allowed to enroll in the study after discussion with the medical monitor.
7) Have active cardiac disease, defined as:
   a) Myocardial infarction or unstable angina pectoris within 6 months of C1D1.
   b) History of serious ventricular arrhythmia (ie, ventricular tachycardia or ventricular fibrillation), high-grade atrioventricular block, or other cardiac arrhythmias requiring anti-arrhythmic medications (except for atrial fibrillation that is well controlled with anti-arrhythmic medication); history of QT interval prolongation.
   c) NYHA Class III or greater congestive heart failure or left ventricular ejection fraction of <40%.
8) Have active chronic inflammatory bowel disease (ulcerative colitis, Crohn's disease) or gastrointestinal (GI) perforation within 6 months of enrollment.
9) Have an active serious infection requiring anti-infective therapy (Contact medical monitor for clarification).
10) Have uncontrolled HIV-1/2 viral load (ie, ≥ 200 copies/mL and/or CD4+ count < 350 cells/mm^3) and/or on medications that may interfere with SN-38 metabolism.
11) Have active Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV). In subjects with a history of HBV or HCV, subjects with a detectable viral load will be excluded.

12) Have other concurrent medical or psychiatric conditions that, in the investigator's opinion, may be likely to confound study interpretation or prevent completion of study procedures and follow-up examinations.

13) Have inability to tolerate or are allergic to any potential TPC agent or sacituzumab govitecan or unable or unwilling to receive the doses specified in the protocol.

14) Have inability to complete all specified study procedures for any reason.

15) History of active interstitial lung disease or noninfectious pneumonitis.

Investigational Product, Dosage and Mode of Administration: Sacituzumab govitecan is administered at 10 mg/kg as an IV infusion on days 1 and 8 of a 21-day cycle.

Duration of Study: Approximately 3.5 years

Reference Therapy, Dosage and Mode of Administration: Subjects randomized to TPC arm will have a choice of one of the following SOC chemotherapeutic options:

- Paclitaxel 175 mg/m^2 IV on Day 1 of a 21-day cycle
- Docetaxel 75 mg/m^2 IV on Day 1 of a 21-day cycle
- Vinflunine 320 mg/m^2 IV on Day 1 of a 21-day cycle

Criteria for Evaluation

Primary Endpoint: OS

Secondary Endpoints:

1) PFS by investigator assessment and BICR using RECIST v1.1
2) ORR, CBR and DOR by investigator assessment and BICR using RECIST v1.1
3) Safety and tolerability evaluated by AEs, SAEs, and laboratory changes
4) Change from baseline in the physical functioning, global health status, pain, and fatigue scales of the EORTC QLQ-C30 score

Statistical Methods

A sample size of approximately 696 subjects permits the study to have 90% power to demonstrate a hazard ratio of 0.755 equating to a 2.7-month improvement in OS from 8.3 months to 11.0 months at a 2-sided alpha of 5%. Final OS analysis will occur after 536 OS events have accrued, which is projected to occur 19 months after an enrollment period of 23 months, with yearly discontinuation rate of 10%. There will be an interim analysis of OS after at least 65% of targeted OS events (at least 348 events) are accrued. A Lan-DeMets spending function that approximates O'Brien/Fleming stopping boundaries will be applied to the interim OS analysis. Refer to the Statistical Analysis Plan for additional details regarding the interim analysis.

The primary analysis population consists of all randomized subjects who will be included in an intent-to-treat analysis. Kaplan-Meier (KM) curves will be constructed for time-to-event endpoints, and the estimate and 95% CI of the median survival time of the time-to-event endpoints will be estimated. A stratified log-rank test stratified by randomization factors will be used to compare the treatment groups for the time-to-event endpoints of the primary endpoint of OS and secondary endpoint of PFS. Estimates and 95% confidence intervals (CIs) of hazard ratios of OS and PFS will be based on stratified Cox proportional hazard regression model.

Multiplicity adjustment: To ensure the overall Type I error rate is strictly controlled at a 2-sided alpha of 0.05, a hierarchical testing strategy will be performed based on the primary endpoint of OS and key secondary endpoints of PFS based on BICR and physical functioning score of EORTC QLQ-C30. If the planned primary OS analysis is significant, then the secondary endpoints of PFS based on BICR and physical functioning score will be tested sequentially at the same alpha level as OS. If the planned secondary endpoint of PFS based on BICR is positive, then the EORTC QLQ-C30 physical functioning score will be tested.

All subjects administered at least one dose of sacituzumab govitecan or TPC will be included in the evaluation of safety and tolerability. Safety and tolerability will be evaluated from AEs, standard safety laboratories, physical examination, ECG, and vital signs.

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

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LIST OF ABBREVIATIONS

The following abbreviations are used in this study protocol.

ADA	Anti-Drug Antibody
ADC	Antibody-Drug Conjugate
ADL	Activities of Daily Living
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
ASCO	American Society of Clinical Oncology
AUC	Area Under Plasma Concentration
BICR	Blinded Independent Central Review
BOR	Best Overall Response
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
C1D1	Cycle 1 Day 1
CBC	Complete Blood Count
CBR	Clinical Benefit Rate
CFR	Code of Federal Regulation
CI	Confidence Interval
CL2A	Coupled by a proprietary hydrolyzable linker 2
C_{max}	Maximum Plasma Concentration
CME	Cystoid Macular Edema
COVID-19	Coronavirus Disease 2019
CPI	Checkpoint Inhibitor
CR	Complete Response
CSR	Clinical Study Report
CT	Computed Tomography
CYP	Cytochrome P450 Enzyme
DNA	Deoxyribonucleic Acid
DOR	Duration of Objective Tumor Response
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30

EOT	End of Treatment
EU	European Union
EuroQOL EQ-5D-5L	European Quality of Life 5-dimensions 5-levels
FDA	Food and Drug Administration
FFPE	Formalin-Fixed, Paraffin-Embedded
FGFR	Fibroblast Growth Factor Receptor
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
G-CSF	Granulocyte-Colony Stimulating Factor
GI	Gastrointestinal
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	Human Immunodeficiency Virus
hRS7	Humanized RS7 Anti-Trop-2 Immunoglobulin G
IC_{50}	Half Maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Council on Harmonization
IEC	Independent Ethics Committee
IgG1	Immunoglobulin G subclass 1
IgG1κ	Immunoglobulin G subclass 1 κ light chain
IMMU-132	Company Code for Sacituzumab Govitecan
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IULN	Institutional Upper Limit of Normal
IV	Intravenous
IWRS	Interactive Web-Based Response System
KM	Kaplan-Meier
LDH	Lactate Dehydrogenase
mAb	Monoclonal Antibody
MDRD	Modification of Diet in Renal Disease
MMAE	Monomethyl auristatin E
MRI	Magnetic Resonance Imaging
mUC	Metastatic Urothelial Cancer
MTD	Maximum Tolerated Dose
N/A	Not Applicable
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events

NOAEL	No-Observable Adverse Effect Level
NSCLC	Non-Small Cell Lung Cancer
NYHA	New York Heart Association
ORR	Objective Response Rate
OS	Overall Survival
PA6	Protocol Amendment 6
PD	Disease Progression
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PI	Principal Investigator
PK	Pharmacokinetics
PO	equivalent orally
PR	Partial Response
PRES	Posterior Reversible Encephalopathy Syndrome
PS	Performance Status
q3W	Every 3 weeks
QOL	Quality of Life
RECIST v1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SmPC	Summary of Product Characteristics
SOC	Standard of Care
SSR	Special Situation Reports
SUSARs	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment-Emergent Adverse Event
TNBC	Triple-Negative Breast Cancer
TPC	Treatment of Physician’s Choice
Trop-2	Trophoblastic Cell Surface Antigen-2
UC	Urothelial Cancer
UGT1A1	Uridine 5'-diphospho-glucuronosyltransferase 1A1
US	United States
WBC	White Blood Cells
WHO	World Health Organization

1. INTRODUCTION

Urothelial cancer (UC) is the sixth most common malignancy diagnosed in the United States (US) and the ninth most common malignancy globally. In 2019, 430,000 estimated new cases and 165,000 cancer deaths due to UC are anticipated globally {Cumberbatch 2019}. The overall 5-year survival rate of UC is estimated as 77% with a 4.6% 5-year survival rate predicted for subjects with metastatic urothelial cancer (mUC) {Surveillance Epidemiology and End Results (SEER) Program 2019}.

Platinum-based (either cisplatin or carboplatin) combination chemotherapy remains the standard first-line treatment for advanced UC. Recent approvals of anti-programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) checkpoint inhibitors (CPI) have added to the armamentarium to treat advanced UC. Platinum-based combination therapies with either cisplatin or carboplatin have achieved response rates ranging from 36 to 71% and 28 to 56%, respectively, in the first-line palliative setting {De Santis 2012, Galsky 2012}. However, randomized Phase II studies have shown significant differences in survival between carboplatin and cisplatin with median overall survival (OS) of 9 versus 16 months, respectively {Bellmunt 1997, Dogliotti 2007}. Prior to the approval of anti-PD-1/PD-L1 CPIs, the only approved option for subjects upon progression on or after platinum-based combination chemotherapy was taxanes globally or vinflunine in the European Union (EU). Based on a recent review of over 400 subjects that is representative of worldwide results, single-agent chemotherapy achieved response rates of 6 to 14% with median progression-free survival (PFS) of 3 to 4 months and OS of 7 to 8 months {Niegisch 2018, Raggi 2016}.

Anti-PD-1/PD-L1 CPI have offered significant improvement in efficacy and has supplanted chemotherapy in the second-line palliative setting. Pembrolizumab has demonstrated a durable response rate of 21.1% compared to 11.4% for single-agent chemotherapy comparator and received full approval for treatment of subjects with mUC who have failed prior platinum-based chemotherapy upon demonstration of an OS benefit of 10.3 months compared to 7.4 months for single-agent chemotherapy {Bellmunt 2017}.

Upon failure of anti-PD-1/PD-L1 therapy in the second-line palliative setting, single-agent chemotherapy consisting of taxanes or vinflunine or clinical trials remain the only fully approved alternative options per National Comprehensive Cancer Network (NCCN) guidelines {Mar 2019}. Clinical data demonstrate that patients receiving taxanes or vinflunine as second-line therapy have an objective response rate (ORR) of 11% and survival of only 7 months {Bellmunt 2017}. In a small group of selected patients with fibroblast growth factor receptor (FGFR) 2/3 alterations, erdafitinib has recently received accelerated approval in patients with these alterations who have progressed after platinum-containing chemotherapy.

The antibody-drug conjugate (ADC) enfortumab vedotin, comprised of a microtubule-disrupting agent, monomethyl auristatin E (MMAE), coupled by a protease-cleavable linker to a fully human immunoglobulin G, subclass 1 (IgG1) kappa monoclonal antibody (mAb) targeting Nectin-4, has recently received accelerated approval in the US for the treatment of adult patients with locally advanced or mUC who have previously received an anti-PD-1 or PD-L1 CPI and a

platinum-containing chemotherapy in the neo-adjuvant/adjuvant, locally advanced, or metastatic setting {Challita-Eid 2016, PADCEV 2019}. PADCEV was approved in the EU on 24 February 2022 for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and a PD-L1 inhibitor. Accelerated approval was based on the achievement of a confirmed ORR of 44% and a median response duration of 7.6 months in a single-arm Phase II study in subjects with mUC who were previously treated with both platinum chemotherapy and anti-PD-1/PD-L1 therapy {Rosenberg 2019}. Whether this response rate will translate into a survival benefit remains to be seen. Nevertheless, upon progression on all available therapies, single-agent chemotherapy remains the standard of care (SOC) globally.

CPI received initial approval for cisplatin-ineligible subjects as first-line palliative therapy with similarly encouraging results in single-arm Phase II studies {Balar 2017, Rosenberg 2016}. These studies reported ORR of approximately 23 to 24% and 6-month PFS of approximately 30%. The atezolizumab study reported a median follow-up of 11.7 months and a median OS of 11.4 months {Rosenberg 2016}. At a median follow-up of 11.5 months, the KEYNOTE-052 pembrolizumab study reported a confirmed ORR of 29% and a median OS of 11.5 months {Vuky 2018}. However, labels for both drugs have since limited use of CPI in the first line to those with tumors showing elevated PD-L1 expression.

Given that single-agent chemotherapy remains the only approved treatment option after platinum-based chemotherapy and anti-PD-1/PD-L1 therapy {Mar 2019}, novel therapies that exceed a 10% overall response rate and median survival of 8 months would be clinically meaningful. In summary, metastatic or locally advanced unresectable UC is a serious condition with limited treatment options for subjects who have failed prior treatments with anti-PD-1/PD-L1 and/or platinum-based regimens. There is an unmet medical need for additional treatment options for these subjects.

1.1. Mechanism of Action of Sacituzumab Govitecan

Sacituzumab govitecan is a trophoblast cell surface antigen-2 (Trop-2)-directed ADC that comprises SN-38, a topoisomerase I inhibitor and active metabolite of irinotecan, coupled by a linker (CL2A) to the humanized mAb hRS7 immunoglobulin G, subclass 1, κ light chain (IgG1κ), which binds to Trop-2. Trop-2 is a transmembrane calcium signal transducer glycoprotein of the tumor associated calcium signal transducer gene family.

Pharmacology data suggest that sacituzumab govitecan binds to Trop-2-expressing cancer cells and is internalized with the subsequent release of SN-38 via hydrolysis of the linker. SN-38 interacts with topoisomerase I and prevents re-ligation of topoisomerase I-induced single strand breaks. The resulting deoxyribonucleic acid (DNA) damage leads to apoptosis and cell death. The hydrolysable linker may permit release of SN-38 in the acidic microenvironment of the tumor without Trop-2 binding.

1.2. Mechanism of Action of Treatment of Physician's Choice (TPC) Agents

1.2.1. Paclitaxel

Paclitaxel is an antimicrotubule chemotherapy agent of the taxane family. Paclitaxel promotes assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of normal dynamic reorganization of the microtubule network resulting in cell cycle arrest and apoptosis.

Paclitaxel is indicated and approved as a single-line treatment for numerous types of cancers, including bladder tumors. Refer to paclitaxel package insert or summary of product characteristics (SmPC) for additional information.

1.2.2. Docetaxel

Docetaxel is a second-generation taxane, derived from paclitaxel. It is an antimicrotubule agent which acts by binding beta-tubulin, enhancing its proliferation and stabilizing its conformation, thus inhibiting proper assembly of the mitotic spindle and inducing apoptosis.

Docetaxel should not be administered to patients with hepatic impairment. Refer to package insert or SmPC for additional information.

1.2.3. Vinflunine

Vinflunine is a vinca alkaloid, indicated as second-line treatment of advanced/metastatic urothelial carcinoma following administration of a platinum-containing regimen. Vinflunine binds to tubulin, inhibiting polymerization required for the formation of microtubules. This mechanism of action disrupts microtubule function, leading to cell cycle arrest and apoptosis.

Refer to the SmPC for additional information.

1.3. Background on Study Interventions

Study intervention and its marketing authorization status is provided in Appendix 18.2. For further information on sacituzumab govitecan, refer to the current Investigator's Brochure.

1.4. Nonclinical Experience

1.4.1. Pharmacology

Sacituzumab govitecan has been evaluated for in vitro cytotoxicity and in vivo efficacy in a variety of human solid tumor types, including prostate, non-small cell lung cancer (NSCLC), colon, pancreatic, squamous cell lung {Cardillo 2011}, gastric {Cardillo 2015}, and triple-negative breast cancer (TNBC) {Cardillo 2017, Goldenberg 2015}. In general, half maximal inhibitory concentration (IC_{50})-values ranged from 1 to 83 nM across various disease indications {Cardillo 2011, Cardillo 2017, Goldenberg 2015}. In vivo, significant anti-tumor effects mediated by sacituzumab govitecan therapy were noted in tumor xenograft disease models of TNBC, NSCLC, colon, pancreatic, gastric, and squamous cell lung.

Additional information regarding nonclinical pharmacology of sacituzumab govitecan can be found in the current edition of the Investigator's Brochure.

1.4.2. Toxicology

In acute toxicity studies in Swiss-Webster Mice, sacituzumab govitecan at doses of up to 750 mg/kg/dose (ie, cumulative doses of up to 1500 mg/kg) caused minimal loss (<10%) in body weight. There was no evidence of hematological toxicity and no abnormal histology findings. Transient increases in hepatic transaminases were observed that returned to normal by the end of the study.

In cynomolgus monkeys, sacituzumab govitecan administered 50 mg/kg/dose (human equivalent dose = 16 mg/kg/dose) for four treatment cycles (Days 1 and 8 of a 21-day cycle) was considered a no-observable adverse effect level (NOAEL) and 120 mg/kg/dose administered 3 days apart was associated with lethality. In general, the observed toxicities were dose-dependent and considered reversible. Target organs included the female reproductive tract, skin (hair loss, pigmentation), kidney (periarteritis), lymphoid organs (lymphoid depletion), bone marrow (reduced cellularity) with concomitant reductions in red cells, white cells and platelets and the gastrointestinal (GI) tract (necrosis, erosions, inflammation, fibrosis, hemorrhage and edema).

SN-38 was negative for mutagenicity in a bacterial reverse mutation test and was found to be clastogenic in an in vitro mammalian cell micronucleus test. Neither the carcinogenicity, nor effects of sacituzumab govitecan on fertility, early embryonic development or pre- and post-natal development have been assessed. However, SN-38 is a camptothecin and hence is likely carcinogenic. Furthermore, SN-38 is a known developmental toxicant.

Additional information regarding nonclinical toxicology of sacituzumab govitecan can be found in the current edition of the Investigator's Brochure.

1.5. Clinical Experience

The clinical safety and efficacy of sacituzumab govitecan is being evaluated in several clinical studies. The largest experience to date is a Phase 1/II study (IMMU-132-01) entitled "Phase I/II Study of Sacituzumab govitecan (IMMU-132; hRS7-SN-38 Antibody Drug Conjugate) in Epithelial Cancers". Approximately 500 subjects were enrolled in this study regardless of Trop-2 expression and treated with sacituzumab govitecan monotherapy. Doses of 8-18 mg/kg were tested with the 10 mg/kg dose selected for further investigation.

The mUC data were generated in a 45-subject cohort of the first-in-human trial, IMMU-132-01. Subjects were treated at the 10 mg/kg and showed meaningful clinical activity with an ORR of 31%, a median PFS of 5.5 and a median OS of 16.3 months. Based on these encouraging findings in the first-in-human study, a dedicated Phase II study, IMMU-132-06 (TROPHY U-01), entitled "A Phase II Open-Label, Study of IMMU-132 in Metastatic Urothelial Cancer After Failure of Platinum-Based Regimen or Anti-PD-1/PD-L1 Based Immunotherapy," conducted under US Food and Drug Administration (FDA) Investigational New Drug (IND) 140084 was initiated in August 2018. This is a Phase II, open-label study of sacituzumab govitecan in previously treated subjects with metastatic or locally advanced unresectable UC. Subjects are enrolled into 1 of 2 cohorts irrespective of Trop-2 expression. Cohort 1 is enrolling 100 subjects who have received both prior platinum therapy and anti-PD-1/PD-L1 therapy while

Cohort 2 is enrolling 40 subjects who are platinum ineligible and have failed prior anti-PD-1/PD-L1 therapy. Initial data generated in a 35-subject interim analysis of Cohort 1 confirmed and extended the activity demonstrated in Study IMMU-132-01, with an ORR of 29% and a PFS of approximately 7.2 months in a heavily pre-treated population with a median of 3 prior lines of therapy. This is significantly higher than 10% response rate anticipated with single-agent chemotherapy.

Further, the safety profile of sacituzumab govitecan was comparable to previous data generated for this agent in mUC and other indications and compares favorably to the toxicity profile of the historical comparators to be used in this study.

Additional information regarding clinical studies can be found in the current edition of the Investigator's Brochure.

1.5.1. Pharmacokinetics

1.5.1.1. Pharmacokinetics

The serum pharmacokinetics (PK) of sacituzumab govitecan and free SN-38 were evaluated in a Phase II study in a population of subjects with mUC who received sacituzumab govitecan as a single agent at a dose of 10 mg/kg (Days 1 and 8 of a 21-day cycle). Sacituzumab govitecan and free SN-38 have a maximum plasma concentration (C_{max}) of 224000 (23.0%) ng/mL and 67.3 (43.6%) ng/mL, respectively, and area under plasma concentration curve through 168 hours (AUC_{0-168}) of 5,270,000 (30.8%) ng/mL and 1970 (36.6%), respectively.

Additional information regarding PK parameters of sacituzumab govitecan can be found in the current edition of the Investigator's Brochure.

1.5.1.2. Distribution

Based on population pharmacokinetic analysis, the central volume distribution of sacituzumab govitecan is 2.96 L. The reported plasma protein binding of SN-38 is approximately 95%, primarily to albumin.

1.5.1.3. Elimination

The mean half-life of sacituzumab govitecan and free SN-38 is 15.3 and 19.7 hours, respectively. Based on population pharmacokinetic analysis, the clearance of the sacituzumab govitecan is 0.14 L/h.

1.5.1.4. Metabolism

No metabolism studies with sacituzumab govitecan have been conducted. SN-38 (the small molecule moiety of sacituzumab govitecan) is metabolized via Uridine 5'-diphospho-glucuronosyltransferase 1A1 (UGT1A1). The glucuronide metabolite of SN-38 (SN-38G) was detectable in the serum of subjects.

1.5.1.5. Excretion

SN-38 and SN-38G have been reported to be mainly eliminated via biliary excretion.

1.5.2. Immunogenicity

As with all therapeutic proteins, there is potential for an immune response to sacituzumab govitecan. None of the subjects who developed treatment-emergent and confirmed positive anti-drug antibody (ADA) responses experienced any adverse events (AE) suggestive of hypersensitivity or an infusion-related reaction.

1.6. Rationale for Dose Regimen of Sacituzumab Govitecan or TPC Agents (Paclitaxel, Docetaxel, or Vinflunine)

In the Phase I part of Study IMMU-132-01, dose escalation was performed according to a standard 3+3 design and based on planned initial dose levels of 8, 12, and 18 mg/kg administered on Days 1 and 8 of a 21-day cycle. A sacituzumab govitecan dose of 12 mg/kg was formally identified as the maximum tolerated dose (MTD) but was associated with dose delays and reductions in several subjects. In order to determine a maximum acceptable dose, additional subjects were treated at the 8 mg/kg dose level, and an intermediate dose cohort of 10 mg/kg was added. Both dose levels were shown to be better tolerated in the first cycle than the formally determined MTD of 12 mg/kg, allowing repeated cycles with a better safety profile. Interim analyses demonstrated that subjects receiving the 10 mg/kg dose achieved a comparable treatment duration as subjects receiving 8 mg/kg. However, compared with the 8 mg/kg dose level, there was no worsening of AE incidences or severity with the 10 mg/kg dose. The 10 mg/kg dose achieved a better ORR, clinical benefit rate, and PFS than the 8 mg/kg dose in TNBC subjects, specifically {Ocean 2017}. Based on these results, 10 mg/kg administered on Days 1 and 8 of a 21-day cycle was chosen as the dose for further study. Additional information regarding safety and efficacy of sacituzumab govitecan can be found in the current edition of Investigator's Brochure.

Paclitaxel, docetaxel, and vinflunine were selected as the comparator drugs as these chemotherapy agents are part of standard of care for advanced unresectable/metastatic urothelial cell cancer that progressed after treatment with a platinum-containing regimen and immunotherapy. Treatment of physician's choice agents were also selected based on availability in participating countries. Dosing recommendations for TPC agents contained within the study protocol follow current package inserts or SmPC guidelines.

1.7. Summary of Sacituzumab Govitecan Safety Data

The safety profile for sacituzumab govitecan was similar in the treatment of metastatic TNBC and mUC. The most common AEs were nausea, diarrhea, neutropenia, fatigue, alopecia, anemia, vomiting, and constipation. The most clinically relevant Grade 3 or Grade 4 AEs with sacituzumab govitecan were neutropenia and diarrhea. The most frequent AEs that led to treatment modification were neutropenia and diarrhea. The frequent AEs leading to permanent discontinuation of study drug were fatigue, diarrhea, pneumonia, and neutropenia.

Neutropenia occurred in the first cycle of treatment and resolved within approximately 1 week of onset. Most cases of neutropenia were not febrile, were nonserious, and could be managed with granulocyte-colony stimulating factor (G-CSF) administration and/or dose reduction after Cycle 1.

Diarrhea with sacituzumab govitecan occurred within the first treatment cycle (median time of 12 days to first event) and resolved within approximately 1 week of onset. Most of the cases of diarrhea were nonsevere, nonserious, and did not lead to either a treatment interruption or dose reduction.

Higher incidences of neutropenia, febrile neutropenia, and anemia were seen in subjects who were homozygous for the *UGT1A1*28* allele compared with subjects who were heterozygous for the *UGT1A1*28* allele and subjects who were homozygous for the wild-type allele.

For further information on sacituzumab govitecan, refer to the current edition of the Investigator's Brochure.

1.8. Risk/Benefit Assessment for the Study

Sacituzumab govitecan received accelerated approval in the US (13 April 2021) for subjects with locally advanced UC or mUC who have previously received a platinum-containing chemotherapy and either a PD-1 or PD-L1 inhibitor based on data from 113 subjects treated in the Phase 2 mUC Study IMMU-132-06. In Study IMMU-132-06, at a median follow-up of 9.1 months, an ORR of 27.4% was observed (31 of 113 subjects; 95% confidence interval [CI], 19.5 to 36.6), with 77% of subjects demonstrating a decrease in measurable disease. Median duration of response was 7.2 months (95% CI, 4.7 to 8.6 months), with a median PFS and OS of 5.4 months (95% CI, 3.5 to 7.2 months) and 10.9 months (95% CI, 9.0 to 13.8 months) observed, respectively {Tagawa 2021}. In comparison, current SOC single-agent chemotherapies for this subject population achieved response rates of 6 to 14% with median PFS of 3 to 4 months and OS of 7 to 8 months based on a recent review of over 400 subjects, representative of worldwide results {Niegisch 2018, Raggi 2016}.

The known and potential risks of sacituzumab govitecan include gastrointestinal symptoms such as nausea, vomiting, and diarrhea; neutropenia; hypersensitivity; and embryo-fetal toxicity. As of September 2020, in 795 subjects who received single-agent sacituzumab govitecan at a starting dose of 10 mg/kg, the median relative dose intensity was 99.1%, with 7.5% of subjects experiencing treatment-emergent adverse events (TEAEs) leading to discontinuation; < 1% discontinued sacituzumab govitecan due to neutropenia (including febrile neutropenia) or diarrhea, and no subjects discontinued due to nausea or vomiting, indicating that routine supportive measures are successful in managing toxicities.

Toxicities have been successfully managed with dose delay, interruption, or appropriate supportive care medications. Gastrointestinal toxicities have been managed primarily by drug interruption and supportive care therapies. Nausea and vomiting appear to be managed with readily available medications like anti-nausea medications, and loperamide has been used to treat diarrhea such that no subjects have discontinued study treatment due to these toxicities. Neutropenia has been observed with an approximately 9 to 10% risk of febrile neutropenia, but has been managed with use of G-CSF support per European Society for Medical Oncology guidelines in addition to dose delays and occasionally dose reductions to permit continued dosing. Despite the discontinuations due to neutropenia, a median relative dose intensity of 96.9% was observed in the UC population.

The risk due to study treatment with sacituzumab govitecan is comparable to the toxicities related to SOC therapies, which include taxanes (paclitaxel or docetaxel) or vinflunine, as demonstrated in a recent Phase 3 study (EV-301) that used these agents as SOC in the same population as targeted in this study. Study EV-301 assessed the OS benefit of enfortumab vedotin compared to the above SOC therapies in subjects with locally advanced UC or mUC who had progressed after platinum and checkpoint inhibitor therapy and reported that 17.5% of subjects in the investigator-chosen chemotherapy arm (randomized to standard docetaxel, paclitaxel, or vinflunine) experienced a TEAE leading to discontinuation and reported Grade ≥ 3 treatment-related TEAEs of decreased neutrophil count (13.4%), anemia (7.6%), neutropenia (6.2%), febrile neutropenia (5.5%), diarrhea (1.7%), and nausea (1.4%) {Powles 2021}.

Section 6.3 delineates how to prevent, address, and mitigate sacituzumab govitecan toxicities through dose modification, interruption, or use of supportive therapies to prevent or manage expected toxicities. The risk of embryo-fetal toxicity is mitigated through strict contraception requirements, pregnancy testing, and subject education. Close monitoring of subjects with routine laboratory tests (Table 1) and visits for sacituzumab govitecan administration at least twice every 21 days also further mitigates these risks by facilitating prompt diagnosis and thus management of adverse reactions.

Additionally, the study has instituted an independent Data Monitoring Committee (DMC), which will be convened at regular intervals to assess the progress of the study and review safety and efficacy data.

Finally, while an infectious disease pandemic may pose additional risks to study drug availability, the study visit schedule and adherence to protocol-specified safety monitoring or laboratory assessments has been instituted. Further details are provided in Appendix 18.9.

Given the high unmet medical need of this population, in which a median survival of 8 months is observed with currently available therapies, the potential clinical benefit observed in Study IMMU-132-06, and the manageable toxicity profile of sacituzumab govitecan, the Sponsor believes that sacituzumab govitecan offers a favorable risk/benefit profile to support subject enrollment in this study.

2. STUDY OBJECTIVES AND PURPOSE

2.1. Primary Objective

To assess OS with sacituzumab govitecan in comparison with treatment of physician's choice (TPC) in subjects with metastatic or locally advanced unresectable UC

2.2. Secondary Objectives

1) To assess PFS of sacituzumab govitecan in comparison with TPC by investigator assessment and blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Appendix 18.5)

2) To assess ORR, clinical benefit rate (CBR), and duration of objective tumor response (DOR) with sacituzumab govitecan in comparison with TPC by investigator assessment and BICR using RECIST v1.1

3) To assess safety and tolerability of sacituzumab govitecan in comparison with TPC

4) To assess Quality of Life (QOL) based on European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30, Appendix 18.6) with sacituzumab govitecan in comparison with TPC

2.3. Exploratory Objectives

1) To assess and compare efficacy in a subset defined by tumor expression of Trop-2 and ascertain the role of expression of Trop-2 as a biomarker for response

2) To investigate potential blood and tumor biomarkers of response

3) To investigate potential correlation between serum sacituzumab govitecan PK and the development of immunogenicity (ADA)

4) To characterize the PK of sacituzumab govitecan in metastatic UC subjects

5) To assess additional QOL endpoints of sacituzumab govitecan in comparison with TPC

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This is a Phase III, global, multicenter, open-label randomized controlled trial in which approximately 696 subjects with metastatic or locally advanced unresectable UC who have progressed after prior therapy with platinum-based regimen and anti-PD-1/PD-L1 therapy will be randomized in a 1:1 ratio to either sacituzumab govitecan arm or TPC arm.

Subjects in the TPC arm will have 1 of 3 SOC chemotherapeutic options including paclitaxel, docetaxel, and vinflunine (in countries where vinflunine is approved and is commercially available). Subjects will be stratified by their type of prior platinum (cisplatin or carboplatin), Bellmunt risk factors (0-1, 2-3) and prior type of therapy in which platinum was administered (neo-adjuvant/adjuvant, locally advanced unresectable/metastatic). The most recent line of platinum therapy should be used for the stratification factor. The Bellmunt score is based on the presence of three risk factors: liver metastases, hemoglobin <10 g/dL, and Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≥1. These are independent prognostic factors for predicting survival in patients with platinum-refractory mUC on second-line chemotherapy. Patients with 0, 1, 2 and 3 risk factors demonstrate median OS of 14, 7.2, 3.8 and 1.7 months, respectively {Bellmunt 2010}.

Subjects randomized to the sacituzumab govitecan arm will receive 10 mg/kg of sacituzumab govitecan intravenously (IV) on Day 1 and Day 8 of 21-day cycles. Those randomized to the TPC arm will have the choice of receiving paclitaxel, docetaxel, and vinflunine administered IV at SOC doses of 175, 75 and 320 mg/m^2, respectively, on Day 1 of 21-day cycles, and the determined dosing schedule for these treatments should be adhered to. After a subject is randomized to a TPC treatment, the subject must continue with the same treatment for the duration of the study.

Subjects will be treated until PD, unacceptable toxicity, withdrawal of consent, or until another treatment discontinuation criterion is met (see Section 5.3, Criteria for Treatment Discontinuation). All subjects will be followed for survival every 8 weeks after study drug discontinuation. Treatment beyond PD may be permitted in subjects deemed to be receiving clinical benefit as per investigator's assessment.

Response will be assessed by RECIST v1.1 every 6 weeks for the first 12 months on study and every 9 weeks thereafter until there is evidence of PD, including subjects who discontinue prematurely due to toxicity.

An independent DMC will be convened at regular intervals to assess the progress of the study and review safety per an approved DMC charter.

The DMC will also meet at the time of interim analysis when at least 65% of total OS events have been accrued to independently review this data.

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

Primary Endpoint: The primary endpoint is OS.

Secondary Endpoints: The secondary endpoints include:

1) PFS by investigator assessment and BICR using RECIST v1.1
2) ORR, CBR, and DOR by investigator assessment and BICR using RECIST v1.1
3) Safety and tolerability evaluated by AEs, SAEs, and laboratory changes
4) Change from baseline in the physical functioning, global health status, pain, and fatigue scales of the EORTC QLQ-C30 score (Appendix 18.6).

Study modifications after the final OS analysis and implementation of Protocol Amendment 6 (PA6):

After the final OS analysis and following implementation of PA6, subjects in the sacituzumab govitecan arm who are still receiving treatment may continue treatment as part of the study for as long as they are deriving clinical benefit. Radiographic tumor assessments per protocol will be discontinued; however, treatment response should continue to be evaluated per standard of care. Information on drug administration and safety assessments will continue to be collected, as per Table 2. Subjects in the TPC arm will be discontinued from the study; however, they may receive commercially available TPC treatment outside of the study, if deriving continued clinical benefit. Subjects in either treatment arm, who were being followed for survival and subsequent therapy at the time of PA6 implementation, will be discontinued from the study and survival follow-up with subsequent therapy information will no longer be collected.

3.2. Number of Subjects

Approximately 696 subjects will be enrolled in the study.

3.3. Treatment Assignment

This is a randomized, open-label, global study with no blinding.

3.4. Safety and Survival Follow-Up

After discontinuation of treatment (see Section 5.3, Criteria for Treatment Discontinuation), all subjects must complete an end of treatment (EOT) visit within 30 days after the last dose of the study drug. Subjects will then be followed every 8 weeks for survival unless the subject explicitly indicates their desire to forego survival follow-up in writing to their study investigator. Subjects will be followed every 8 weeks until death, withdrawal of consent, loss to follow-up, or completion of study by the sponsor, whichever occurs first. Follow-up assessment(s) may be by telephone or visit and will include documentation of any subsequent therapy administered for their cancer.

After completion of the final OS analysis and following implementation of PA6, subjects who previously discontinued treatment will no longer be followed for survival follow-up and subsequent therapy and will discontinue the study.

3.5. End of Treatment and End of Study

EOT for a subject occurs when there is PD, unacceptable toxicity, withdrawal of consent or until another treatment discontinuation criterion is met (See Section 5.3, Criteria for Treatment Discontinuation).

End of study for a subject occurs when there is a death event, withdrawal of consent, documentation of loss to follow-up, or completion of the study by the Sponsor (See Section 5.4, Criteria for Study Discontinuation).

After completion of the final OS analysis and following implementation of PA6:

- Subjects in the TPC arm will have an EOT visit, as described in Section 3.4, and will discontinue the study. There will be no additional assessments including survival follow-up and subsequent therapy collection. Subjects in the TPC arm who are still deriving clinical benefit should be transitioned to commercially available therapy, per local regulations.
- Subjects in the sacituzumab govitecan arm may continue treatment as part of the study, for as long as they are deriving clinical benefit. After they meet one of the criteria for treatment discontinuation (see Section 5.3), they will have an EOT visit as described in Section 3.4. There will be no additional assessments including survival follow-up and subsequent therapy collection.
- Subjects in either treatment arm will have the end of study at the same time as the EOT visit. However, if at the time of an EOT visit, subjects have unresolved AEs, the end of study may be delayed until all AEs have been resolved or stabilized.

4. PROCEDURES

4.1. Informed Consent

No study-specific procedure or alteration of subject care will be undertaken until informed consent has been obtained from the subject or legal representative. However, procedures such as laboratory work or imaging that were performed per SOC may be utilized for screening purposes if obtained within the proposed screening window. The investigator or qualified designee will explain the nature and scope of the study, potential risks and benefits of participation and answer all questions for the subject and/or legally authorized representative. Subjects must be informed of available alternative treatment options prior to consenting to participate in this study.

If the subject agrees to participate, the informed consent form (ICF) must be signed, dated, and witnessed, with a copy given to the subject. The consenting process must be well documented by each investigational site.

4.2. Screening

Subjects must complete all screening procedures within 28 days of signing the ICF. SOC procedures used for screening must meet the 28-day window for screening. No waivers or exceptions will be granted for subject eligibility or throughout the study.

Subjects are permitted to re-screen only once for the study.

4.2.1. Screen Failures

Subjects who are consented to participate in the clinical study, and who do not meet one or more criteria required for participation in the study during the screening procedures, are considered screen failures. Screen failure subject's data will be recorded in electronic case report form (eCRF), including the reason for they were ineligible for randomization. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects, to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, informed consent date, screen failure details, including date of screen failure, AEs, and any SAE.

4.3. Randomization

Subjects will be assigned to a treatment based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study.

After screening, eligible subjects will be randomized to 1 of 2 arms. Each arm will receive either sacituzumab govitecan or TPC (investigators choice of 1 of 3 SOC chemotherapeutic options including paclitaxel, docetaxel, and vinflunine) as described in Table 1. Once a subject is randomized to a TPC, the subject must continue with the same treatment for the duration of the study. Randomization will be performed centrally by an interactive web response system (IWRS).

Subjects will be stratified by their type of prior platinum (cisplatin or carboplatin), Bellmunt risk factors (0-1, 2-3), and prior type of therapy in which platinum was administered (neo-adjuvant/adjuvant, locally advanced unresectable/metastatic). The most recent line of platinum therapy should be used for the stratification factor.

4.4. Study Procedures

All subjects must be dosed within 3 calendar days of enrollment into the study. Enrollment occurs upon receipt of randomization number. Clear documentation as to the reason the subject was not dosed should be provided on the relevant eCRF. Unless otherwise specified, collection windows for study time points and visits are permitted either 1 day before or within 2 days after scheduled visits and ±5 business days for response assessments. Treatment delays for reasons other than required for resolution of treatment-related toxicity are not permitted.

The schedule of assessments for all subjects before implementation of PA6 is presented in Table 1. The schedule of assessments for all subjects who continue treatment after the final OS analysis and following implementation of PA6 is presented in Table 2.

For study procedures regarding efficacy parameters, please refer to Section 8.1.

For study procedures regarding safety parameters, please refer to Section 10.1.

For study procedures regarding all other evaluations, please refer to Section 9.

Table 1. Schedule of Assessments (Before Implementation of PA6)

Phase	**Pre-treatment**		**Treatment**		**Post-treatment**	
Period	**Screening**	**Baseline[1]**	**Treatment Cycle 1 through Last Cycle (21-day cycle)**		**End of Treatment[2]**	**Follow-up**
Day	**Days -28 to -1**	**Days -3 to 1**	**Day 1**	**Day 8**	**Within 30 days after final treatment**	**Every 8 weeks**
Informed Consent	X					
Inclusion and Exclusion Criteria	X					
Demography	X					
Medical/Surgical History	X					
Prior anti-Cancer Therapy	X					
Prior Radiation Therapy	X					
Cisplatin ineligibility (if applicable)[3]	X					
ECOG[4,5]	X	X	X		X	
Vital Signs[6]	X		X		X	
Serum Pregnancy Test[7]	X					
Urine Pregnancy Test[7]		X	X		X	X
Follicle-Stimulating Hormone (FSH)[8]	X					
Physical Exam[5,9]	X		X		X	
Height	X					
Weight[10]	X		X		X	
ECG[11]		X	X			
Hematology[5,12]		X	X	X	X	
PT/INR and PTT[13]	X					
Blood Chemistry[5,14]		X	X	X	X	
LDH and Uric Acid[15]	X					
Urinalysis[16]	X					
Hepatitis B Surface Antigen, Hepatitis B Core Antibody, Hepatitis C Antibody Tests (and viral load if applicable)	X					

Phase	**Pre-treatment**		**Treatment**		**Post-treatment**	
Period	**Screening**	**Baseline[1]**	**Treatment Cycle 1 through Last Cycle (21-day cycle)**		**End of Treatment[2]**	**Follow-up**
Day	**Days -28 to -1**	**Days -3 to 1**	**Day 1**	**Day 8**	**Within 30 days after final treatment**	**Every 8 weeks**
EORTC QLQ-C30 and EuroQOL EQ-5D-5L QOL Questionnaires[5,17]		X	X		X	
Sacituzumab Govitecan Administration[18]			X	X		
TPC Administration (Paclitaxel, Docetaxel or Vinflunine)[19]			X			
PK Sampling[20]			X	X		
Immunogenicity (ADA)[21]			X		X	
CT or MRI Tumor Assessments[22]	X	Throughout Study[22]				X
Blood Biomarker Samples[23]		X	Throughout Study[23]		X	
Optional Archival or Fresh Biopsy for Trop-2 and Other Biomarker Testing[24]		X				
Optional *UGT1A1* genotype[25]	X					
Brain MRI (if known/suspected Brain Metastases)[26]	X					
AEs/SAEs	X	Throughout Study			X	X[27]
Concomitant Medications	X	Throughout Study			X	
Subsequent Therapy						X
Survival Information						X

1 All baseline assessments may be done on C1D1 prior to dosing.
2 EOT visit within 30 days of the last dose of study drug.
3 Cisplatin ineligibility criteria will be documented during screening. It is defined as meeting one of the following criteria:
   1. Creatinine Clearance <60 mL/min
   2. Grade ≥2 Audiometric Hearing Loss
   3. Grade ≥2 Peripheral Neuropathy
   4. NYHA Class III heart failure
   5. ECOG PS ≥2
4 ECOG PS score will be obtained at screening, baseline, prior to dosing every 6 weeks for first 12 months from C1D1 and every 9 weeks thereafter, and at EOT visit.
5 Any assessment performed on Day 1 and Day 8 (sacituzumab govitecan arm) or Day 1 (TPC arm) may be done within 24 hours of actual dosing date.
6 Vital signs (heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature) required at Screening, on Day 1 of each cycle prior to infusion, and the EOT visit.

7 In females of childbearing potential, the urine pregnancy test at baseline does not need to be conducted if the serum pregnancy test at screening was performed within 72 hours before study treatment administration on C1D1. Pregnancy testing will be performed thereafter on Day 1 of each treatment cycle starting from Cycle 2 through last cycle, and every 28 days after the last dose of study drug up to 6 months after the last dose of study drug per the duration of required contraception, as described in Appendix 18.7. Testing during the post-treatment period may be done at home and the result is self-reported by the subject. If a urine pregnancy test is positive or equivocal, a confirmatory serum pregnancy test will be required.

8 Conduct as needed per Appendix 18.7 for determination of childbearing potential.

9 A full physical examination and total body examination of all major body systems (eg, general appearance, skin, neck [including thyroid], ears, eyes, nose, throat, lungs, heart, abdomen, back, lymph nodes, and extremities and a clinical neurological examination), and body weight must be performed at Screening. More focused physical examination (at minimum cardiac, lung and abdominal examination) must be performed during study visits; however, abnormal findings of any body system must be reported.

10 Body weight will be reported on D1 of every cycle.

11 Twelve (12)-lead ECG will be obtained at baseline, and/or prior to infusion on C1D1. For subjects receiving vinflunine, ECGs will also be obtained prior to infusion on C2D1 and C3D1. As per the summary of product characteristics for certain TPC agents, additional cardiac monitoring, including echocardiography, may be required. Abnormal findings should be evaluated as clinically indicated, including repeated ECGs. ECGs may be done at other timepoints during the study if clinically indicated. ECGs are to be performed at rest in the supine position.

12 CBC with platelets and WBC differential with absolute cell counts for all subjects is required at baseline, Day 1 and 8 of every Cycle, and the EOT visit (not required at C1D1 if baseline sample collected within 72 hours prior). Hematology samples will not be collected for subjects on the TPC arm on Day 8 of each cycle. May be obtained more frequently at the discretion of the managing physician if abnormal results warrant follow-up. Results of unscheduled tests should be documented. Results from the baseline or C1D1 assessments should be obtained prior to study drug dosing on C1D1. Subjects must have adequate hematologic counts without transfusion or G-CSF support within 2 weeks of study drug initiation (Section 5.1). See Section 6.3.2.2 for when sacituzumab govitecan should be administered based on ANC.

13 PT/INR and PTT at Screening and as clinically indicated.

14 Serum chemistries include glucose, creatinine, BUN, total bilirubin, AST, ALT, alkaline phosphatase, serum albumin, total protein, sodium, potassium, calcium, chloride, magnesium, and phosphorus. Bicarbonate or HCO3 is an optional assessment. Serum chemistries are required in all subjects at baseline, Day 1 and 8 of every cycle (not required to be repeated at C1D1 if baseline sample collected within 72 hours prior), and the EOT visit. Chemistry samples will not be collected for subjects on the TPC arm on Day 8 of each cycle. Prior to administration of sacituzumab govitecan at C1D1 and at any other time point, subjects are required to have creatinine clearance ≥ 30 mL/min.

15 LDH and uric acid at Screening and as clinically indicated. May be obtained more frequently at the discretion of the managing physician if abnormal results warrant follow-up. Results of unscheduled tests should be documented.

16 Urinalysis will be performed locally on a freshly voided clean sample by dipstick for protein, glucose, blood, pH, and ketones. If dipstick findings are abnormal based on the investigator's judgment, then a microscopic evaluation will be performed to assess the abnormal findings. Urinalysis will be performed at Screening only and as clinically indicated with details regarding protein, casts, WBC, red blood cell count, specific gravity and presence of bacteria to be recorded.

17 QOL will be obtained at baseline, prior to dosing on D1 of every cycle starting from C2D1, and at the EOT visit. EuroQOL EQ-5D-5L will also be assessed at initial determination of PD. The questionnaires may be administered together and in sequence order, at the beginning of the visit prior to the other study procedures, with the EORTC QLQ-C30 presented first, followed by the EQ-5D-5L.

18 Permitted time window for administration is 1 day prior and 2 days after the expected dosing day. The first infusion is to be administered over 3 hours; subsequent infusions may be administered over 1 to 2 hours if previous infusions were well tolerated.

19 Vinflunine can be used as a comparator option in countries where it is approved and is commercially available for the treatment of metastatic or locally advanced unresectable UC. **Note: subjects in the TPC arm will have study assessments on Day 1 of each cycle only.**

20 Serum samples will be collected only for subjects receiving sacituzumab govitecan for PK analysis. Collection times for PK samples are Cycle 1 and Cycle 5 (Day 1: pre-dose, 30 and 60 minutes post end of infusion; Day 8: pre-dose only); Cycle 2–Cycle 4 (Day 1: pre-dose only). The collection window for PK sample is -30 minutes for pre-dose and +10 minutes for post dose samples (at the end of infusion).

21 Serum samples will be collected only for subjects receiving sacituzumab govitecan for immunogenicity ADA analysis at pre-dose on Day 1 of Cycles 1, 3, 5, 7, 9, 11 and every 3 cycles thereafter (eg, Cycles 14, 17, etc.), and at the EOT visit. The collection window for ADA samples is -30 minutes.

22 CT or MRI with IV contrast (chest, abdomen, pelvis; Brain MRI, if known/suspected brain metastasis), unless known history of anaphylaxis to contrast or there are other conditions that would preclude a subject from receiving contrast, is required in all subjects after the start of treatment and every 6 weeks for first 12 months from C1D1 and then every 9 weeks afterwards until the occurrence of progression of disease. Scans may be performed within ±5 days of the scheduled visits. For each subject, the same imaging technique should be used throughout the study. For subjects with evidence of CR and PR, a confirmatory scan a minimum of 4-6 weeks later must be obtained after initial documentation of response. Additional CT/MRI can be performed at the discretion of the physician to assess disease status as medically indicated. These results should be recorded. If study drug is discontinued due to clinical progression or toxicity without evidence of radiologic progression, CT or MRI scan of target lesions is required to document radiologic progression if clinically feasible. Subjects should continue radiologic response assessments per protocol-required schedule, until radiologic progression of disease or initiation of new therapy.
23 Blood samples for biomarker analysis will be collected at CCI [redacted].
24 For evaluation of Trop-2 expression and other biomarkers, archival tissue can be submitted. If a biopsy is obtained as part of SOC, a sample of this may be submitted if archival tissue is not available. Fine needle aspirations and bone biopsies are not acceptable. This testing is optional and not required for eligibility.
25 UGT1A1 samples are to be shipped to the central lab. Samples will be collected at screening and the UGT1A1 genotype will be determined at baseline; this testing is not required for eligibility. See Appendix 18.10 for China-specific requirements.
26 Brain MRI is only needed in subjects with known or suspected brain metastases at the study entry.
27 Only treatment-related AEs will be collected.

Abbreviations: ADA = Anti-drug Antibody; AE = Adverse Event; ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase; BUN = Blood Urea Nitrogen; C1D1 = Cycle 1 Day 1; CBC = Complete Blood Count; CR = Complete Response; CT = Computed Tomography; ECG = Electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EuroQOL EQ-5D-5L = European Quality of Life 5-dimensions 5-levels; EOT = End of Treatment; FFPE = formalin-fixed, paraffin-embedded; G-CSF = Granulocyte-Colony Stimulating Factor; INR = International Normalized Ratio; IV = Intravenous; LDH = Lactate Dehydrogenase; MRI = Magnetic Resonance Imaging; NYHA = New York Heart Association; PA = Protocol Amendment; PK = Pharmacokinetics; PR = Partial Response; PS = Performance Status; PT = Prothrombin Time; PTT = Partial Thromboplastin Time; QOL = Quality of Life; SAE = Serious Adverse Event; SOC = Standard of Care; TPC = Treatment of Physician's Choice; WBC = White Blood Count.

Table 2. Modified Schedule of Assessments (After Implementation of PA6)

Phase	**Treatment**		**Post-treatment**
Period	**Treatment Cycles Post-PA6 through Last Cycle (21-day cycle)**		**End of Treatment/ End of Study**
Day	**Day 1**	**Day 8**	**Within 30 days after final treatment**
Re-Consent[1]	X		
Vital Signs[2]	X		X
Weight[3]	X		X
Hematology[4,5]	X	X	X
Blood Chemistry[4,6]	X	X	X
Sacituzumab Govitecan Administration[7]	X	X	
AEs/SAEs	X	X	X
Concomitant Medications	X	X	X
Urine Pregnancy Test[8]	X		X

1 Re-consent for active subjects should be performed at the first visit following local protocol amendment approval.
2 Vital signs (heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature) required, on Day 1 of each cycle prior to infusion, and at the EOT visit.
3 Body weight will be reported on Day 1 of every cycle.
4 Any assessment performed on Days 1 and 8 (sacituzumab govitecan arm) may be done within 48 hours of actual dosing date.
5 CBC with platelets and WBC differential with absolute cell counts for all subjects is required at Days 1 and 8 of every cycle and the EOT visit. Hematology may be obtained more frequently at the discretion of the managing physician if abnormal results warrant follow-up. Results of unscheduled tests should be documented. Subjects must have adequate hematologic counts without transfusion or G-CSF support within 2 weeks of study drug initiation (Section 5.1). See Section 6.3.2.2 for when sacituzumab govitecan should be administered based on ANC.
6 Serum chemistries include creatinine, total bilirubin, AST, ALT, sodium, potassium, magnesium, and phosphorus. Serum chemistries are required in all subjects at baseline, Days 1 and 8 of every cycle, and the EOT visit. Prior to administration of sacituzumab govitecan at any other time point, subjects are required to have creatinine clearance ≥ 30 mL/min, as assessed by the Cockcroft-Gault equation or other validated instruments (eg, MDRD equation; see Appendix 18.4).
7 Permitted time window for administration is 1 day prior and 2 days after the expected dosing day.
8 Pregnancy testing for WOCBP will be performed on Day 1 of each treatment cycle and at EOT. If a urine pregnancy test is positive or equivocal, a confirmatory serum pregnancy test will be required.

Abbreviations: AE = Adverse Event; ALT = Alanine Aminotransferase; ANC = absolute neutrophil count; AST = Aspartate Aminotransferase; CBC = Complete Blood Count; EOT = End of Treatment; G-CSF = Granulocyte-Colony Stimulating Factor; MDRD = Modification of Diet in Renal Disease; PA = Protocol Amendment; SAE = Serious Adverse Event; WBC = White Blood Count, WOCBP = Women of Child-Bearing Potential

5. SELECTION AND WITHDRAWAL OF SUBJECTS

5.1. Subject Inclusion Criteria

Subjects meeting all the following inclusion criteria at Screening/Baseline will be eligible for participation in the study.

1) Female or male subjects, ≥18 years of age, able to understand and give written informed consent.
2) Subjects with histologically documented UC that is metastatic or locally advanced unresectable defined as:

   — Tumor (T) 4b, any node (N) or

   — Any T, N 2-3

   Tumors of upper and lower urinary tract are permitted. Mixed histologic types are allowed if urothelial is the predominant histology.
3) ECOG PS score of 0 or 1 (see Appendix 18.3).
4) Subjects with progression or recurrence following receipt of platinum-containing regimen and anti-PD-1/PD-L1 therapy for metastatic or locally advanced unresectable disease will be enrolled.
   a) Subjects with recurrence or progression ≤12 months following completion of cisplatin-containing chemotherapy given in the neo-adjuvant/adjuvant setting may utilize that line of therapy to be eligible for the study. The 12-month period is counted from completion of surgical intervention or cisplatin therapy, respectively. These subjects must receive anti-PD-1/PD-L1 therapy in the metastatic or locally advanced unresectable setting to be eligible.
   b) Subjects who received either carboplatin or anti-PD-1/PD-L1 therapy in the neo-adjuvant/adjuvant setting will not be able to count that line of therapy towards eligibility for the study.
   c) Cisplatin-ineligible subjects who meet one of the below criteria and who were treated with carboplatin in the metastatic or locally advanced unresectable settings may count that line of therapy towards eligibility. They must then have received anti-PD-1/PD-L1 therapy in metastatic or locally advanced unresectable setting to be eligible for the study.

      Cisplatin ineligibility is defined as meeting one of the following criteria:

      i) Creatinine Clearance <60 mL/min
      ii) Grade ≥2 Audiometric Hearing Loss
      iii) Grade ≥2 Peripheral Neuropathy
      iv) New York Heart Association (NYHA) Class III heart failure
      v) ECOG PS ≥2

d) Anti PD-1/PD-L1 therapy administered as part of maintenance therapy may be counted towards eligibility for the study.

e) Subjects who have progressed after receiving enfortumab vedotin in prior lines of therapy, and subjects who are either ineligible or unable to tolerate enfortumab vedotin therapy, are eligible to enroll in the study.

f) Subjects who received only concurrent chemoradiation for bladder preservation without further systemic therapy are not eligible to enroll in the study. The substitution of carboplatin for cisplatin does not constitute a new regimen provided no new chemotherapeutic agents were added to the regimen and no progression was noted prior to the change in platinum.

5) Subjects with previously treated brain metastases may participate in the study provided they have stable central nervous system disease for at least 4 weeks prior to the first dose of study drug and stabilization of all neurologic symptoms, have no evidence of new or enlarging brain metastases, and are not using steroids > 20 mg of prednisone (or equivalent) daily for brain metastases for at least 7 days prior to first dose of the study drug.

6) Adequate hematologic counts without transfusion or growth factor support within 2 weeks of study drug initiation (hemoglobin ≥9 g/dL, absolute neutrophil count [ANC] ≥ 1500/mm^3, and platelets ≥100,000/μL).

7) Adequate hepatic function (bilirubin ≤1.5 x institutional upper limit of normal [IULN], aspartate aminotransferase [AST] and alanine aminotransferase [ALT] ≤2.5 x IULN or ≤5 x IULN if known liver metastases and serum albumin ≥3 g/dL).

   Docetaxel will only be an option in TPC arm for subjects with a total bilirubin ≤1 x IULN, and an AST and/or ALT ≤1.5 x IULN if alkaline phosphatase is also >2.5 x IULN.

8) Creatinine clearance ≥30 mL/min as assessed by the Cockcroft-Gault equation or other validated instruments (eg, Modification of Diet in Renal Disease [MDRD] equation; see Appendix 18.4).

9) 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 18.7.

5.2. Subject Exclusion Criteria

Subjects meeting any of the following exclusion criteria at Screening/Baseline will not be enrolled in the study.

1) Women who are pregnant or lactating (see Appendix 18.7).

2) Have had a prior anti-cancer mAb/ADC within 4 weeks prior to C1D1 or have had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to C1D1. Subjects participating in observational studies are eligible.

3) Have received prior chemotherapy for UC with any available SOC therapies in the control arm (ie, either prior paclitaxel and docetaxel in countries where vinflunine is not an approved therapy, or either prior paclitaxel, docetaxel and vinflunine in countries where vinflunine is approved and is commercially available).

4) Have not recovered (ie, ≤Grade 1) from AEs due to previously administered chemotherapeutic agent.

   — Note: Subjects with ≤Grade 2 neuropathy or any grade of alopecia are an exception to this criterion and will qualify for the study.

   — Note: If subjects received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study therapy.

5) Have previously received topoisomerase 1 inhibitors.

6) Have an active second malignancy.

   — Note: Subjects with a history of malignancy that have been completely treated and with no evidence of active cancer for 3 years prior to enrollment, or subjects with surgically cured tumors with low risk of recurrence are allowed to enroll in the study after discussion with the medical monitor.

7) Have active cardiac disease, defined as:

   a) Myocardial infarction or unstable angina pectoris within 6 months of C1D1

   b) History of serious ventricular arrhythmia (ie, ventricular tachycardia or ventricular fibrillation), high-grade atrioventricular block, or other cardiac arrhythmias requiring anti-arrhythmic medications (except for atrial fibrillation that is well controlled with anti-arrhythmic medication); history of QT interval prolongation.

   c) NYHA Class III or greater congestive heart failure or left ventricular ejection fraction of <40%.

8) Have active chronic inflammatory bowel disease (ulcerative colitis, Crohn's disease) or GI perforation within 6 months of enrollment.

9) Have an active serious infection requiring anti-infective therapy (contact medical monitor for clarification).

10) Have uncontrolled HIV-1/2 viral load (ie, ≥ 200 copies/mL and/or CD4+ count < 350 cells/mm^3) and/or on medications that may interfere with SN-38 metabolism.

11) Have active Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV). In subjects with a history of HBV or HCV, subjects with a detectable viral load will be excluded.

12) Have other concurrent medical or psychiatric conditions that, in the investigator's opinion, may be likely to confound study interpretation or prevent completion of study procedures and follow-up examinations.

13) Have inability to tolerate or are allergic to any potential TPC agent or sacituzumab govitecan or unable or unwilling to receive the doses specified in the protocol.

14) Have inability to complete all specified study procedures for any reason.

15) History of active interstitial lung disease or noninfectious pneumonitis.

5.3. Criteria for Treatment Discontinuation

Subjects will discontinue the treatment under any of the following conditions:

1) Withdrawal of consent from further treatment with study drug.

2) Lost to follow-up: Subjects will be considered lost to follow-up when there is no response to 2 attempts one month apart by phone and a registered letter. After these 3 failed attempts, lost to follow-up will be documented.

3) An AE that, in the opinion of the investigator or the sponsor, contraindicates further dosing.

4) Initiation of alternative anti-tumor therapy, including any investigational agent.

5) Pregnancy (see Appendix 18.7).

6) More than a 5-week dose delay from the last dose.

7) Failure to resolve a toxicity within 3 weeks of the last dose of study drug.

8) PD with no evidence of clinical benefit.

9) Subject non-compliance.

10) Other.

Note: "Other" will include subjects in the TPC arm who, following implementation of PA6, will discontinue the study treatment to transition to standard-of-care supply.

5.4. Criteria for Study Discontinuation

Subjects will discontinue the study under any of the following conditions:

1) Death.

2) Withdrawal of consent from study.

3) Lost to follow-up: Subjects will be considered lost to follow-up when there is no response to 2 attempts one month apart by phone and a registered letter. After these 3 failed attempts, lost to follow-up will be documented.

4) Sponsor completes the study.

5) Other.

Note: “Other” will include an EOT with documentation of resolution or stabilization of AEs (if applicable) after the final OS analysis and following implementation of PA6.

6. TREATMENT OF SUBJECTS

6.1. Description of Study Drug

Sacituzumab govitecan is a humanized mAb with a hydrolysable linker through which SN-38 is conjugated to the humanized mAb hRS7 IgG1κ to enhance the delivery of SN-38 to Trop 2 -expressing tumors, while reducing systemic toxicity. SN-38 is the active metabolite of irinotecan.

6.2. Investigational Medicinal Product, Dosage and Mode of Administration

Sacituzumab govitecan is administered at 10 mg/kg as an IV infusion on days 1 and 8 of a 21-day cycle until PD, toxicity, withdrawal of consent, or other treatment discontinuation criteria are met. The permitted time window for administration is 1 day prior and 2 days after the expected dosing day.

Sacituzumab govitecan is administered via IV infusion as described below with additional information available in the current version of the Pharmacy Manual. Sacituzumab govitecan should not be administered as an IV push or bolus. Sacituzumab govitecan is a cytotoxic drug, and applicable special handling and disposal procedures should be followed.

- Administer the first infusion over 3 hours. Subsequent infusions may be administered over 1 to 2 hours if previous infusions were well tolerated. Monitor the subject during and for at least 30 minutes after infusion.
- Protect the infusion bag from light.
- An infusion pump may be used.
- Confirm compatibility with polypropylene infusion bags.
- In-line filters and other ancillary infusion equipment are not recommended for use.
- Do not mix sacituzumab govitecan, or administer as an infusion, with other medicinal products.
- Upon completion of the infusion, flush the IV line with 20 mL 0.9% Sodium Chloride Injection, USP.

Post-infusion monitoring is described in Section 6.3.2.4. Because of the potential for life-threatening infusion-related reactions, sacituzumab govitecan should only be administered in a setting in which appropriately trained medical staff, emergency equipment, and medications are available in the event that resuscitation is required.

6.3. Treatment of Sacituzumab Govitecan-Associated Toxicities

Instructions for the preparation, infusion, and handling of sacituzumab govitecan are provided in the current version of the Pharmacy Manual. The following sections provide guidance for sacituzumab govitecan administration and management of treatment-related toxicities, including modification of dosing and treatment discontinuation. Toxicities should be managed in accordance with standard institutional practices and accepted treatment guidelines.

6.3.1. Preventative Medications

Infusion-Related Reactions: Pre-medication for prevention of infusion-related reactions with antipyretics and histamine 1 and histamine 2 blockers should be administered before each sacituzumab govitecan infusion per institution's SOC. Corticosteroids (hydrocortisone 50 mg or equivalent orally [PO] or IV) may be administered prior to subsequent infusions.

Nausea and Vomiting: sacituzumab govitecan is considered to be moderately emetogenic. Pre-medication with a 2-drug antiemetic regimen is recommended. If nausea and vomiting are persistent, a 3-drug regimen may be used, including a 5-hydroxytryptamine 3 inhibitor (ondansetron or palonosetron, or other agents according to local practices), a neurokinin 1-receptor antagonist (fosaprepitant or aprepitant), and dexamethasone (10 mg PO or IV). Anticipatory nausea can be treated with olanzapine. The recommended treatment of delayed nausea and vomiting is described in Section 6.3.2.1.

6.3.2. Management of Sacituzumab Govitecan Toxicities

The National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0 is used to grade the severity of all AEs. The guidelines for management of toxicities associated with sacituzumab govitecan are based on the assessment of severity according to these criteria. Toxicities should be managed in accordance with standard medical practice and treatment guidelines. All clinically appropriate imaging or laboratory testing should be utilized to fully assess a toxicity to determine the appropriate treatment. Appropriate follow-up studies should be utilized to follow all toxicities to resolution. Subjects with known UGT1A1 *28 polymorphisms (ie, the 1/28 or 28/28 polymorphisms), may have a higher risk of developing treatment-related toxicities. Additional monitoring may be required in those subjects. Subjects suspected of having underlying *UGT1A1* *28 or 6 polymorphisms due to increased episodes of diarrhea or neutropenia should have their polymorphism assessed. If found to have a polymorphism, these data should be recorded in the eCRF with dosing adjusted per institutional standards. Instructions for sacituzumab govitecan dose reduction for treatment-related toxicities are provided in Section 6.3.2.4.

6.3.2.1. Gastrointestinal Toxicities

Nausea, vomiting, and diarrhea are frequent sacituzumab govitecan-associated toxicities. Appropriate treatment, including, as needed, fluid and electrolyte replacement, is required to minimize the risk of serious consequences such as dehydration. Instructions for sacituzumab govitecan dose reduction for treatment-related GI toxicities are provided in Section 6.3.2.4.

Nausea and Vomiting

Instructions for the use of pre-medications for prophylactic treatment of nausea and vomiting and anticipatory nausea are provided in Section 6.3.1. Withhold sacituzumab govitecan for Grade 3 nausea or Grade 3 or 4 vomiting at the time of scheduled treatment administration and resume with additional supportive measures when resolved to Grade ≤ 1.

Diarrhea

Dietary modification should be recommended for the management of diarrhea, including adequate fluid intake to maintain hydration. Loperamide can be administered at the onset of treatment-related diarrhea, at an initial dose of 4 mg, followed by 2 mg with every episode of diarrhea to a maximum dose of 16 mg/day. Discontinue loperamide 12 hours after diarrhea resolves. Additional supportive measures may also be employed as clinically indicated. If diarrhea is not resolved after 24 hours, consider adding diphenoxylate/atropine and/or opium tincture, as clinically indicated.

Consider adding octreotide 100 to 150 mcg subcutaneous three times per day if diarrhea persists. Withhold sacituzumab govitecan for Grade 3 or 4 diarrhea at the time of scheduled treatment administration and resume when resolved to Grade ≤ 1. For Grade 3 or 4 diarrhea, consider hospitalization, and treat with IV fluids, and octreotide. Antibiotics can be administered as clinically indicated.

Subjects who exhibit an excessive cholinergic response to treatment with sacituzumab govitecan (eg, abdominal cramping, diarrhea, salivation, etc.) can receive appropriate pre-medication (eg, atropine) for subsequent treatments.

6.3.2.2. Neutropenia

Complete blood counts (CBCs) must be obtained prior to each sacituzumab govitecan infusion. Sacituzumab govitecan should be administered only if ANC meet the following criteria:

- Day 1: ANC ≥1500/mm^3
- Day 8: ANC ≥1000/mm^3

Sacituzumab govitecan should not be administered in cases of neutropenic fever.

Use of prophylactic G-CSF is strongly recommended in subjects who are at the risk of developing febrile neutropenia. The selection of a G-CSF agent will be determined by the investigator in accordance with institutional and local guidelines. Patient characteristics associated with high risk of febrile neutropenia are defined by the American Society of Clinical Oncology (ASCO) guidelines {Smith 2015} and are listed below:

- Age ≥65 years
- Advanced disease
- Previous chemotherapy or radiation therapy
- Pre-existing neutropenia or bone marrow involvement with tumor
- Infection
- Open wounds or recent surgery
- Poor performance status or poor nutritional status
- Poor renal function
- Liver dysfunction, most notably elevated bilirubin

- Cardiovascular disease
- Multiple comorbid conditions
- HIV infection

Prompt use of G-CSF is also recommended in patients treated with sacituzumab govitecan who develop neutropenia, as detailed in Table 3. Patients who develop febrile neutropenia should initiate anti-infective treatment without delay.

6.3.2.3. Overdose

Overdose is defined as administration of a dose that is 10% higher than the calculated dose. In the event of an overdose, closely monitor the subject per standard institutional guidelines. Any AE resulting from overdose should be reported as described in Section 10.2.2.

6.3.2.4. Sacituzumab Govitecan Dose Modification Guidelines

Dose Delays

Sacituzumab govitecan is to be administered in 21-day cycles on Day 1 and Day 8; the next cycle should start a minimum 14 days after the Day 8 dose (ie, the Day 8 infusion will be counted as the first day of that 14-day period). Visit windows of one day prior to and two days after the scheduled infusion are permitted. The scheduled Day 1 and Day 8 infusions may be delayed for up to one week for treatment-related toxicities.

Instructions for dose delays and dose reductions for specific toxicities are summarized below. For specific toxicities not described in Sections 6.3.2.1 to 6.3.2.2, dosing may be delayed for >Grade 2 toxicities for a maximum of one week. If the toxicity has improved to ≤Grade 2, the dose should be administered at that time. For a toxicity that delays Day 8 dosing, if the toxicity has not resolved to ≤Grade 2 within one week, dosing should resume with the next scheduled cycle, ie, the next dose will be Day 1 of the following cycle. Regardless of whether the Day 8 dose is delayed for toxicity, there should be a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle (day of delay is counted as day 1 of this 14-day period). Treatment interruptions for reasons other than resolution of toxicities/procedures are not permitted outside of the permitted visit windows.

Dose Reductions and Discontinuation

The major toxicities of sacituzumab govitecan are expected to be GI symptoms and hematologic suppression. All subjects will be closely monitored over the course of their treatment and aggressively medically managed, including dose reduction and interruption, in order to prevent the need for treatment discontinuation and serious complications of these toxicities. All efforts to avoid dose reduction should be taken to address toxicity prior to institution of dose reduction. Sacituzumab govitecan dose reductions and interruptions will be managed based on toxicity severity, as assessed by the NCI-CTCAE v5.0. Leukopenia or lymphopenia in the absence of neutropenia will not require dose delay or dose modification. The dose of sacituzumab govitecan must not be re-escalated following a dose reduction. Table 3 summarizes recommendations for sacituzumab govitecan dose reductions and discontinuations for treatment-related toxicities Grade 3 or higher.

Table 3. Recommended Dose-Reduction Schedule for Sacituzumab Govitecan

Event NCI-CTCAE v5.0	Occurrence	Recommended dose reduction or action
Severe Neutropenia		
Grade 4 neutropenia ≥7 days or less if clinically indicated, OR Grade 3-4 febrile neutropenia, OR At time of scheduled treatment, Grade 3-4 neutropenia, which delays dosing by 2 or 3 weeks for recovery to ≤ Grade 1	First	Administer G-CSF as soon as clinically indicated
	Second	25% dose reduction; administer G-CSF as soon as clinically indicated
	Third	50% dose reduction; administer G-CSF as soon as clinically indicated
	Fourth	Discontinue treatment; administer G-CSF as soon as clinically indicated
At time of scheduled treatment, Grade 3-4 neutropenia, which delays dosing beyond 3 weeks for recovery to ≤ Grade 1	First	Discontinue treatment; administer G-CSF as soon as clinically indicated
Severe Non-Neutropenic Toxicity		
Grade 4 non-hematologic toxicity of any duration, OR Any Grade 3-4 nausea, vomiting or diarrhea due to treatment that is not controlled with antiemetics and anti-diarrheal agents, OR Other Grade 3-4 non-hematologic toxicity persisting > 48 hours despite optimal medical management, OR At time of scheduled treatment, Grade 3-4 non-neutropenic hematologic or non-hematologic toxicity, which delays dosing by 2 or 3 weeks for recovery to ≤ Grade 1	First	25% dose reduction
	Second	50% dose reduction
	Third	Discontinue treatment
In the event of Grade 3-4 non-neutropenic hematologic or non-hematologic toxicity, which does not recover to ≤ Grade 1 within 3 weeks	First	Discontinue treatment

Abbreviations: G-CSF = Granulocyte-Colony Stimulating Factor; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events v5.0

6.4. TPC Treatments Dosage and Mode of Administration

The SOC treatment(s) to be used in this trial are outlined below in Table 4. Treatment on the TPC arm will be prepared and administered as per the approved product label. The body surface area (BSA) in m^2 should be calculated as per local guidelines. The investigator will take responsibility for and take all necessary steps to maintain records and ensure appropriate supply, storage, handling, distribution, and usage of trial treatments in accordance with the protocol, approved product label and any applicable laws and regulations. Subjects must be able to be dosed with the doses specified for the assigned comparator arm.

Table 4. Standard-of-Care Trial Treatments

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Paclitaxel	175 mg/m²	q3W	IV infusion	Day 1 of each cycle	Active comparator
Docetaxel*	75 mg/m²	q3W	IV infusion	Day 1 of each cycle	Active comparator
Vinflunine**	320 mg/m²	q3W	IV infusion	Day 1 of each cycle	Active comparator

Abbreviations: ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase; ECOG PS = Eastern Cooperative Oncology Group Performance Status; IULN = Institutional Upper Limit of Normal; IV = intravenous; q3W = every 3 weeks; mUC = Metastatic Urothelial Cancer; WHO = World Health Organization

* Docetaxel will only be a comparator option for subjects with a total bilirubin ≤1 x IULN, and an AST and/or ALT ≤1.5 x IULN if alkaline phosphatase is also >2.5 x IULN.

** In case of WHO/ECOG PS of 1 or PS of 0 and prior pelvic irradiation, vinflunine should be started at the dose of 280 mg/m². In the absence of any hematological toxicity during the first cycle causing treatment delay or dose reduction, the dose will be increased to 320 mg/m² every 3 weeks for the subsequent cycles. See Section 6.4.2.3 for dose modification guidelines for vinflunine.

Note: Vinflunine will only be a comparator option in countries where vinflunine is approved and is commercially available for the treatment of mUC.

6.4.1. Dose Administration for TPC Arm

6.4.1.1. Dose Administration for Paclitaxel

Trial treatment of paclitaxel should be administered on Day 1 of each 3-week cycle after all procedures/assessments have been completed. Dosing of Paclitaxel must be 175 mg/m^2 administered as an IV infusion administered over 3 hours. See Section 6.4.2.1 for guidelines on adjustment of dose due to AE {TAXOL® 2011} for cycle 2 and beyond if needed. Caution should be exercised when paclitaxel is concomitantly administered with known inhibitors of cytochrome P450 enzyme (CYP)3A4 or CYP2C8. Concomitant administration of known inducers of CYP3A4 or CYP2C8 is not recommended.

All subjects should be premedicated prior to paclitaxel administration in order to prevent severe hypersensitivity reactions. Such pre-medication may consist of dexamethasone 20 mg PO administered approximately 12 and 6 hours before paclitaxel, diphenhydramine (or its equivalent) 50 mg IV 30 to 60 minutes prior to paclitaxel, and cimetidine (300 mg) or ranitidine (50 mg) IV 30 to 60 minutes before paclitaxel. The appropriate pre-medication regimen may be determined by the investigator.

6.4.1.2. Dose Administration for Docetaxel

Trial treatment of docetaxel should be administered on Day 1 of each 3-week cycle after all procedures/assessments have been completed.

Dosing of docetaxel must be 75 mg/m² administered as an IV infusion over 1 hour. See Section 6.4.2.2 for guidelines on adjustment of dose due to AE {TAXOTERE 2020} for Cycle 2 and beyond if needed. Caution should be exercised when docetaxel is concomitantly administered with inducers or inhibitors of CYP3A4.

All subjects should be premedicated with oral corticosteroids, such as dexamethasone 16 mg per day (eg, 8 mg twice daily) for 3 days starting 1 day prior to docetaxel administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. The appropriate pre-medication regimen may be determined by the investigator.

6.4.1.3. Dose Administration for Vinflunine

Trial treatment of vinflunine should be administered on Day 1 of each 3-week cycle after all procedures/assessments have been completed.

Dosing of vinflunine must be 320 mg/m^2 administered as an IV infusion over 20 minutes. In case of WHO/ECOG PS of 1 or PS of 0 and prior pelvic irradiation, vinflunine should be started at the dose of 280 mg/m^2. See Section 6.4.2.3 for guidelines on adjustment of dose due to AE {Javlor 2021} for cycle 2 and beyond if needed. The concomitant use of other QT/QTc interval-prolonging medicinal products with vinflunine should be avoided. Similarly, the concomitant use of potent inhibitors or inducers of CYP3A4 must also be avoided.

6.4.2. Recommended Dose Modification Guidelines for Paclitaxel, Docetaxel and Vinflunine

The following sections contain recommendations for dose modifications for paclitaxel, docetaxel, and vinflunine. However, sites should defer to SOC for management of TPC toxicities.

In general, treatment with paclitaxel, docetaxel or vinflunine will be withheld for drug-related Grade 4 hematologic toxicities and for non-hematologic toxicity ≥Grade 3. Dose modifications will be applied for all subsequent doses. Specific dose modification guidance for paclitaxel, docetaxel, and vinflunine are found below in Section 6.4.2.1, Section 6.4.2.2, and Section 6.4.2.3 respectively. Dose modifications or management of any toxicities for paclitaxel, docetaxel, or vinflunine should also be considered according to local product labels.

6.4.2.1. Specific Dose Modifications for Paclitaxel

Paclitaxel 175 mg/m^2 will be administered as an IV infusion on Day 1 of each 21-days cycle over 3 hours. Paclitaxel should not be administered to subjects with baseline neutrophil counts of less than 1500 cells/mm^3. Subjects should not be re-treated with subsequent cycles of paclitaxel until neutrophils recover to a level >1500 cells/mm^3. If subjects develop significant conduction abnormalities during paclitaxel infusion, appropriate therapy should be administered, and continuous cardiac monitoring should be performed during subsequent therapy with paclitaxel.

Cystoid macular edema (CME) has been reported in subjects treated with paclitaxel. Subjects with impaired vision should undergo a prompt and complete ophthalmologic examination. If CME is diagnosed, paclitaxel treatment should be discontinued and appropriate treatment initiated.

Dose modifications for subjects receiving paclitaxel are detailed below in Table 5.

Table 5. Paclitaxel Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	Grade	Occurrence	Hold Treatment	Dose Modification (Paclitaxel initial dose of 175 mg/m²)	Treatment Discontinuation
Peripheral Neuropathy	Grade 1, 2		No	135 mg/m^2	N/A
	Grade 3, 4		Yes	N/A	Discontinue treatment upon onset
Neutropenia	Grade 1, 2, 3 or Grade 4 lasting ≤7 days	All	Hold treatment until neutrophils recover to >1500 cells/mm^3	N/A	N/A
	Grade 4 lasting >7 days	1	Hold treatment until neutrophils recover to >1500 cells/mm^3	135 mg/m²	Treatment discontinuation should be considered
		2	Hold treatment until neutrophils recover to >1500 cells/mm^3	100 mg/m²	Treatment discontinuation should be considered
		3	Yes	N/A	Definitive Treatment Discontinuation
Neutropenic fever		1	Hold until ANC ≥1500/L	135 mg/m^2	Treatment discontinuation should be considered
		2	Hold until ANC ≥1500/L	100 mg/m^2	Treatment discontinuation should be considered
		3	Yes	N/A	Definitive Treatment Discontinuation
Thrombocytopenia	Grade 1,2,3	All	Hold treatment until platelets recover to >100,000 cells/µL	N/A	N/A
	Grade 4	1	Hold treatment until platelets recover to >100,000 cells/µL	135 mg/m²	Treatment discontinuation should be considered
		2	Hold treatment until platelets recover to >100,000 cells/µL	100 mg/m²	Treatment discontinuation should be considered
		3	Yes	N/A	Definitive Treatment Discontinuation
Anemia	Grade 1,2,3	All	Until anemia resolves to Grade 1 or baseline	N/A	N/A
	Grade 4	1	Until anemia resolves to Grade 1 or baseline	135 mg/m²	Treatment discontinuation should be considered
		2	Until anemia resolves to Grade 1 or baseline	100 mg/m²	Treatment discontinuation should be considered
		3	Yes	N/A	Definitive Treatment Discontinuation

Abbreviations: ANC = absolute neutrophil count; N/A = not applicable

6.4.2.2. Specific Dose Modifications for Docetaxel

Docetaxel 75 mg/m² will be administered as an IV infusion on Day 1 of each 21-days cycle over 1 hour. Docetaxel should not be given to subjects with bilirubin >1 x IULN, or to subjects with AST and/or ALT >1.5x IULN with concomitant alkaline phosphatase >2.5 x IULN. Docetaxel should also not be given to subjects with a neutrophil count of <1500 cells/mm^3.

Severe fluid retention has been reported following docetaxel therapy. Subjects should be premedicated with oral corticosteroids prior to each docetaxel administration to reduce the incidence and severity of fluid retention (See Section 6.4.1.2). Subjects with pre-existing effusions should be closely monitored from the first dose for the possible exacerbation of the effusions. Subjects developing peripheral edema may be treated with standard measures, eg, salt restriction, oral diuretic(s).

CME has been reported in subjects treated with docetaxel. Subjects with impaired vision should undergo a prompt and comprehensive ophthalmologic examination. If CME is diagnosed, docetaxel treatment should be discontinued and appropriate treatment initiated.

Localized skin of the extremities (palms of the hands and soles of the feet) with edema followed by desquamation has been observed. Severe symptoms such as eruptions followed by desquamation that led to interruption or discontinuation of docetaxel treatment were reported. Severe cutaneous adverse reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis have been reported in association with docetaxel treatment. Subjects should be informed about the signs and symptoms of serious skin manifestations and monitored closely. If signs and symptoms suggestive of these reactions appear, discontinuation of docetaxel should be considered.

Dose modifications for subjects receiving docetaxel are detailed below in Table 6.

Table 6. Docetaxel Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	Grade	Occurrence	Hold Treatment	Dose Modification (Docetaxel initial dose of 75 mg/m²)	Treatment Discontinuation
Peripheral Neuropathy	Grade 1, 2		No	60 mg/m^2	N/A
	Grade 3, 4		Yes	N/A	Discontinue upon onset
Neutropenia	Grade 1, 2, 3 or Grade 4 lasting ≤7 days	All	Hold treatment until neutrophils recover to >1500 cells/mm^3	N/A	N/A
	Grade 4 lasting >7 days	1	Hold treatment until neutrophils recover to >1500 cells/mm^3	60 mg/m^2	Treatment discontinuation should be considered
		2	Hold treatment until neutrophils recover to >1500 cells/mm^3	50 mg/m^2	Treatment discontinuation should be considered
		3	Yes	N/A	Definitive Treatment Discontinuation

Toxicity	Grade	Occurrence	Hold Treatment	Dose Modification (Docetaxel initial dose of 75 mg/m²)	Treatment Discontinuation
Neutropenic fever		1	Hold until ANC ≥1500/L	60 mg/m^2	Treatment discontinuation should be considered
		2	Hold until ANC ≥1500/L	50 mg/m^2	Treatment discontinuation should be considered
		3	Yes	N/A	Definitive Treatment Discontinuation
Thrombocytopenia	Grade 1,2,3	All	Hold treatment until platelets recover to >100,000 cells/µL	N/A	N/A
	Grade 4	1	Hold treatment until platelets recover to >100,000 cells/µL	60 mg/m^2	Treatment discontinuation should be considered
		2	Hold treatment until platelets recover to >100,000 cells/µL	50 mg/m^2	Treatment discontinuation should be considered
		3	Yes	N/A	Definitive Treatment Discontinuation
Anemia	Grade 1,2,3	All	Until anemia resolves to Grade 1 or baseline	N/A	N/A
	Grade 4	1	Until anemia resolves to Grade 1 or baseline	60 mg/m^2	Treatment discontinuation should be considered
		2	Until anemia resolves to Grade 1 or baseline	50 mg/m^2	Treatment discontinuation should be considered
		3	Yes	N/A	Definitive Treatment Discontinuation

Abbreviations: ANC = absolute neutrophil count; N/A = not applicable

6.4.2.3. Specific Dose Modifications for Vinflunine

The recommended dose is 320 mg/m² vinflunine as 20-minute IV infusion on Day 1 of each 21-day cycle.

Severe hyponatremia, including cases due to syndrome of inappropriate antidiuretic hormone secretion, has been observed with the use of vinflunine. Therefore, regular monitoring of serum sodium levels is recommended during treatment with vinflunine.

Cases of posterior reversible encephalopathy syndrome (PRES) have been observed after administration of vinflunine. The typical clinical symptoms are, with various degrees: neurological (headache, confusion, seizure, visual disorders), systemic (hypertension), and gastrointestinal (nausea, vomiting). Radiological signs are white matter abnormalities in the posterior regions of the brain. Blood pressure should be controlled in subjects developing symptoms of PRES. To confirm the diagnosis, brain imaging is recommended. Clinical and radiological features usually resolve rapidly without sequelae after treatment discontinuation. Discontinuation of vinflunine should be considered in subjects who develop neurological signs of PRES.

Dose delay or modification for subjects receiving vinflunine are detailed below in Table 7 and Table 8.

Table 7. Vinflunine Dose Delay for Subsequent Cycles Due to Toxicity

Toxicity	Day 1 treatment administration
Neutropenia (ANC <1000/mm³) or Thrombocytopenia (platelets <100,000/µL)	• Delay until recovery (ANC ≥1000/mm³ and platelets ≥100,000/ µL) and adjust the dose if necessary (see Table 8) • Discontinuation if recovery has not occurred within 2 weeks
Organ toxicity: moderate, severe or life threatening	• Delay until recovery to mild toxicity or none, or to initial baseline status and adjust the dose if necessary (see Table 8) • Discontinuation if recovery has not occurred within 2 weeks

Abbreviation: ANC = absolute neutrophil count

Dose Adjustments Due to Toxicity

Table 8. Vinflunine Dose Modification Guidelines for Drug-Related Adverse Events

	Dose Adjustment		
	Vinflunine Initial dose of 320 mg/m²		
Toxicity	1st event	2nd consecutive event	3rd consecutive event
Neutropenia Grade 4 (ANC < 500/mm³) > 7 days	280 mg/m²	250 mg/m²	Definitive Treatment discontinuation
Febrile Neutropenia			
Mucositis or Constipation Grade 2 ≥5 days or Grade ≥3 any duration[1]			
Any other toxicity Grade ≥3 (severe or life-threatening) (except Grade 3 vomiting or nausea[2])			

Abbreviations: ANC = absolute neutrophil count; IV = intravenous; NCI-CTC = National Cancer Institute-Common Terminology Criteria

1 NCI-CTC Grade 2 constipation is defined as requiring laxatives, Grade 3 as an obstipation requiring manual evacuation or enema, Grade 4 as an obstruction or toxic megacolon. Mucositis Grade 2 is defined as “moderate”, Grade 3 as “severe” and Grade 4 as “life-threatening”.

2 NCI-CTC Grade 3 nausea is defined as no significant intake, requiring IV fluids. Grade 3 vomiting as ≥6 episodes in 24 hours over pre-treatment; or need for IV fluids.

6.5. Concomitant Medications

Medications initiated prior to the first dose of study drug will be recorded as prior medications. Medications initiated following receipt of the first dose of study drug until 30 days after treatment discontinuation will be captured as concomitant medications. Medication information will be entered in the appropriate eCRF with information regarding dose, indication, route of administration and dates of administration. Medications used for prophylaxis of anticipated study drug AEs as outlined in the protocol should be recorded with rationale for prophylactic intent in the eCRF.

Subjects must avoid the use of Chinese traditional medicine and any other traditional medicine during the study.

No anti-cancer therapies, aside from the study drug (sacituzumab govitecan or TPC) are permitted during this study. However, palliative and/or supportive medications, such as pain medications, bone modifying medications (bisphosphonates or denosumab), anti-emetics or anti-diarrheal medications, transfusions and growth factor support are allowed at the investigator's discretion.

Palliative radiotherapy is permitted, but presence of new or worsening metastases will be considered PD. Palliative radiation of a target lesion will render that target lesion and subsequent tumor assessments "Not evaluable" and should be avoided.

However, if there is clear evidence of clinical benefit, treatment (sacituzumab govitecan or TPC) may be continued after completion of palliative radiotherapy. In this case, sacituzumab govitecan administration should be interrupted one week before the procedure and reinstated no earlier than two weeks after the procedure. In the event that a subject requires surgery, sacituzumab govitecan should be interrupted one week before the procedure if clinically feasible and dosing should be held for 2 weeks after the procedure. Dosing may resume thereafter if the subject is clinically stable. Extensive surgical procedures such as abdominal, cranial surgeries for example, may require suspension of dosing for 4 weeks before dosing may resume to allow for an adequate period for healing.

The medical monitor must approve continuation of therapy with sacituzumab govitecan prior to resumption of dosing.

There are no substantial safety data regarding the concurrent administration of the coronavirus disease 2019 (COVID-19) vaccine and sacituzumab govitecan, paclitaxel, docetaxel, or vinflunine. Subjects are allowed to receive the COVID-19 vaccine to reduce the risk and complications of COVID-19 infection. The study visits should continue as planned if vaccination occurs while the subject is on the study.

6.6. Drug Interactions

No formal drug-drug interaction studies with sacituzumab govitecan have been conducted. SN-38 (the active metabolite of sacituzumab govitecan) is metabolized via human UGT1A1. Concomitant administration of inhibitors or inducers of UGT1A1, with sacituzumab govitecan should be avoided due to the potential to either increase (inhibitors) or decrease (inducers) the exposure to SN-38, unless there are no therapeutic alternatives. A list of example UGT1A1 inhibitors and inducers is provided in Appendix 18.8.

For subjects who are treated on TPC arm, manage drug-drug interactions as per package insert (see Section 6.4.1).

6.6.1. UGT1A1 Inhibitors

Co-administration of sacituzumab govitecan with inhibitors of UGT1A1 may increase systemic exposure to the active metabolite, SN-38. Do not administer UGT1A1 inhibitors with sacituzumab govitecan unless there are no therapeutic alternatives. A list of example UGT1A1 inhibitors is provided in Appendix 18.8.

6.6.2. UGT1A1 Inducers

Exposure to SN-38 may be substantially reduced in subjects concomitantly receiving UGT1A1 enzyme inducers. Do not administer UGT1A1 inducers with sacituzumab govitecan unless there are no therapeutic alternatives. A list of example UGT1A1 inducers is provided in Appendix 18.8.

6.7. Treatment Compliance

Sacituzumab govitecan will be administered at selected study centers under the supervision of the investigator or sub-investigator(s). The pharmacist will maintain records of study drug receipt, preparation, and dispensing, and return/destruction, including the applicable lot numbers, subject's body weight, and total drug administered in milligrams. Any discrepancy between the calculated dose and dose administered and the reason for the discrepancy must be recorded in the source documents.

7. STUDY DRUG MATERIALS AND MANAGEMENT

7.1. Study Drug

The Investigational Medicinal Product (IMP) is supplied as a sterile, off-white to yellowish lyophilized powder in single-dose glass vials. It is formulated in 2-(N-morpholino) ethane sulfonic acid buffer containing trehalose and polysorbate 80 and contains no preservatives. Following reconstitution, the concentration of the IMP is 10 mg/mL. The pH of the reconstituted solution is approximately 6.5.

7.2. Storage and Handling

The glass vials of IMP must be stored under refrigeration (2°C to 8°C) and protected from light until use. Since the formulated drug product contains no preservative, vials should be used only once. After reconstitution, the infusion should be initiated as soon as possible.

Refer to the current version of the Pharmacy Manual for additional details.

7.3. Study Drug Packaging and Labeling

Vials are intended for clinical use only and the label includes the study name or code, name of the IMP, lot number, and strength. Additional information regarding study drug packaging and labeling is presented in the current version of the Pharmacy Manual. Study drug storage, preparation, administration, accountability and handling and disposal should be performed as outlined in the current version of the Pharmacy Manual.

7.4. Accountability for Study Drug(s)

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

Each investigational site must keep accountability records that capture:

- The date received, quantity, and condition of study drug vials.
- The date, subject’s number, and the quantity of study drug vials dispensed.
- The date, quantity of used and unused study drug vials destroyed on site or returned, along with the initials of the person recording the information.

7.4.1. Study Drug Return or Disposal

Gilead recommends that used and unused study drugs, which includes vials, be destroyed at the site. If the site has an appropriate standard operating procedure for drug destruction as determined by Gilead, the site may destroy used (empty or partially empty) and unused study drug vials in accordance with that site's approved procedural documents. A copy of the site's approved procedural document will be obtained for the electronic trial master file. If the study drug is destroyed at the site, the investigator must maintain accurate records for all study drugs destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drugs. Study drug accountability records must be filed at the site and copies will be provided to Gilead.

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

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

8. ASSESSMENT OF EFFICACY

8.1. Efficacy Parameters

The computed tomography (CT) or magnetic resonance imaging (MRI) scans with contrast of chest/abdomen/pelvis and any other involved disease sites are to be obtained in all subjects at screening and every 6 weeks for first 12 months from C1D1 and then every 9 weeks until the occurrence of PD and discontinuation of treatment. Scans may be performed within ±5 days of the scheduled visits. Target and non-target lesions must be determined by the clinical site at baseline. The same imaging technique should be used throughout the study for tumor assessment unless there is a clear clinical contraindication.

Subjects who discontinue treatment due to clinical progression in the absence of PD should have a scan documenting progression if clinically feasible or until initiation of alternate therapy. Subjects who discontinue treatment due to toxicity will continue to obtain radiologic response assessments on the protocol-required schedule until PD or initiation of new therapy. Response should be confirmed with a scan approximately 4 to 6 weeks later. Additional CT or MRI scans may be performed at the discretion of the physician to assess disease status as medically indicated.

Tumor response and PD will be determined using RECIST v1.1. Palliative radiotherapy is permitted, but presence of new or worsening metastases will be considered PD. Palliative radiation of a target lesion will render that target lesion and subsequent tumor assessments "Not Evaluable" and should be avoided, if feasible.

If the radiologic assessment does not confirm PD, subjects should continue to be assessed by RECIST v1.1 per the protocol Schedule of Assessments (Table 1). The results of all imaging including those not specified as protocol assessments will be recorded on the eCRF.

Tumor response will be assessed by investigators and BICR according to RECIST v1.1. To maintain independence, the BICR will not be informed of the investigator reports of PD. One intervening non-evaluable assessment is allowed between an initial and confirmatory tumor response of PR or CR.

Subjects who continue treatment after the final OS analysis and following implementation of PA6 will be expected to have scans performed per standard of care, as indicated by local practice. Tumor response data will no longer be collected for this study; however, disease status should still be monitored by the treating physician to determine if progression has occurred, and whether the subject is continuing to derive clinical benefit.

9. OTHER EVALUATIONS

9.1. Pharmacokinetics Evaluations

Serum samples for PK analyses will be collected from subjects receiving sacituzumab govitecan only as instructed below:

- Samples will be obtained for the first 5 cycles of treatment only
  - Cycle 1 and Cycle 5 sampling time points:
    - C1D1 and C5D1: Pre-dose, 30 min, and 60 min post end of infusion
    - C1D8 and C5D8: Pre-dose only
  - Cycle 2–Cycle 4 sampling time points:
    - C2D1 Pre-dose
    - C3D1 Pre-dose
    - C4D1 Pre-dose

The collection window for PK sample is -30 minutes for pre-dose and +10 minutes for post dose samples at the end of infusion.

9.2. Immunogenicity Evaluations

Serum samples for immunogenicity (ADA) analysis will be collected from all subjects receiving sacituzumab govitecan only at pre-dose (-30 minutes) on Day 1 of Cycles 1, 3, 5, 7, 9, 11, and every 3 cycles thereafter (eg, Cycle 14, 17, etc.), and at the EOT visit. Serum samples will be evaluated by the Sponsor's designee using a validated assay. ADA results will be summarized.

ADA samples for subjects continuing sacituzumab govitecan treatment after the final OS analysis and following implementation of PA6 will not be collected.

9.3. *UGT1A1* Genotype

UGT1A1 genotype will be evaluated from a blood sample collected as specified in the Schedule of Assessments (Table 1). The *UGT1A1* genotype will be determined at baseline; this testing is not required for eligibility.

9.4. QOL Assessment

QOL assessments with EORTC QLQ-C30 and EuroQOL EQ-5D-5L questionnaires will be obtained at baseline, prior to dosing on D1 of every cycle starting from C2D1, and at the EOT visit. The EQ-5D-5L will also be assessed at initial determination of PD. The questionnaires may be administered together and in sequence order, at the beginning of the visit prior to the other study procedures, with the EORTC QLQ-C30 presented first, followed by the EQ-5D-5L.

The 30-item EORTC QLQ-C30 from the EORTC Quality of Life Group is used to assess 15 scales:

- Global health status/Quality of Life;
- Five functional scales: physical, role, cognitive, emotional, and social; and
- Nine symptom/item scales: fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties.

The health status questionnaire EQ-5D-5L, developed by the EuroQol Group, consists of 2 parts:

- The descriptive system with which patients rate the severity of their experience in 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) along 5 levels of severity; and
- The EQ-5D visual analogue scale (EQ-VAS) for patients to self-rate their health state.

Subjects continuing treatment after the final OS analysis and following implementation of PA6 will not be required to complete any quality-of-life questionnaires.

9.5. Biomarker Testing

9.5.1. Biomarker Samples to Address the Study Objectives

9.5.1.1. Trop-2 Analysis

For Trop-2 expression evaluation, archival tissue is requested as specified in Table 1.

If a biopsy is obtained as part of SOC, a sample of this may be submitted if archival tissue is not available. Fine needle aspiration and bone biopsies are not acceptable.

This testing is optional and not required for eligibility.

9.5.2. Additional Optional Biomarkers

Biological specimens will be collected from all subjects who provide consent to participate in this study and consent to the optional biomarker collection and may be used to evaluate the association of systemic (blood) and/or tissue-based biomarkers with study drug response (including efficacy and/or AEs) and dose. Biomarker samples may also be used to better understand the mechanism of action of sacituzumab govitecan, disease biology, and relevant biological pathways in metastatic solid tumor diseases.

Because biomarker science is a rapidly evolving area of investigation, and AEs in particular are difficult to predict, it may not be possible to specify prospectively all tests that may be done on the specimens provided. The specific analyses may include but are not limited to the biomarkers and assays listed below and may include genetic testing. The testing outlined below is based upon the current state of scientific knowledge. It may be modified during or after the end of study to remove tests no longer indicated and/or to add new tests based upon new state-of-the-art knowledge. Samples to measure biomarkers may include but will not be limited to the following:

- Archival tissue; if a biopsy is obtained as part of SOC, a sample of this may be submitted if archival tissue is not available.
- Blood samples for biomarker analysis will be collected from all subjects who provided consent to the optional biomarker collection.
- Optional blood collection for germline sequencing. These samples should be collected at the baseline/C1D1 visit. If the optional sample is not collected at C1D1, it can be collected at any other visit. These samples may be used as a control sample for the molecular profiling of the tumor tissues as described above.

Tissue samples may be used for molecular profiling of the tumor tissue, using mutation panels and/or whole exome sequencing and RNA sequencing and/or protein analyses to identify potential markers that correlate with response to study treatment. Tumor tissue samples may include normal cells.

Blood samples collected for biomarker analysis may be used to monitor disease progression and responses to study treatment.

Samples collected for biomarker assessments will be destroyed no later than 15 years after the end of study or per country requirements.

9.5.3. Biomarker Samples for Optional Genomic Research

In addition to the study-specific ICF to be signed by each subject participating in the study, subjects will be required to document agreement to provide additional samples for optional genomic research. Additional samples will be obtained from subjects who agree to participate and provide their additional specific consent. These samples should be collected at the baseline/C1D1 visit but may be collected at any time during the study or at a separate post study visit, if necessary.

The specimens collected for optional genomic research may be used to advance the development of the drug and/or increase knowledge and understanding of the biology of the disease under investigation or related diseases. These specimens may also be used to study the association of biomarkers with biological pathways, disease pathogenesis, progression, and/or treatment outcomes, including efficacy, AEs, and the processes of drug absorption and disposition. In addition, these specimens may be used to develop biomarker and/or diagnostic assays and establish the performance characteristics of these assays. The collection and analysis of optional genomic research specimens may facilitate the design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for subjects in the future.

The samples collected for optional genomic research will be destroyed no later than 15 years after the end of study or per country requirements.

9.5.4. Biomarker Samples for Optional Future Research

In addition to the study-specific ICF to be signed by each subject participating in the study, subjects will be required to document agreement to provide additional samples or to allow the use of the remainder of their already-collected tissue, biomarker, PK, immunogenicity, and *UGT1A1* specimens for optional future research, including genomics, in accordance with applicable regulations.

The specimens collected for optional future research may be used to advance development of the drug and/or increase knowledge and understanding of the biology of the disease under investigation and related diseases. These specimens may also be used to study the association of biomarkers with biological pathways, disease pathogenesis, progression, and/or treatment outcomes, including efficacy, AEs, and the processes of drug absorption and disposition. In addition, these specimens may be used to develop biomarker and/or diagnostic assays and establish the performance characteristics of these assays. The collection and analysis of optional future research specimens may facilitate the design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future. See Appendix 18.10 for China-specific requirements.

10. ASSESSMENT OF SAFETY

10.1. Safety Parameters

10.1.1. Demographic/Medical History

Basic demographic and baseline characteristics will be collected as indicated in Table 1. In addition to the evaluation of a subject's medical history in terms of study eligibility, all relevant medical conditions will be documented on the appropriate eCRF. Events that occur after signing of informed consent but prior to initiation of study drug(s), unless due to a protocol-mandated procedure, should be recorded on the Medical History eCRF.

The subject's entire oncology history will be collected on the appropriate eCRF including cancer histology, stage, and date of diagnosis, prior surgeries/ treatments received for cancer, dates of treatment administration, intent of administered regimen (neo-adjuvant, adjuvant, or metastatic), best response achieved, and date of progression.

10.1.2. Vital Signs

Vital signs will include blood pressure, pulse, respiratory rate and body temperature and will be taken as indicated in Table 1 after the subject has been resting for at least 5 minutes during screening. If the subject experiences an infusion-related reaction, then all vital signs will be recorded on the eCRF.

10.1.3. Body Weight and Height

Body weight and height will be measured as indicated in Table 1.

10.1.4. Physical Examination

A full physical examination and total body examination of all major body systems (eg, general appearance, skin, neck [including thyroid], ears, eyes, nose, throat, lungs, heart, abdomen, back, lymph nodes, and extremities and a clinical neurological examination), and body weight must be performed. More focused physical examination (at minimum cardiac, lung and abdominal examination) must be performed during study visits; however, abnormal findings of any body system must be reported.

Physical exam data for subjects continuing sacituzumab govitecan treatment after the final OS analysis and following implementation of PA6 will not be collected; however, physical exams should be performed per institutional practice. Any abnormal findings identified should be recorded as an AE, unless already documented as part of medical history or if the abnormal finding is a manifestation of the disease under study.

10.1.5. Electrocardiogram

For all subjects, local 12-lead electrocardiograms (ECGs) will be taken as indicated in Table 1. For subjects receiving vinflunine, ECGs will also be obtained prior to infusion on C2D1 and C3D1. Per the summary of product characteristics for certain TPC agents, additional cardiac monitoring, including echocardiography, may be required. Abnormal findings should be evaluated as clinically indicated, including repeated ECGs. ECGs may be done at other timepoints during the study if clinically indicated. ECGs are to be performed at rest in the supine position. Clinically significant abnormal findings should be noted and the appropriate clinical work-up should be initiated until the condition has stabilized.

The following will be measured or calculated: heart rate, PR interval, QRS, QT, QTcF or QTcB, and rhythm.

10.1.6. ECOG Performance Status

The ECOG PS will be assessed as indicated in Table 1.

The ECOG PS will not be collected for subjects continuing sacituzumab govitecan treatment after the final OS analysis and following implementation of PA6.

10.1.7. Laboratory Assessments

All clinical laboratory samples for safety will be collected and analyzed by the site's local laboratory with appropriate clinical action taken based on the investigator's clinical judgment. All investigations will be assessed for all subjects as indicated in Table 1. Additional and more frequent tests may be performed at the investigator's discretion. The specific details of each assessment will be recorded on the appropriate eCRF. Clinically significant abnormal results should be repeated within 48 hours to confirm abnormality or more frequently as per Principal Investigator (PI) discretion and followed until resolution. The panels of laboratory tests to be performed are shown below:

10.1.7.1. Hematology

Hemoglobin, white blood cell (WBC) count with differential (including ANC), and platelet count to be performed as indicated in Table 1.

10.1.7.2. Coagulation

Prothrombin time (PT) or international normalized ratio (INR) and partial thromboplastin time (PTT) will be obtained as indicated in Table 1.

10.1.7.3. Blood Chemistry

Total protein, albumin, total bilirubin, alkaline phosphatase, ALT, AST, creatinine (estimated glomerular filtration rate using a validated model; Appendix 18.4), blood urea nitrogen or urea, glucose, sodium, potassium, magnesium, chloride, calcium, phosphorus, bicarbonate (an optional assessment) will be obtained as indicated in Table 1.

For subjects continuing sacituzumab govitecan treatment after the final OS analysis and following implementation of PA6, total bilirubin, creatinine, ALT, AST, sodium, potassium, magnesium, and phosphorous will be collected and reported. Clinically significant abnormal results of any other analytes performed as institutional practice should be recorded and reported as an AE.

10.1.7.4. Lactate Dehydrogenase and Uric Acid

Lactate dehydrogenase (LDH) and uric acid will only be required at Screening and if clinically indicated.

10.1.7.5. Urinalysis

Urinalysis will be performed locally on a freshly voided clean sample by dipstick for protein, glucose, blood, pH, and ketones. If dipstick findings are abnormal based on the investigator's judgment, then a microscopic evaluation will be performed to assess the abnormal findings. Urinalysis will be performed at Screening only and as clinically indicated with details regarding protein, casts, WBC, red blood cell count, specific gravity, and presence of bacteria to be recorded. Only abnormal results will be captured on the eCRF.

10.1.7.6. Pregnancy Test

In female subjects of childbearing potential, pregnancy testing will be performed according to the Schedule of Assessments (Table 1) and as presented in Appendix 18.7.

10.1.7.7. Follicle-Stimulating Hormone (FSH)

FSH testing will be conducted as needed per Appendix 18.7 for determination of childbearing potential.

10.2. Adverse Event Reporting

All subjects must be carefully monitored for AEs as defined below. Sufficient information must be obtained by the investigator to determine whether the event meets criteria for immediate reporting to the Sponsor (ie, SAEs and pregnancies). All AEs should be assessed in terms of their seriousness, severity, and relationship to the study drug, per the definitions in the following sections.

10.2.1. Safety Reporting Definitions

10.2.1.1. Adverse Events

An AE is defined as any untoward medical occurrence in a subject administered a medicinal product that does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not related to the IMP.

An AE may include worsening or exacerbation of the disease under study; worsening or exacerbation of pre-existing conditions or events; intercurrent illnesses; or drug interactions. Anticipated fluctuations of pre-existing conditions that do not represent a clinically significant exacerbation or worsening are not considered AEs.

The AEs should be recorded using medical terminology and whenever possible, a diagnosis should be provided for clearly associated signs, symptoms, and/or abnormal laboratory results. If the final diagnosis is not known at the time of initial detection, the provisional diagnosis or signs or symptoms should be recorded and updated when the final diagnosis is available.

Surgical procedures are not AEs; they are therapeutic measures for conditions that require surgery. The condition, provided it develops or is a worsening of a pre-existing condition for which the surgery is required, is the AE.

10.2.1.2. Serious Adverse Events

The SAE is any untoward medical occurrence that at any dose:

- Is fatal (results in death)
- Is life-threatening: The subject was at immediate risk of death from the AE as it occurred. This does not include an event that, had it occurred in a more severe form, or allowed to continue, might have caused death.
- Requires inpatient hospitalization or prolongation of existing hospitalization (in the absence of a precipitating, clinical AE that is not in itself an SAE).
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug).
- An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatments in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

The SAE does not include:

- PD (See Section 10.2.2.6.)
- Hospitalization for a routine clinical procedure as stipulated by the protocol
- Pre-planned treatments or surgical procedures requiring hospitalization (The conditions should be documented as appropriate in the eCRF.)
- Hospitalization for non-medical reasons (ie, social admissions, hospitalizations for social, convenience or respite care)

10.2.1.3. Special Situation Reports

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

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

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

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

- An overdose is defined as an accidental or intentional administration of a quantity of a study drug given per administration or cumulatively, which is above the maximum recommended dose as per protocol or in the product 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).

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

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

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

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

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

10.2.2. Adverse Event and Special Situation Reporting

10.2.2.1. Reporting Period for Adverse Events and Special Situation Reports

The safety reporting period is the period during which all AEs must be recorded in the eCRF, and SAEs must be reported to the Sponsor or its designee according to the instructions in this section and Section 10.2.5. The safety reporting period begins when the subject signs the informed consent and continues until 30 days after the last dose of study drug or initiation of alternate therapy. Following initiation of study drug, collect all AEs, regardless of cause or relationship, until 30 days after last administration of study drug and report the AEs on the eCRFs as instructed. All SAEs, regardless of cause or relationship, that occur after the subject consents to participate in the study (ie, signing the ICF) and throughout the duration of the study, including the posttreatment follow-up visit, must be reported on the applicable eCRFs and to Gilead Global Patient Safety as instructed in Section 10.2.5. This also includes any SAEs resulting from protocol-associated procedures performed after the ICF is signed. All study drug SSRs that occur from study drug initiation and throughout the duration of the study, including the posttreatment follow-up visit, must be reported to the Sponsor.

10.2.2.2. Adverse Event Collection and Documentation

Identification and Recording of Adverse Events

It is the responsibility of the investigator to document all AEs that occur during the study. All AEs, regardless of seriousness, severity, or relationship to the study drug that occur during the safety reporting period, must be recorded in the AE page of the CRF. AEs should be elicited by asking the subject a non-leading question (eg, “have you experienced any new or changed symptoms since we last asked/since your last visit?”). AEs can also represent abnormal findings from physical examinations, laboratory tests and other study procedures such as ECGs. The investigator must review all laboratory and test data; abnormal findings should be assessed to determine if they meet the criteria for AEs (Section 10.2.1.1, Section 10.2.2.5).

For all AEs, the investigator must pursue and obtain information adequate to assess whether it meets the criteria for classification as an SAE and, therefore, requires immediate notification to the Sponsor or its designee (Section 10.2.5). In addition, sufficient information must be obtained by the investigator to perform a causality assessment, which must be done for every AE.

Follow-up by the investigator is required until the event or its sequelae resolve or stabilize, as assessed by the investigator. The outcome of each AE must be provided.

AEs should be recorded using medical terminology and whenever possible, a diagnosis should be provided for clearly associated signs, symptoms, and/or abnormal laboratory results.

To assist in the Sponsor’s assessment of each case, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

Adverse events and SAEs resulting from SSRs must be reported in accordance to the AE and SAE reporting guidance summarized in Sections 10.2.2.2 and 10.2.5.

Serious Adverse Events Reporting Process

SAEs are to be recorded on the SAE Form and forwarded to the Sponsor or the Sponsor's designee in accordance with the timelines summarized in Section 10.2.5. The investigator should include a detailed description of the event(s), including the clinical course, criteria for seriousness, treatments administered, action taken with respect to study drug, rationale for the investigator's assessment, including causality, and other relevant information, such as possible alternative etiologies.

Information captured on both the SAE Form and entered into the eCRF should be consistent.

Special Situation Reporting Process

All SSRs will be recorded on the Special Situation Report form and forwarded to the Sponsor or Sponsor's designee in accordance with the timelines summarized in Section 10.2.5.

10.2.2.3. Assessment of Adverse Event Severity

The severity of AEs will be graded using the latest version of the NCI-CTCAE v 5.0. For each SAE, the highest severity grade should be reported. If a CTCAE criterion does not exist, the investigator should assess the severity according to the criteria in Table 9.

Table 9. Grading for Adverse Events Not Listed in NCI-CTCAE

CTCAE Grade	Severity	Definition
Grade 1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[1]
Grade 3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL[2, 3]
Grade 4	Life-threatening	Life-threatening consequences; urgent intervention indicated[3]
Grade 5	Death	Results in death

Abbreviations: ADL = Activities of daily living; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events; SAE = serious adverse event

1 Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
2 Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
3 These events should be assessed to determine if they meet the definition of SAEs.

10.2.2.4. Assessment of Adverse Event Causality

The investigator's causality assessment is required for all AEs including both non-serious and serious AEs. The causality assessment is the determination of whether there exists a reasonable possibility that the study drug caused or contributed to an AE. In order to determine causality, the investigator should consider the temporal relationship of the onset of the event to the start of study drug; the course of the event and, in particular, whether the event resolves or improves with dose reduction or study drug discontinuation; the known toxicities of the study drug; events expected to occur in subjects with the disease under study; and concomitant medications and comorbidities which may have a known association with the event. Causality is to be assessed as follows:

- Related: Plausible time relationship to study drug administration; plausible time relationship of improvement or resolution with study drug dose reduction or discontinuation; event cannot be explained by the underlying disease, comorbidities, or concomitant medications
- Possibly related: a reasonable time sequence to administration of study drug, but which could also be explained the underlying disease, comorbidities, or concomitant medications
- Unlikely related: a temporal relationship to drug administration which makes a causal relationship improbable and the underlying disease, comorbidities, or concomitant medications provide a plausible explanation
- Not related: a causal relationship to the study drug can be easily ruled out

10.2.2.5. Adverse Events Based on Abnormal Test Findings

An abnormal test finding that meets any one of the criteria below should be considered an AE:

- Test result is associated with accompanying symptoms.
- Test result requires additional diagnostic testing or medical/surgical intervention.
- Test result leads to a change in study drug dosing (eg, dose modification, interruption, or permanent discontinuation) or concomitant drug treatment (eg, addition, interruption, or discontinuation) or any other change in a concomitant medication or therapy.
- Test result leads to any of the outcomes included in the definition of an SAE. (Note: This would be reported as an SAE, Section 10.2.5).
- Test result is considered an AE by the investigator.

Laboratory results that fall outside the reference range and do not meet one of the criteria above should not be reported as AEs. Repeating an abnormal test, in the absence of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

Any abnormal test finding that meets the criteria for an SAE (Section 10.2.1.2) should be reported as such.

10.2.2.6. Disease Progression

In this protocol, PD is an efficacy endpoint and should not be reported as an AE. It is important to differentiate expected PD from an AE. Events that are clearly consistent with the expected pattern of PD should not be considered AEs. Expected PD refers to an event that is unequivocally related to PD, and that the clinical course is consistent with what would be expected for the subject's disease. A clinical event in the setting of PD would be considered an AE if it could not unequivocally be attributed to or consistent with expected PD.

Hospitalization due to signs and symptoms of PD (as defined above) should not be reported as an SAE.

In most cases, PD will be based on RECIST v1.1 criteria. If PD is based on the subject's symptoms, every effort should be made to document progression using objective criteria.

10.2.3. Reporting Deaths

Death is an outcome of an SAE and not, in itself, an SAE. When death is an outcome, the event(s) resulting in death should be reported (eg, "pulmonary embolism" with a fatal outcome). The appropriate diagnosis (ie, cause of death) should be recorded and assigned severity Grade 5. The time period for reporting AEs (including fatal AEs) continues up to 30 days after the last dose of study drug. Deaths which occur more than 30 days after the last dose of study drug are to be reported if they are assessed by the investigator as related to study drug. Fatal AEs meeting these criteria are SAEs and should be reported to the Sponsor or the Sponsor's designee in accordance with the timelines specified in Section 10.2.5.

Deaths related to PD of the underlying disease during the study will not be reported as an SAE (see Section 10.2.2.6) if, in the investigator's judgment, the event is unequivocally due to the expected course of progression of the underlying disease, and not due to another cause.

10.2.4. Reporting Exposure During Pregnancy

The investigator should report pregnancies in female study subjects who are identified after initiation of study drug and throughout the study, including the protocol-required post-treatment follow-up period or 6 months after the last dose of study drug, whichever is longer, to Gilead Global Patient Safety using the pregnancy report form within 24 hours of becoming aware of the pregnancy using the pregnancy report form.

The investigator should report pregnancies in female partners of male subjects who are identified after initiation of study drug and throughout the study, including the protocol-required post-treatment follow-up period or 3 months after the last dose of study drug, whichever is longer, to Gilead Global Patient Safety within 24 hours of becoming aware of the pregnancy using the pregnancy report form.

Contact details for transmitting the pregnancy report form are as follows:

Gilead Global Patient Safety
Email: Safety_FC@gilead.com
or
Fax: 1-650-522-5477

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

All other premature terminations of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE, as described in Section 10.2.2. 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 10.2.2. Furthermore, any SAE occurring as an adverse pregnancy outcome after the study must be reported to the Gilead Global Patient Safety.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome of the pregnancy/partner pregnancy should be reported to Gilead Global Patient Safety using the pregnancy report form. If the end of the pregnancy/partner pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead Global Patient Safety. Gilead Global Patient Safety contact information is as follows: email: Safety_FC@gilead.com and fax: +1 (650) 522-5477.

Refer to Appendix 18.7 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

10.2.5. Investigator Immediate Reporting Requirements

All SAEs, SSRs, and pregnancies must be reported to the Sponsor or the Sponsor's designee immediately, and no later than 24 hours of becoming aware of the event.

The initial SAE report should be as complete as possible (Section 10.2.2.2); however, reporting should not be delayed in order to obtain more information. All follow-up information should be reported within 24 hours of the investigator's awareness of the information. The investigator is required to provide follow-up information in response to queries from the Sponsor or the Sponsor's designee. Hospital discharge summaries should be provided for subjects who are hospitalized and autopsy findings, if available, should be provided for subjects who die.

All SAEs, SSRs, and pregnancies should be reported to the following:

- Email: Refer to SAE/Special Situation Report/pregnancy report forms for email instructions.
- Fax: Refer to the SAE Form Completion Guidelines for the Patient Safety fax number.

10.2.6. Investigator Notification to Local Institutional Review Boards

The investigator must notify their local Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) about certain AEs including suspected unexpected serious adverse reactions (SUSARs) in accordance with their IRBs'/IECs' policies and procedures and Good Clinical Practice (GCP)/International Conference on Harmonization (ICH) guidelines.

10.2.7. Sponsor Responsibilities

The Sponsor or its designee will be responsible for reporting all AEs, SAEs and SUSARs to the appropriate regulatory authorities, investigators, and Central IRBs/IECs in accordance with all applicable regulations and guidance documents.

11. STATISTICS

11.1. Sample Size Determination

A sample size of approximately 696 subjects permits the study to have at least 90% power to demonstrate a hazard ratio of 0.755 equating to a 2.7-month improvement in OS from 8.3 to 11.0 months at a 2-sided alpha of 5%. Final OS analysis will occur after 536 OS events have accrued, which is projected to occur 19 months after enrollment period of 23 months, with yearly discontinuation rate of 10%.

There will be an interim analysis of OS after at least 65% of targeted OS events (at least 348 events) are accrued. A Lan-DeMets spending function that approximates O'Brien/Fleming stopping boundaries will be applied to the interim OS analysis. Refer to the statistical analysis plan (SAP) for additional details regarding the interim analysis.

11.2. Statistical Analyses

Corresponding to the primary and secondary objectives, the primary and secondary analyses, including definitions of primary and secondary endpoints, populations for analysis, and statistical methods are described in this section. Additional details of the statistical methods will be provided in the SAP, including any updates from the original statistical analyses planned. Summary statistics for continuous variables will include n, mean, standard deviation, median and range. Categorical variables will be presented as frequency counts and percentages. Data listings will be created to support tables and figures.

The primary analysis population consists of all randomized subjects who will be included in an intent-to-treat analysis. Kaplan-Meier (KM) curves will be constructed for time-to-event endpoints, and the estimate and 95% CI of the median survival time of the time-to-event endpoints will be estimated. A stratified log-rank test stratified by randomization strata will be used to compare the treatment groups for the time-to-event endpoints of the primary endpoint of OS and secondary endpoint of PFS. Estimates and 95% CIs of hazard ratios of OS and PFS will be based on stratified Cox proportional hazard regression model.

Multiplicity adjustment: To ensure the overall Type I error rate is strictly controlled at a 2-sided alpha of 0.05, a hierarchical testing strategy will be performed based on the primary endpoint of OS and key secondary endpoints of PFS based on BICR and physical functioning score of EORTC QLQ-C30. If the planned primary OS analysis is significant, then the secondary endpoints of PFS based on BICR then the EORTC QLQ-C30 physical functioning score will be tested sequentially at the same alpha level as OS.

All subjects administered at least one dose of sacituzumab govitecan or TPC will be included in the evaluation of safety and tolerability. Safety and tolerability will be evaluated from AEs, standard safety laboratories, physical examination, ECG, and vital signs.

11.2.1. Endpoints

Overall Survival:

OS is defined as the time from the date of randomization to the date of death, regardless of cause. If a subject is not known to have died, OS will be censored at the date the subject is last known to be alive.

Objective Response Rate:

ORR is defined as the proportion of subjects who achieved a complete response (CR) or PR as best overall response (BOR). Best overall response is determined by investigator assessment and BICR, based on tumor assessments recorded between the first dose of study drug and the date of first objectively documented PD per RECIST v1.1, or the date of subsequent anti-cancer treatment, whichever occurs first. For subjects without documented PD or subsequent anti-cancer treatment, all available response designations will contribute to the BOR assessment.

Progression-free Survival:

PFS is defined as the time from the date of randomization to the date of the first objectively documented PD, per RECIST v1.1, as determined by investigator assessment and BICR, or death regardless of cause, whichever occurs first. Subjects who do not progress or die will be censored on the date of their last radiographic tumor assessment. Subjects who do not have any post-treatment radiographic tumor assessment and do not die will be censored on the date they were randomized to treatment. Subjects who start any subsequent anti-cancer treatment without PD will be censored at the last radiographic tumor assessment prior to the initiation of the subsequent anti-cancer treatment. Subjects who progress or die after more than one missed scheduled tumor assessment will be censored at the last date of radiographic assessment prior to the missed tumor assessment.

Duration of Objective Tumor Response:

DOR will be assessed for subjects who have a confirmed BOR of CR or PR. DOR is defined as the time from the date when the criteria are first met for a CR or PR to the first date that PD is documented as determined by investigator assessment and BICR per RECIST v1.1, or date of death, whichever occurs first. Subjects who neither progress nor die will be censored on the date of their last radiographic tumor assessment.

Clinical Benefit Rate:

CBR is defined as the percentage of subjects with advanced or metastatic cancer who have achieved CR, PR and stable disease (SD) for ≥6 months to therapeutic intervention in a clinical study. CBR will be determined by investigator assessment and BICR per RECIST v1.1.

Quality of Life:

The QOL endpoints included as secondary objectives will compare mean change from baseline of the physical functioning, global health status, pain, and fatigue scales of the EORTC QLQ-C30. Exploratory objectives will compare mean change from baseline for the remaining scales of the EORTC QLQ-C30. Additional exploratory QOL endpoints include time to improvement, time to worsening, proportion improved, and proportion worsened for each scale of the EORTC QLQ-C30.

11.2.2. Efficacy Analyses

The survival curves of OS will be compared between sacituzumab govitecan and the TPC via a two-sided, stratified log-rank test using stratification factors employed in the randomization. The hazard ratio and corresponding two-sided 95% CI will be estimated in a stratified Cox proportional-hazards model. The OS curves for each treatment arm will be estimated using the KM product-limit method. Median OS and corresponding 95% CIs will be computed by the Brookmeyer and Crowley method with log-log transformation.

PFS will be compared between sacituzumab govitecan and the TPC via a two-sided, stratified log-rank test using stratification factors employed in the randomization. The hazard ratio and corresponding two-sided 95% CI will be estimated in a stratified Cox proportional-hazards model. The PFS curves for each treatment arm will be estimated using the KM product-limit method. Median PFS and corresponding 95% CIs will be computed by the Brookmeyer and Crowley method with log-log transformation.

Milestone survival rates (PFS rates) will be estimated using KM estimates on the survival curve. The associated two-sided 95% CIs will be calculated based on the Greenwood formula and log-log transformation.

DOR will be summarized for subjects who achieve confirmed PR or CR using the KM product-limit method. Median DOR, along with two-sided 95% CIs will also be calculated using the Brookmeyer and Crowley method. In addition, the percentage of responders still in response at different time points (for example, 6 and 12 months) will be presented based on the KM estimates.

ORR will be analyzed and compared between sacituzumab govitecan and TPC using the Cochran Mantel-Haenszel test stratified by the stratification factors used in the randomization. The 2-sided 95% CIs of ORR will be calculated using the Clopper-Pearson exact method.

Mixed model repeated measures analysis will compare mean change from baseline of global health status, pain, and fatigue scales of the EORTC QLQ-C30.

11.2.3. Safety Analyses

Safety analyses will be based on All Treated Subjects. All safety analyses will be summarized by treatment arm. TEAEs and SAEs, laboratory test results, and vital signs will be summarized. Safety data will be summarized using descriptive statistics.

11.2.4. Subgroup Analyses

To evaluate whether the treatment effect is consistent under stratification factors used in randomization, the estimate of the between-group treatment effect with a 95% CI for the primary and secondary efficacy endpoints will be estimated and plotted graphically.

11.2.5. Exploratory Analyses

Trop-2 results will be summarized by descriptive statistics according to tumor immunohistochemistry score. Correlation between efficacy and Trop-2 tumor expression level will be explored based on efficacy variables such as ORR and OS, if deemed appropriate.

Descriptive statistics will be used to summarize PK parameters based on a non-compartmental model on subjects with adequate serum concentration data. Data from this study may be combined with data from other studies with sacituzumab govitecan for population PK and exposure-response analyses. If applicable, results from such analyses may be summarized in a separate report, rather than in a clinical study report. Population PK and exposure-response analyses of data from this study may not be conducted.

ADA results will be summarized, and the impact of immunogenicity, if detected, will be evaluated in relation to PK and clinical responses, safety/tolerability, and efficacy.

Other exploratory analyses of tumor and blood markers may be conducted with details and results included in a separate biomarker-specific report.

A separate prespecified QOL analysis following FDA and European Medicines Agency Patient-Reported Outcome Guidelines will be performed.

12. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

12.1. Study Monitoring

Monitoring procedures developed by the Sponsor or its designee will be followed, in order to comply with ICH GCP, FDA and applicable guidelines. On-site review of subject's eCRFs, electronic medical/health records or paper source documentation for completeness, and accuracy will be required as well as a review of all applicable regulatory documents will be performed. All available source documents should be obtained by the investigator and provided to the Sponsor's designee for review at each monitoring visit. Monitoring visits to the study site will be conducted periodically during the study to ensure that GCP and all aspects of the protocol are followed.

Queries may be issued in the eCRF system to be addressed by the appropriate study site personnel within a timely manner when clarification of eCRF data are required to ensure data accuracy and completeness. The Sponsor's designee will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent communications.

Regulatory authorities, the IRBs/IECs, and/or the Sponsor's Clinical Quality Assurance group or designee may request access to all source documents, subjects' eCRFs, and other study documentation for on-site audit or inspection. Access to these documents must be guaranteed by the investigator, who must cooperate and provide support at all times for these activities.

12.2. Audits and Inspections

Representatives of regulatory authorities or the Sponsor 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 Sponsor's study monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or the Sponsor access to records, facilities, and personnel for the effective conduct of any inspection or audit.

12.3. Institutional Review Board/Independent Ethics Committee

The PI must obtain IRB/IEC approval for the investigation. Initial IRB/IEC approval, and all materials approved by the IRB/IEC for this study including the subject consent form and recruitment materials must be maintained by the investigator and made available for inspection.

13. QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor has ethical, legal and scientific obligations to follow this study carefully in a detailed and orderly manner in accordance with established research principles and applicable regulations.

The study site may be subject to review by the IRB/IEC, to quality assurance audits performed by the Sponsor's designee and/or to inspection by appropriate regulatory authorities. investigator(s) and their relevant personnel must agree to be available and participate with audit visits conducted at a reasonable time in a reasonable manner, investigator/Institution must guarantee direct access to source documents by the Sponsor and its designee, and appropriate regulatory authorities.

Global regulatory authorities may also audit the investigator during or after the study. The investigator should contact the Sponsor's designated contact immediately if this occurs and must fully cooperate with regulatory authority audits conducted at a reasonable time in a reasonable manner.

14. ETHICS

14.1. Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The investigator must submit written approval to the Sponsor before he or she can enroll any subject into the study.

The PI is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The PI is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the study drug. The Sponsor or its designee will provide this information to the PI.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

14.2. Ethical Conduct of the Study

This study is planned to be conducted in the North America, Europe, and potentially elsewhere. The study will be performed in accordance with ICH GCP guidelines, the Declaration of Helsinki, 18th World Medical Assembly, Helsinki, Finland, 1964 and later revisions (as mandated for European studies), and applicable local regulatory requirements and laws. In the US, ethical protection is provided by compliance with GCPs as described in ICH and 21 Code of Federal Regulation (CFR) 50 (Protection of Human Subjects).

The IRB and the IEC will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the subjects. The study will only be conducted at sites where IRB/IEC approval has been obtained.

The investigator is responsible for providing their IRB/IEC with any required study documents, progress reports and safety updates and is responsible for notifying the IRB/IEC promptly of all SAEs occurring at the site.

All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to the Sponsor or the designee.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/IEC and the Sponsor or its designee in writing within 5 working days after the implementation.

14.3. Written Informed Consent

It is the responsibility of the investigator to give each subject (or the subject's legally authorized representative) full and adequate verbal and written information regarding the objective and procedures of the study including the possible risks and benefits involved. Written subject information, approved by the IRB/IEC, must be given to each subject before any study-related procedure is undertaken. During the consent process, the subject must be informed about their right to withdraw from the study at any time. The subject must also be given ample time to read the written ICF and have all study-related questions answered to the satisfaction of the subject (or the subject's legally acceptable representative). It is the responsibility of the investigator to obtain a signature from each subject, the subject's legally acceptable representative (if applicable), and from the persons conducting the informed consent discussion prior to undertaking any study-related procedure. The subject (or the subject's legally acceptable representative) must be given a copy of the signed and dated ICF.

The investigator is also responsible for providing the subject (or the subject's legally acceptable representative) with any clinical study updates that may affect the subject's willingness to continue participation in the study. The informed consent process must be documented in the subject's medical or source chart. The written subject information must not be changed without prior approval by the Sponsor or its designee and the IRB/IEC.

Per ICH E6 4.3.3, it is recommended that the investigator notify the subject's primary care physician of the subject's participation in the study if the subject agrees to the investigator informing the primary care physician.

14.4. Good Clinical Practice

The study will be conducted in accordance with the ICH E6 GCP and the appropriate local and national regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the study drugs as described in the protocol and Investigator's Brochure.

Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files for this study should be established at the beginning of the study, maintained for the duration of the study, and retained according to the appropriate regulations.

14.5. Protocol Compliance

The investigator will conduct the study in compliance with the protocol provided by the Sponsor or its designee and given approval by the IRB/IEC and the appropriate regulatory authorities. Modifications to the protocol should not be made. Changes to the protocol will require written IRB/IEC approval prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to the subject. The IRB/IEC may provide, if applicable, regulatory authorities permit, expedited review and approval for minor change(s) in ongoing studies that have the approval of the IRB/IEC. The Sponsor's designee will submit all protocol modifications to the regulatory authorities in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to subjects, the investigator will contact the Sponsor's designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented in the subject's source documentation.

14.6. Subject Data Protection

Information collected in this clinical study is subject to the Health Insurance Portability and Accountability Act of 1996 (HIPAA) as described in 45 CFR 160 and 45 CFR 164, as well as the REGULATION (EU) 2016/679 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 27 April 2016 (on the protection of natural persons with regard to the processing of personal data and on the free movement of such data). The study investigator is responsible for informing subjects of their rights under HIPAA and General Data Protection and obtaining any necessary HIPAA authorizations. In compliance with the provisions of that policy, the Sponsor or designee will not collect any protected health information and will only collect de-identified health information. Any clinical study information referred to in this section is understood to be compliant with the provisions of the Privacy Act. The information obtained during the conduct of this clinical study is confidential, and disclosure to third parties other than those noted below is prohibited.

Information obtained during the conduct of this study will be used by the Sponsor or designee in connection with the development of the study drug. The study investigator is obliged to provide the Sponsor or designee with complete test results and all data developed in this study. This information may be disclosed to other physicians participating in the study, to the FDA, or to national and local health authorities. To ensure compliance with all current Federal Regulations and the ICH/GCP guidelines, data generated by this study must be available for inspection upon request by representatives of the FDA, national and local health authorities, the Sponsor, designee, and the IRB/IEC for each study site.

14.7. Financial Disclosure

In accordance with 21 CFR Part 54, FDA requires that certain financial interests and arrangements between sponsors of clinical investigations be disclosed in marketing applications. Since the results of this study may eventually be used in a marketing application, compliance with this Federal statute is essential. In order to comply with the provisions of this regulation, the Sponsor requests that every investigator and sub-investigator mentioned on FDA Form 1572 or its equivalent fill out a financial disclosure form. Under the provisions of 21 CFR Part 54, the term clinical investigator includes the spouse and each dependent child of the investigator.

The provisions of 21 CFR Part 54 specify disclosure of significant equity interests in the Sponsor that exceed $50,000, or significant payments of other sorts made by the Sponsor to the investigator that have a monetary value of more than $25,000, exclusive of the costs of conducting the clinical study or other clinical studies (eg, grants to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation), during the time the clinical investigator is carrying out the study or for 1 year following the completion of the study. If a change in financial interest occurs throughout the study, the investigator is obligated

to notify the Sponsor. To assist the Sponsor or designee in providing the FDA with the required information, please complete the financial disclosure form and return a signed copy. All information provided in the financial disclosure form will be regarded as strictly confidential and will only be disclosed to the FDA.

14.8. Sponsor Discontinuation Criteria

The Sponsor reserves the right to discontinue the study prior to inclusion of the intended number of subjects but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the investigator must contact all participating subjects within a time period set by the Sponsor. As directed by the Sponsor's designee, all study materials will be collected and all CRFs completed to the greatest extent possible.

15. DATA HANDLING AND RECORD KEEPING

15.1. Inspection of Records

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

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation and any subject records in order to verify the adherence to the protocol and the accuracy of the data recorded in the eCRF. The study monitor is responsible for routine review of the case report form/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 investigator agrees to cooperate with the study monitor to ensure that any problems detected through any type of monitoring (central, off-site, on-site) are resolved.

15.2. Retention of Records

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

The investigator's study file will contain the protocol/amendments, eCRFs, IRB/IEC, and governmental approval with correspondence, the ICF(s), drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

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

- Subject identification
- Documentation that subject meets eligibility criteria (ie, medical history, physical examination, and confirmation of diagnosis [to support inclusion and exclusion criteria])
- Documentation of the reason(s) a consented subject is not enrolled
- Participation in study (including study number)
- Study discussed and date of informed consent
- Dates of all visits
- Documentation that protocol-specific procedures were performed

- Results of efficacy parameters, as required by the protocol
- Start and end date (including dose regimen) of study drug, including dates of dispensing and return
- Record of all AEs and other safety parameters (start and end date; causality and severity) and documentation that adequate medical care has been provided for any AE
- Concomitant medication (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 for at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (eg, US, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, for 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 the Sponsor. The investigator must notify the Sponsor before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, The Sponsor 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 the Sponsor 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.

15.3. Electronic Case Report Forms

An eCRF casebook will be completed by an authorized study personnel member whose training for this function is completed in the electronic data capture (EDC) system unless otherwise directed. The eCRF casebook will only capture the data required per the protocol schedule of events and procedures, unless collected by a nonelectronic data capture vendor system (eg, central laboratory). The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only after all data related to eligibility are available. Data entry should be performed in accordance with the case report form Completion Guidelines provided by the Sponsor. Subsequent to data entry, a study monitor may perform source data verification. System-generated or manual queries will be issued in the EDC system as data discrepancies are identified by the study monitor or the Sponsor personnel who routinely review the data for completeness, correctness, and consistency. The site investigator, site coordinator, or other designee is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). Original entries as well as any changes to data fields will be

stored in the audit trail of the system. Regular oversight by the principal investigator of the data entered into the EDC system is expected to occur on an ongoing basis throughout the study to ensure quality and completeness. At a minimum, before any interim, final, or other time points (as instructed by the Sponsor), the investigator will apply his/her electronic signature to confirm that the forms have been reviewed and that the entries accurately reflect the information in the source documents. At the conclusion of the study, The Sponsor will provide the site investigator with a read-only archive copy of the data entered. This archive must be stored in accordance with the records retention requirements outlined in Section 15.2.

15.4. Confidentiality

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

The investigator agrees that all information received from the Sponsor, including but not limited to the IB, this protocol, eCRFs, study drug information, and any other study information, remains the sole and exclusive property of the Sponsor 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 the Sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the investigational site to any third party or otherwise into the public domain.

16. STUDY REPORTS AND PUBLICATIONS

A clinical study report (CSR) will be prepared and provided to the regulatory agency(ies) when applicable and in accordance with local regulatory requirements. The Sponsor 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.

For studies with sites in countries following the EU Regulation No. 536/2014, a CSR will be submitted within 1 year (6 months for pediatric studies, in accordance with Regulation [EC] No. 1901/2006) after the global end of study (as defined in Section 3.5).

Investigators in this study may communicate, orally present, or publish study data in scientific journals or other scholarly media in accordance with the Gilead clinical trial agreement. Study results will be made publicly available (including posted to the Clinical Trials Information System and ClinicalTrials.gov) in accordance with local regulatory requirements.

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18. APPENDICES

18.1. Investigator Signature Page

GILEAD SCIENCES, INC.
(IMMUNOMEDICS, INC. IS NOW PART OF THE GILEAD GROUP OF COMPANIES)
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404

STUDY ACKNOWLEDGMENT

A Randomized Open-Label Phase III Study of Sacituzumab Govitecan Versus Treatment of Physician's Choice in Subjects with Metastatic or Locally Advanced Unresectable Urothelial Cancer

IMMU-132-13, Protocol Amendment 6, 30 August 2024

This protocol has been approved by Gilead Sciences, Inc. (Immunomedics, Inc. is now part of the Gilead group of companies). The following signature documents this approval.

PPD	*[See appended electronic signature]*
Name (Printed) Director, Clinical Development	Signature
[See appended electronic signature]	
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

18.2. Marketing Authorization Status of Study Interventions

Study Intervention Name	Category	Authorized in ≥ 1 Country Following EU Regulation No. 536/2014	Authorized in ≥ 1 ICH Country	Authorized by Swissmedic
Sacituzab govitecan	Study drug	Yes	Yes	Yes
Docetaxel	Comparator	Yes	Yes	Yes
Paclitaxel	Comparator	Yes	Yes	Yes
Vinflunine	Comparator	Yes	Yes	No

EU = European Union; ICH = International Council for Harmonisation
a Rationale described in Section 1.

18.3. Performance Status Criteria

ECOG Performance Status Scale	
Grade	**Descriptions**
0	Normal activity Fully active, able to carry on all pre-disease performance without restriction
1	Symptoms, but ambulatory Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work)
2	In bed <50% of the time Ambulatory and capable of all self-care, but unable to carry out any work activities, up and about more than 50% of waking hours
3	In bed >50% of the time Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair
5	Dead

Abbreviation: ECOG = Eastern Cooperative Oncology Group

18.4. Cockcroft-Gault Formula AND Modification of Diet in Renal Disease (MDRD) Study Equation for Creatinine Clearance

Cockcroft-Gault Formula

C_{Cr}={((140–age) x body weight)/(72xS_{Cr})} x 0.85 (if female)

Abbreviations/ Units

C_{Cr} (creatinine clearance) = mL/minute

Age = years

Weight = kg

SCr (serum creatinine) = mg/dL

MDRD Equation

eGFR = 175 x (SCr)-1.154 x (age)-0.203 x 0.742 [if female] or x 1.212 [if Black]

Abbreviations/ Units

eGFR (estimation of glomerular filtration rate) = mL/min/1.73 m²

SCr (serum creatinine) = mg/dL

Age = years

The equation does not require body weight or height variables because the results are reported normalized to 1.73 m² BSA, which is an accepted average adult surface area.

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18.5. Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

New response evaluation criteria in solid tumors {Eisenhauer 2009} are summarized below. Timing of assessments has been modified to fit this protocol.

Measurable/Non-Measurable Lesions:

Each tumor lesion or site of disease identified at baseline is categorized as either a measurable lesion or a non-measurable lesion according to the following definitions.

Lesion Type	Qualifying Definition
Measurable	Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of: • 10 mm by CT scan (CT scan slice thickness no greater than 5 mm.) • 10 mm calliper measurement by clinical exam (lesions which cannot be accurately measured with callipers should be recorded as non-measurable) •20 mm by chest X-ray. Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.
Non-Measurable	All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with 10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Abbreviation: CT = Computed Tomography.

Special considerations regarding lesion measurability: Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment.

Bone lesions:

- Bone scan, positron emission tomography (PET) scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

Lesions with prior local treatment:

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 28 days before the beginning of the treatment.

Target Lesions:

Target lesions are selected from measurable lesions at baseline on the basis of their size and suitability for accurate repeated measurements by imaging techniques or clinical judgment. The sum of the longest diameter for all target lesions provides a quantitative means of characterizing objective tumor response to treatment as follows:

Evaluation Criteria used for Categorizing Treatment Response of Target Lesions	
Response Category	**Definition**
Complete Response	Disappearance of all target lesions
Partial Response	≥30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter
Progressive Disease	≥20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
Stable Disease	Neither sufficient shrinkage to qualify for Partial Response nor sufficient increase to qualify for Progressive Disease, taking as reference the smallest sum longest diameter since the treatment started

Non-Target Lesions:

Non-target lesions are other lesions (or sites of disease) not identified as target lesions at baseline. These include both non-measurable lesions as well as measurable lesions exceeding the maximum number allowed per organ or in total. The response of non-target lesions to treatment is evaluated on the basis of their presence or absence as follows:

Evaluation Criteria Used for Categorizing Treatment Response of Non-Target Lesions	
Response Category	**Definition**
Complete Response	Disappearance of all non-target lesions and normalization of tumor marker levels initially above upper limits of normal
Progressive Disease	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions
Stable Disease	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits

New Lesions:

New lesions not present at baseline should be recorded at time of occurrence.

Overall Response:

The overall response is the best response recorded from the start of the treatment until PD/recurrence (taking as reference for PD) the smallest measurements recorded since the treatment started). To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments 4-6 weeks after initial documentation, with the exception of one intervening non-evaluable assessment allowed before confirmation.

In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once with a minimum interval of at least 6-8 weeks from enrolment.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR*
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD**
Any	PD	Yes or No	PD**
Any	Any	Yes	PD**

Abbreviations: CR = Complete Response; PD = Disease Progression; PR = Partial Response; SD = Stable Disease

* When evaluation of possible CR depends on distinguishing residual disease from normal tissue, fine needle aspirate/biopsy is recommended before confirming the complete response status.

** Subjects without objective evidence of PD, but with globally deteriorated health status requiring discontinuation of treatment should be classified as having “symptomatic deterioration” at that time, with every effort made to document the objective progression, even after discontinuation of treatment.

Duration of Objective Tumor Response:

The duration of objective tumor response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded since the treatment started). SD is measured from the start of the treatment until the criteria for PD are met, taking as reference the smallest measurements recorded since the treatment started.

18.6. Quality of Life Questionnaires

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: □□□□
Your birthdate (Day, Month, Year): □□□□□□□□
Today's date (Day, Month, Year): □□□□□□□□

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
During the past week:				
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4

14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EuroQoL EQ-5D-5L

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ☐
I have slight problems in walking about ☐
I have moderate problems in walking about ☐
I have severe problems in walking about ☐
I am unable to walk about ☐

SELF-CARE

I have no problems washing or dressing myself ☐
I have slight problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ☐
I have slight problems doing my usual activities ☐
I have moderate problems doing my usual activities ☐
I have severe problems doing my usual activities ☐
I am unable to do my usual activities ☐

PAIN / DISCOMFORT

I have no pain or discomfort ☐
I have slight pain or discomfort ☐
I have moderate pain or discomfort ☐
I have severe pain or discomfort ☐
I have extreme pain or discomfort ☐

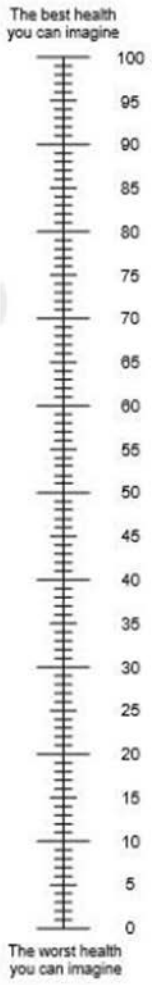
ANXIETY / DEPRESSION

I am not anxious or depressed ☐
I am slightly anxious or depressed ☐
I am moderately anxious or depressed ☐
I am severely anxious or depressed ☐

I am extremely anxious or depressed ☐

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine. 0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



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

1) Definitions

a. Definition of Childbearing Potential

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

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

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

b. Definition of Male Fertility

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

2) Contraception Requirements for Female Subjects

a. Study Drug Effects on Pregnancy and Hormonal Contraception

Sacituzumab govitecan is contraindicated in pregnancy because a malformative effect has been demonstrated/suspected or is unknown, taking into consideration class effects and genotoxic potential. Based on the assessment of published data related to CYP450 enzyme inhibition and induction experiments for SN-38, efficacy of hormonal contraception is not expected to be impacted due to sacituzumab govitecan administration. A dedicated oral contraceptive drug-drug interaction clinical study has not been conducted. Refer to the latest version of the Investigator's Brochure for additional information.

Vinflunine studies in animals have shown embryotoxicity and teratogenicity. There are no data available on the use of vinflunine in pregnant women. If pregnancy occurs during treatment, the subject should be informed about the risk for the unborn child and be monitored carefully. There is no contraindication to hormonal contraception according to the vinflunine prescribing information. Refer to Regional Prescribing Information for additional information.

Based on the mechanism of action and findings in animals, docetaxel can cause fetal harm when administered to a pregnant woman. Docetaxel has been shown to be both embryotoxic and fetotoxic in rabbits and rats. There is no contraindication to hormonal contraception according to the docetaxel prescribing information. Refer to Regional Prescribing Information for additional information.

Paclitaxel can cause fetal harm when administered to a pregnant woman. Studies in animals have shown reproductive toxicity. Based on the published literature, paclitaxel is a potentially genotoxic agent at clinical doses, based upon its pharmacodynamic mechanism of action. There are limited data on the use of paclitaxel in human pregnancy. There is no contraindication to hormonal contraception according to the paclitaxel prescribing information. Refer to Regional Prescribing Information 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 that have a failure rate of less than 1% per year. Subjects must have a negative serum pregnancy test during screening and a negative urine pregnancy test is required at baseline prior to study treatment administration on C1D1. The baseline urine pregnancy test does not need to be conducted if the screening pregnancy test was performed within 72 hours before study treatment administration on C1D1. Pregnancy tests will be performed thereafter on Day 1 of each treatment cycle starting from Cycle 2 through last cycle and every 28 days after the last dose of study drug until the end of contraception requirement. If a urine pregnancy test is positive or equivocal, a confirmatory serum pregnancy test will be required.

Duration of required contraception for female subjects in this clinical study should start from the screening visit until 6 months after the last dose of study drug.

Female subjects must agree to 1 of the following contraceptive methods:

Complete abstinence from intercourse of reproductive potential. True 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:

- Nonhormonal intrauterine device (IUD)
- Hormonal IUD (must be used in conjunction with a barrier method)
- Bilateral tubal occlusion (upon medical assessment of surgical success)
- Vasectomy in the male partner (upon medical assessment of surgical success)

Or

Female subjects who wish to use a hormonally based method must use it in conjunction with a barrier method, preferably a male condom. Hormonal methods are restricted to those associated with the inhibition of ovulation. Hormonally based contraceptives and barrier methods permitted for use in this protocol are as follows:

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

  a) Oral contraceptives (either combined or progesterone only) (see Appendix 18.8 for a list of UGT1A1 inducers and Section 6.6.2).

  b) Injectable progesterone

  c) Subdermal contraceptive implant

  d) Transdermal contraceptive patch

  e) Contraceptive vaginal ring

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

  a) Male condom (with or without spermicide)

  b) Female condom (with or without spermicide)

  c) Diaphragm with spermicide

  d) Cervical cap with spermicide

  e) Sponge with spermicide

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

Female subjects must also refrain from egg donation, cryopreservation of germ cells, and in vitro fertilization during treatment and until the end of contraception requirement. Female subjects should be advised to seek advice of the Investigator about egg donation and cryopreservation of germ cells before treatment.

3) Contraception Requirements for Male Subjects

It is theoretically possible that a relevant systemic concentration of study drug may be achieved in a female partner from exposure of the male subject's seminal fluid and poses a potential risk to an embryo/fetus. Therefore, male subjects with female partners of childbearing potential must use condoms during treatment and until 6 months after the last dose of study drug. If the female partner of childbearing potential is not pregnant, additional highly effective contraception recommendations should also be considered.

Male subjects must also refrain from sperm donation, and/or cryopreservation of germ cells during treatment and until the end of contraception requirement. Male subjects should be advised to seek advice of the Investigator about sperm donation and cryopreservation of germ cells before treatment.

4) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence for the duration of exposure to IMP, withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method. A female condom and a male condom should not be used together.

5) Procedures to be Followed in the Event of Pregnancy

Female subjects will be instructed to notify the investigator if they become pregnant or suspect they are pregnant at any time from start of the study and throughout the study (including the post study drug follow-up period) or 6 months after the last dose of study drug, whichever is longer. Study drug must be discontinued immediately upon consultation with the medical monitor.

Male subjects whose partner has become pregnant or suspects she is pregnant from start of study and throughout the study (including the post study drug follow-up period) or 3 months after the last study drug dose, whichever is longer, must also report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 10.2.4.

18.8. UGT1A1 Inhibitors and Inducers

Inducers of UGT1A1	Inhibitors of UGT1A1
Carbamazepine	Amitriptyline
Efavirenz	Atazanavir
Ethinylestradiol	Dacomitinib
Lamotrigine	Dasabuvir
Phenobarbital	Deferasirox
Phenytoin	Eltrombopag
Primidone	Enasidenib
Rifampicin	Erlotinib
Ritonavir	Flunitrazepam
Tipranavir	Flurbiprofen
	Fostamatinib
	Gemfibrozil
	Glecaprevir
	Indinavir
	Indomethacin
	Ketoconazole
	Nilotinib
	Ombitasvir
	Paritaprevir
	Pazopanib
	Pexidartinib
	Pibrentasvir
	Probenecid
	Propofol
	Regorafenib
	Rucaparib
	Silibinin
	Sorafenib
	Valproic acid

18.9. Pandemic Risk Assessment and Mitigation Plan

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

These risks can be summarized as follows:

1) Study drug supplies

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

      Mitigation plan: At the earliest opportunity, the site will schedule in-person subject visits and return to the regular protocol schedule of procedures.

   b) Shipments of study drug could be delayed because of transportation issues. Without study drug, enrolled subjects would not be able to continue receiving the study drug as planned per protocol.

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

2) Subject safety monitoring and follow-up:

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

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

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

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

      iii) If applicable, confirm electronic diary questionnaires and patient-reported outcomes have been completed and transmitted.

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

Mitigation plan: Local laboratories or other vendors may be used as appropriate to monitor subject safety until the subject can return to the site for their regular follow-up per protocol. Any changes in the party conducting laboratory assessments for the study due to the pandemic will be documented accordingly. Pregnancy testing may be performed using a home urine pregnancy test if local laboratory pregnancy testing is not feasible.

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

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

d) The safety of study subjects is important and testing of COVID-19 infection will be based on local clinical guidelines for testing based on signs/symptoms and/or suspected exposure to COVID-19.

Mitigation plan: If subject has a diagnosis of COVID-19 while on this clinical study, study drug may be held until clinical improvement or resolution in accordance with the treating physician's judgment and general sacituzumab govitecan dose delay guidance in the protocol. Additional supportive care and treatment measures for COVID-19 infection on the study will be performed in accordance with local institutional guidelines. Subjects with a COVID-19 infection while participating in the clinical study will have this event documented as an AE in the clinical database.

3) Protocol and monitoring compliance:

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

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

b) Study monitors may be unable to carry out source data review or source data verification, or study drug accountability or assess protocol and Good Clinical Practice compliance. This may lead to delays in source data verification, an increase in protocol deviations, or underreporting of AEs.

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

4) Missing data and data integrity:

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

      Mitigation plan: Implications of a pandemic on methodological aspects for the study will be thoroughly assessed and documented, and relevant actions will be taken as appropriate (eg, modification of the SAP) and in compliance with regulatory authorities' guidance. Overall, the clinical study report will describe the impact of the pandemic on the interpretability of study data.

5) Concurrent administration of the COVID-19 vaccine(s) that are approved or authorized for emergency use by local health authorities:

   b) There may be potential safety issues due to concurrent administration of the COVID-19 vaccine and study drugs.

      Mitigation plan: There is not substantial safety data regarding the concurrent administration of the COVID-19 vaccine and sacituzumab govitecan, paclitaxel, docetaxel, or vinflunine. Subjects are allowed to receive the COVID-19 vaccine to reduce the risk and complications of COVID-19 infection. Investigators and study personnel should provide close surveillance of subjects after COVID-19 vaccine administration and the institutional guidelines should always be followed. The administration of specific COVID-19 vaccine must be documented in the clinical database and AEs associated with COVID-19 vaccine administration should be recorded in the AE eCRF. COVID-19 vaccine administration should be recorded in the prior or concomitant medication eCRF as appropriate. The study visits should continue as planned, if possible, and clinically appropriate if vaccination occurs while the subject is on the study.

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

Since these potential risks are considered mitigated with the implementation of these measures, the expected risk/benefit assessment of sacituzumab govitecan in study subjects remains unchanged.

18.10. Country-Specific Requirements

China

Optional UGT1A1 sample will be collected at baseline instead of screening for the sacituzumab govitecan treatment arm only. This testing is not required for study eligibility.

The collection of biomarker samples for optional future research is not permitted in China.

18.11. Amendment History

A high-level summary of amendment history is provided in tabular form below. Minor changes such as the correction of typographic errors, grammar, or formatting are not detailed.

Separate summary of change documents for earlier amendments are available upon request.

A separate tracked change (red-lined) document comparing the previous version of the protocol to this amendment will be made available upon the publication of this protocol.

Amendment 6 (30 August 2024)

Rationale for Key Changes Included in Amendment 6	Affected Sections
Added country-specific requirements text, deleted emergency contact details, and updated EU CT number to comply with EU-CTR requirements.	Cover page
Incorporated changes from Protocol Clarification Letter 5.0.1.	Cover page
Added plain language short title.	Cover page and synopsis
Removed estimated dates of first subject enrolled and last subject completed to avoid frequent updates.	Synopsis
Added new sections to describe mechanism of action of treatment of physician's choice (TPC) agents used in the study to comply with the EU-CTR requirements.	Section 1
Added a new section and an appendix to clarify the marketing authorization status of study drugs to comply with the EU-CTR requirements.	Section 1.3 and Appendix 18.2
Added rationale for dose selection of TPC agents to comply with the EU-CTR requirements.	Section 1.6
Provided a description of the study modifications after the completion of final analysis of primary endpoints and following implementation of Protocol Amendment 6 (PA6) for the subjects continuing treatment with the study drug.	Synopsis and Section 3.1
Updated the survival follow-up procedures and added a clarification that the subjects who discontinued treatment will not be followed for survival following the implementation of PA6.	Synopsis and Section 3.4
Clarified that following the implementation of PA6, subjects in the TPC arm will discontinue the study treatment while those in the sacituzumab govitecan arm may continue it as long as deriving clinical benefit.	Synopsis and Section 3.5
Specified that the end of study will be delayed until all AEs have been resolved or stabilized for subjects in either treatment arm.	Synopsis and Section 3.5
Specified that the subjects in survival follow-up at the time of implementation of PA6 will discontinue the study.	Synopsis and Section 3.5
Added a new schedule of assessment table for the subjects who are continuing sacituzumab govitecan treatment after the final overall survival (OS) analysis and following implementation of PA6.	Section 4.4

Rationale for Key Changes Included in Amendment 6	Affected Sections
Added a new treatment discontinuation criterion that covers study treatment discontinuation after the final OS analysis and following implementation of PA6 for all the subjects in the TPC arm.	Section 5.3
Added a new study discontinuation criterion to allow study discontinuation for the subjects in either treatment arm who have all AEs resolved or stabilized after the final OS analysis and following implementation of PA6.	Section 5.4
Removed the statement cross referencing to Section 6.3.2.4 for the treatment-related details of infusion-related reaction.	Section 6.3.1
Updated language to strongly recommend primary prophylaxis in patients with risk factors for febrile neutropenia and included ASCO guidelines with a list of risk factors for febrile neutropenia to make this recommendation more prominent and make guidelines be easily accessible for reference.	Section 6.3.2.2 and Table 3
Corrected drug name from paclitaxel to docetaxel.	Section 6.4.1.2
Added new sections “Accountability for Study Drug(s)” and “Study Drug Return or Disposal” to comply with the EU-CTR requirements.	Sections 7.4 and 7.4.1
Added the language to clarify the efficacy parameters for the subjects who are continuing sacituzumab govitecan treatment after the final OS analysis and following implementation of PA6.	Section 8.1
Clarified that the anti-drug antibody samples will no longer be collected for the subjects who are continuing sacituzumab govitecan treatment after the final OS analysis and following implementation of PA6.	Section 9.2
Clarified that the quality-of-life questionnaires will not be required for the subjects who are continuing sacituzumab govitecan treatment after the final OS analysis and following implementation of PA6.	Section 9.3
Clarified that the physical exam data will no longer be collected for the subjects who are continuing sacituzumab govitecan treatment after the final OS analysis and following implementation of PA6.	Section 10.1.4
Clarified that the ECOG performance status will no longer be collected for the subjects who are continuing sacituzumab govitecan treatment after the final OS analysis and following implementation of PA6.	Section 10.1.6
Added a modified chemistry panel for the subjects who are continuing sacituzumab govitecan treatment after the final OS analysis and following implementation of PA6.	Section 10.1.7.3
Update made to specify that there is only one central fax number for global reporting of serious adverse events.	Section 10.2.5
Added a statement that details of any changes from the original statistical analysis planned will be provided in the Statistical Analysis Plan to comply with the EU-CTR requirements.	Section 11.2
Added a statement that the study results will be disclosed to the public in accordance with local regulatory requirements.	Section 16
Minor changes to correct typographic errors or slight changes to wording that do not impact the meaning of text.	Throughout, as needed

Protocol IMMU-132-13 Amendment 6

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Development eSigned	30-Aug-2024 19:03:25