EU Risk Management Plan for
TRODELVY
(sacituzumab govitecan)

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RMP version to be assessed as part of this application:

Version Number:	Data Lock Point for This RMP:	Date of Final Sign-Off:
4.0	21 April 2023*	Refer to ELECTRONIC SIGNATURES

* Latest PSUR/PBRER data cutoff date

Rationale for submitting an updated RMP:

The milestones for Study IMMU-132-15, 'A Phase 1 Open-label, Dose Escalation Study to Determine an Appropriate Starting Dose of Sacituzumab Govitecan in Subjects with Advanced or Metastatic Solid Tumour and Moderate Liver Impairment', have been updated.

The important risks of severe diarrhoea, hypersensitivity, and embryo-foetal toxicity have been removed. These are known risks that require no further risk minimization measures and are monitored by routine pharmacovigilance activities such as signal detection and adverse reaction reporting.

Summary of significant changes in this RMP:

Part	Module/Annex	Significant Changes to RMP
Part II Safety Specification	Part II: Module SI - Epidemiology of the Indication(s) and Target Populations(s)	None.
	Part II: Module SII - Nonclinical Part of the Safety Specification	None.
	Part II: Module SIII - Clinical Trial Exposure	None.
	Part II: Module SIV - Populations Not Studied in Clinical Trials	None.
	Part II: Module SV - Postauthorization Experience	Updated to reflect current exposure data according to latest PSUR/PBRER.
	Part II: Module SVI - Additional EU Requirements for the Safety Specification	None.
	Part II: Module SVII - Identified and Potential Risks	Updated to reflect removal of specified safety concerns.
	Part II: Module SVIII - Summary of the Safety Concerns	Updated to reflect removal of specified safety concerns.
Part III Pharmacovigilance Plan		Updated milestones for Study IMMU-132-15 in Tables Part III.1 and III.2.
Part IV Plan for Postauthorization Efficacy Studies		None.
Part V Risk Minimization Measures		Updated to reflect removal of specified safety concerns.
Part VI Summary of the Risk Management Plan		Updated to reflect removal of specified safety concerns.
Part VII Annexes	Annex 2 and Annex 8	Updated to reflect changes in Parts II and III above.

Other RMP versions under evaluation:

Not applicable

Details of the currently approved RMP:

Version Number	Approved With Procedure	Date of Approval (Opinion Date)
3.0	EMEA/H/C/005182/II/0020	26 July 2023

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QPPV signature:	Refer to ELECTRONIC SIGNATURES

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ABC	Advanced breast cancer
ABC 5	5th ESO - ESMO international consensus guidelines for advanced breast cancer
ADA	Antidrug antibody
ADC	Antibody-drug conjugate
ADP	Adenosine diphosphate
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AR	Androgen receptor
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the serum concentration-time curve
BLA	Biologics License Application (BLA)
BL1	Basal-like 1
BL2	Basal-like 2
BOR	Best overall response
BRCA	Breast cancer susceptibility gene
CCI	Charlson Comorbidity Index
CCR	California Cancer Registry
CDK	Cyclin-dependent kinase
CHO	Chinese hamster ovary
CI	Confidence interval
CINV	Chemotherapy-induced nausea and vomiting
C_{max}	Maximum observed serum concentration
CNS	Central nervous system
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECL	Electrochemiluminescence
ECOG	Eastern Cooperative Oncology Group
EEA	European Economic Area
EGFR	Epidermal growth factor receptor
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ER	Estrogen receptor
ESME	Epidemiological Strategy and Medical Economics
ESMO	European Society for Medical Oncology

ESO	European School of Oncology
EU	European Union
FGFR	Fibroblast growth factor receptor
G-CSF	Granulocyte colony-stimulating factor
GLP	Good Laboratory Practice
hCG	Human chorionic gonadotropin
HDAC	Histone deacetylase
HED	Human equivalent dose
HER2	Human epidermal growth factor receptor 2
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HLT	High Level Term
HR	Hormone receptor
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgG	Immunoglobulin
IM	Immunomodulatory
ISI	Integrated Summary of Immunogenicity
ISS	Integrated Summary of Safety
IV	Intravenous
LAR	Luminal androgen receptor
M	Mesenchymal
max	Maximum
mBC	Metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
MES	2-(N-morpholino) ethane sulfonic acid
min	Minimum
MSL	Mesenchymal stem-like
mTNBC	Metastatic triple-negative breast cancer
mTOR	Mammalian target of rapamycin
mUC	Metastatic urothelial cancer
Nabs	Neutralizing antibodies
NCI-ODWG	National Cancer Institute Organ Dysfunction Working Group
NK-1	Neurokinin-1
NOAEL	No Observed Adverse Effect Level
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
ORR	Objective response rates
OS	Overall survival
PARP	Poly ADP-ribose polymerase
PD-L1	Programmed death-ligand 1

PD-1	Programmed cell death protein 1
PFS	Progression-free survival
PI3K	Phosphoinositide 3-kinase
PK	Pharmacokinetic
PK-ECG	Pharmacokinetic- electrocardiogram
PL	Package leaflet
PR	Progesterone receptor
PSUR	Periodic safety update report
PT	Preferred term
QPPV	Qualified Person Responsible for Pharmacovigilance
QTc	Corrected QT
QTcB	Corrected QT interval based on Bazett's formula
QTcF	Corrected QT interval based on Fridericia's formula
RIA	Radioimmunoassay
RMP	Risk management plan
SAE	Serious adverse event
SCLC	Small cell lung cancer
SD	Standard deviation
SG	Sacituzumab govitecan
SmPC	Summary of product characteristics
SMQ	Standardised MedDRA query
SOC	System organ class
SN-38G	Glucuronidated SN-38
TEAE	Treatment-emergent adverse event
TNBC	Triple-negative breast cancer
TPC	Treatment of physician's choice
Trop-2	Trophoblast cell surface antigen-2
UDP	Uridine 5'-diphospho-glucuronosyltransferase
UGT	UDP-glucuronosyltransferase
UGT1A1	Uridine diphosphate-glucuronosyl transferase 1A1
UK	United Kingdom
ULN	Upper limit of normal
UNS	Unstable
US	United States
USPI	US Prescribing Information
VEGF	Vascular endothelial growth factor
5-HT3	5-hydroxytryptamine

PART I: PRODUCT OVERVIEW

Table Part I.1. Product Overview

Active substance (INN or common name):	Sacituzumab govitecan
Pharmaco-therapeutic group (ATC Code):	Antineoplastic agents (L01FX17)
Marketing authorisation holder:	Gilead Sciences Ireland UC
Medicinal products to which this RMP refers:	One
Invented name in the European Economic Area (EEA):	TRODELVY®
Marketing authorisation procedure:	Centralised
Brief description of the product:	Chemical class Antineoplastic agent of the topoisomerase I inhibitor class
	Summary of mode of action Sacituzumab govitecan (SG) is a Trop-2-directed antibody-drug conjugate. Sacituzumab is a humanised antibody that recognises Trop-2. The small molecule, SN-38, is a topoisomerase I inhibitor, which is covalently attached to the antibody by a linker. SG binds to Trop-2-expressing cancer cells and is internalised 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 DNA damage leads to apoptosis. SG decreased tumour growth in mouse xenograft models of triple-negative breast cancer.
	Important information about its composition SG is composed of the following 3 components: • The humanised monoclonal antibody, hRS7 IgG1κ, that binds to trophoblast cell surface antigen-2 (Trop-2), a transmembrane calcium signal transducer that is overexpressed in many epithelial cancers, including TNBC • The camptothecin-derived agent, SN-38, a topoisomerase I inhibitor and the active metabolite of SG • A hydrolyzable linker, with the company designation as CL2A, which links the humanised monoclonal antibody to SN-38 SG has a molecular weight of approximately 160 kilodaltons. It is formulated in 2-(N-morpholino) ethane sulfonic acid (MES) buffer containing trehalose dihydrate and polysorbate 80 and contains no preservatives. SG is supplied as a sterile, off-white to yellowish lyophilised powder in single-dose glass vials. The pH of the reconstituted solution is approximately 6.5.

Hyperlink to the product information	TRODELVY Summary of Product Characteristics (SmPC)
Indication in the EEA:	Current: TRODELVY as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, including at least one of them for advanced disease. TRODELVY as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-negative breast cancer who have received endocrine-based therapy, and at least two additional systemic therapies in the advanced setting.
	Proposed: Not applicable
Dosage in the EEA:	Current: The recommended dose of TRODELVY is 10 mg/kg body weight administered as an intravenous infusion once weekly on Day 1 and Day 8 of 21-day treatment cycles.
	Proposed: Not applicable
Pharmaceutical form and strengths:	Current: Powder for concentrate for solution for infusion Off-white to yellowish powder One vial of powder for concentrate for solution for infusion contains 200 mg sacituzumab govitecan.
	Proposed: Not applicable
Will the product be subject to additional monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATION

SI.1. Indication - Metastatic Triple Negative Breast Cancer

TRODELVY as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, including at least one of them for advanced disease.

SI.1.1. Incidence

Globally it is estimated that there were 2.6 million new cases of breast cancer diagnosed in 2020 and approximately 685,000 breast cancer deaths {Sung 2021}. Female breast cancer incidence rates are highest in Australia/New Zealand, Western Europe (Belgium [with the highest global rates], the Netherlands, and France), Northern Europe (United Kingdom [UK], Sweden, Finland, and Denmark), Northern America and Southern Europe (Italy), (95.5, 90.7, 89.4, 86.4, and 79.6 age-standardized rate per 100,000, respectively) {Bray 2018}. In Europe, the age-standardised incidence rate of breast cancer in 2020 ranges between an estimated 100.0 per 100,000 (Bulgaria) to 194.0 per 100,000 (Belgium) {European Cancer Information System (ECIS) 2022}.

SI.1.2. Prevalence

Triple-negative breast cancer (TNBC), which is defined by a lack of tumor-cell expression of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) {Anders 2013}, accounts for approximately 15% of invasive breast cancers in women {DeSantis 2016, Kohler 2015, Plasilova 2016}. World-wide TNBC affects approximately 170,000 to 180,000 women {Anders 2013, Boyle 2012}.

SI.1.3. Demographics of the Population in the Approved Indication

The vast majority of TNBC cases occur in women, with an estimated 15% of invasive breast cancers found to be triple-negative (estrogen-receptor-negative, progesterone-receptor-negative, and HER2-negative), compared with 1% of male breast cancers identified as triple-negative {Breastcancer.org 2014}.

TNBC has some distinct demographic features compared with other breast cancers. Age at diagnosis of TNBC tends to be in people younger than 50 years, whereas other types of breast cancer are more commonly diagnosed in people aged 60 years or older {Breastcancer.org 2020}. However, there is increasing evidence that TNBC may have a bimodal distribution with the first incidence peak in premenopausal patients and a second peak after 70 years of age {Saraiva 2017}.

TNBC is more common in women of African ancestry in comparison to other ethnic groups {Bauer 2007, Carey 2006, Lin 2012, Siddharth 2018} and TNBC in African American women is associated with worse clinical outcomes compared to TNBC in European American women {Dietze 2015}. This is supported by multiple studies including population-based data from the California Cancer Registry (CCR) of 375,761 women newly diagnosed with invasive breast cancer from 1988 to 2006 that found that African American women (identified as Non-Hispanic Blacks) have an increased risk of TNBC compared to White American (identified as Non-Hispanic Whites) and Hispanic American women {Amirikia 2011}. The TNBC incidence rate for women with breast cancer aged 40 to 49 years was 35.1 per 100,000 for Non-Hispanic Blacks, 16.8 per 100,000 for Non-Hispanic Whites, and 15.1 per 100,000 for Hispanic women. Similar patterns were also observed for older women.

Between 2012 to 2016 the American Cancer Society estimated that 21% of breast cancers in Non-Hispanic Blacks were triple negative, which is about double the proportion of this subtype in other racial/ethnic groups (10% Non-Hispanic Whites, 12% American Indian Alaska Native, 12% Hispanic, and 10% Asian Pacific Islander) {American Cancer Society 2019}. Asians also have a lower risk of TNBC than African Americans, with TNBC reported to occur in 18% of Chinese patients with breast cancer, which is similar to Japanese patients (8-14%) {Lin 2009, Yin 2009}.

Other risk factors for the disease include the presence of a breast cancer susceptibility gene (BRCA) mutation, premenopausal status, obesity, and maternal-related factors such as parity and age at first pregnancy {Plasilova 2016, Trivers 2009}. While BRCA1 mutant breast cancers are typically TNBC and TNBC incidences are higher in African American women compared to other ethnic groups, the incidence of germline BRCA1 mutation is higher in European women {Mavaddat 2012, Siddharth 2018}.

A recognized factor linked to TNBC pathogenesis is the metabolic syndrome, which consists of central obesity, insulin resistance, impaired glucose tolerance, dyslipidemia and hypertension {Davis 2012, Mancini 2014}. Oral contraceptive use was identified as another risk factor in a population-based study in which oral contraceptive use for ≥1 year was associated with a 2.5-fold increased risk of TNBC {Dolle 2009}. While cigarette smoking was not associated with TNBC, alcohol drinkers have a reduced risk compared with never drinkers {Boyle 2012}.

SI.1.4. Main Existing Treatment Options

TNBC is insensitive to most of the available targeted therapies for breast cancer treatment since their tumors do not express estrogen receptor, progesterone receptor, or HER2/neu {Mancini 2014}. Therefore, although targeted therapies have benefited patients with other subtypes of breast cancer and several targeted therapies for hormone-receptor-positive and HER2-positive breast cancer are available {Cardoso 2017, Finn 2016, Verma 2012, Zeichner 2016}, sequential single-agent chemotherapy remains the standard of care for patients with metastatic TNBC for most patients {National Comprehensive Cancer Network (NCCN) 2019}. There is no preferred or standard chemotherapeutic regimen used and in general, patients first receive standard chemotherapy regimens that include either a taxane or anthracycline. For those patients with a germline BRCA 1 or 2 mutation and HER2-negative mBC, poly adenosine diphosphate-ribose polymerase (PARP) inhibitors have demonstrated improvements in

progression free survival and are a preferred option for these patients who have previously received an anthracycline or taxane. In addition, for patients whose tumors express PD-L1, anti-PD-L1 and PD1 agents in combination with chemotherapy (atezolizumab+nab-paclitaxel and pembrolizumab+nab-paclitaxel or paclitaxel or gemcitabine/carboplatin) are considered a standard of care in the first line setting.

The majority of patients have disease progression after receiving first-line therapy, and standard therapeutic options are limited to chemotherapy (eg, capecitabine, gemcitabine, vinorelbine or albumin-bound paclitaxel, and combination regimens for patients who present with visceral crisis). Standard chemotherapy is associated with low response rates (10 to 15%) and short progression-free survival (PFS) (2 to 3 months) among patients with pretreated mTNBC {Brufsky 2012, Park 2019, Perez 2010, Twelves 2016}.

The standard of care for advanced TNBC in the European Union (EU) is similar to that found in the US. In the EU, the 5th European School of Oncology (ESO) - European Society for Medical Oncology (ESMO) international consensus guidelines for advanced breast cancer (ABC 5) recommend carboplatin over docetaxel for advanced TNBC patients (regardless of BRCA status) previously treated with anthracyclines with or without taxanes in the (neo) adjuvant setting, based on comparable efficacy and the more favorable toxicity profile of carboplatin {Cardoso 2020}.

For non-BRCA-associated advanced TNBC, there are no data supporting different or specific chemotherapy recommendations, besides platinum, and therefore all chemotherapy recommendations for HER2-negative disease apply for advanced TNBC. While limited data suggest a low level of efficacy for androgen receptor antagonist agents, such as bicalutamide and enzalutamide, since the androgen receptor is a potential target in TNBC, the ABC 5 Guidelines do not recommend these agents for use in routine clinical practice. For patients with PD-L1-positive advanced TNBC either de novo or at least 12 months since (neo)adjuvant chemotherapy, atezolizumab plus nab-paclitaxel is recommended as an option as first-line therapy. Checkpoint inhibitor monotherapy in later lines for advanced TNBC is not recommended due to low response rates. Furthermore, other therapeutic options are not recommended outside clinical studies.

SI.1.5. Natural History of the Indicated Condition including Mortality and Morbidity

TNBC can be classified into 7 subtypes based on DNA microarray expression profiling, labelled as basal-like 1 (BL1), basal-like 2 (BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL), luminal androgen receptor (LAR) and unstable (UNS) {Lehmann 2011, Lehmann 2014}. Basal-like classes, BL1 and BL2, represent the main components of TNBC with a rough frequency of 80% and they are characterized by the enrichment of genes that regulate cell cycle, by cell-cycle checkpoint loss, and by elevated DNA damage response pathways {Mancini 2014}. In 10% to 20% of TNBC it is possible to find a BRCA mutation; indeed, most BRCA1 mutated breast cancers fall into the BL1 and BL2 subtypes {Mancini 2014}.

Tumors with a triple negative phenotype are characterized by their usually large size, higher grade, and early lymph node involvement, aggressive tumor behavior leading to poor outcomes for patients {Mancini 2014, Plasilova 2016}. Therefore, only a few TNBC patients present a good prognosis. Compared with other breast cancer subtypes, TNBCs are typically invasive (ductal, medullary, or metaplastic), Grade 3 tumors with high rates of mitotic division, of which approximately half contain a high rate of p53 mutations {Carey 2010}. For these reasons, they account for a disproportionately high percentage of metastases, distant recurrence, and death among patients with breast cancer {Davis 2012}.

Despite treatment for early stage breast cancer, TNBC patients recur rapidly with the majority having disease recurrence within 3 years of their initial diagnosis {Cheang 2008}. TNBC has the worst 5-year relative survival rate (77% for HR-/HER2-) compared with other breast cancer tumor subtypes (92% for HR+/HER2-; 89% for HR+/HER2+; 83% for HR-/HER2+), based on cancer patients diagnosed during 2009 to 2015 {American Cancer Society 2019}. Metastases in TNBCs are most common in visceral organs including liver, lungs, and the central nervous system (CNS) {Carey 2010}. Metastatic TNBC is incurable, with a median survival of approximately 13.3 months {Kassam 2009}.

The natural history of TNBC is heterogeneous {Saraiva 2017}. Prognosis of stage matched premenopausal TNBC is worse than older age TNBC. Metastases develop preferentially in the viscera in patients that relapse more rapidly, leading to a bad prognosis {Dent 2007, Saraiva 2017}. However, patients with TNBC who later relapse have a tendency to develop bone metastases, and tend to have a better prognosis {Dent 2007, Saraiva 2017}.

SI.1.6. Important Comorbidities

To evaluate the comorbidities of patients with TNBC a surveillance study was conducted using the Charlson Comorbidity Index (CCI), a weighted list of 17 items developed in 1987 and a prominent tool in cancer research, that includes the comorbidities myocardial infarction, congestive heart failure, peripheral vascular disease, cerebral vascular disease, dementia, chronic lung disease, rheumatologic disease, peptic ulcer disease, mild liver disease, diabetes without complications, diabetes with complications, hemiplegia, neoplasia, moderate/severe liver disease, metastatic disease, human immunodeficiency virus (HIV), and renal disease {Charlson 1987, de Groot 2003, Swede 2016}. In this study hypertension was also included as a comorbidity based on the evidence of the prognostic importance of hypertension in distinguishing mortality risk in breast cancer survival disparities between African American and White breast cancer patients {Braithwaite 2009}.

The study found that both TNBCs and comorbidities were more prevalent among African American patients compared with White patients even though the former tended to be significantly younger at diagnosis {Swede 2016}. A greater proportion of White patients had no comorbidities at breast cancer diagnosis relative to African American patients (82.8 % vs 58.9%, p=0.0001). Regarding specific comorbidities, African American patients were more likely than White patients to be diagnosed with hypertension (47.5% vs 30.8%, p=0.001) and Type 2 diabetes (23.3% vs 4.2%, p<0.001).

SI.2. Indication - HR+/HER2- Metastatic Breast Cancer

TRODELVY as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-negative breast cancer who have received endocrine-based therapy, and at least two additional systemic therapies in the advanced setting.

SI.2.1. Incidence

See Section SI.1.1 for breast cancer incidence.

SI.2.2. Prevalence

Hormone receptor-positive (HR+)/HER2- breast cancer is defined as ≥1% of tumour cells staining positive for ER and/or PR, but lacking HER2 expression (immunohistochemistry [IHC] 0 or 1+, or IHC 2+ without amplification by *in situ* hybridization [ISH]) {Allison 2020, Buza 2021}. HR+/HER2- breast cancers comprise approximately 66% of all breast cancers worldwide {Lobbezoo 2013}. By the end of 2020, 7.8 million women globally had been diagnosed with breast cancer within the past 5 years, indicating approximately 5.1 million women with a HR+/HER2- diagnosis between 2015-2020 {World Health Organization (WHO) 2021}.

SI.2.3. Demographics of the Population in the Approved Indication

HR+/HER2- breast cancer is the most common breast cancer subtype among women of all ethnicities. In an observational database study of national health registries in Norway, incidence of luminal A-like (HR+/HER2-) breast cancer was higher among Sub-Saharan immigrants compared to non-immigrants. Luminal B HER2- breast cancer incidence was higher among immigrants from other high-income countries and lower among South Asian immigrants when compared to Norwegian non-immigrants {Hjerkind 2022}. Among women in the UK Million Women Study, racial/ethnic disparities in breast cancer incidence were primarily driven by other risk factors including reproductive history, use of hormone replacement therapy, weight, and alcohol intake {Gathani 2014}.

Established risk factors for HR+/HER2- breast cancer have been reported in several population studies and include age, race, prior breast biopsy, atypical hyperplasia, family history, body mass index (BMI), breast density, and reproductive factors such as age at first birth, age at menarche, and number of live births. In a population-based study using the UK Breast Cancer Family Registry, high parity (3 or more births) and no breastfeeding remained strongly associated with development of HER2- subtypes among all races and ethnicities assessed (non-Hispanic Whites, African Americans/Black, Hispanics, and Asians) {Work 2014}.

In a population-based study from Finland, women with HR+/HER2- breast cancer were reported to be older than women with HER2+ breast cancer or TNBC. This was observed for both early and metastatic patients {Teerenhovi 2021}.

SI.2.4. Main Existing Treatment Options

Systemic treatment for HR+/HER2- mBC typically includes endocrine therapy, targeted therapy, and/or chemotherapy. There are several types of endocrine therapy, targeted therapy, and chemotherapy available, all with varying mechanisms of action. HR+/HER2- mBC tumors are usually responsive to hormonal therapy since endocrine therapy inhibits ER signaling {Yue 2013} hence, endocrine-based therapies are preferred for the initial treatment of HR+/HER2- mBC. Endocrine therapies include aromatase inhibitors (non-steroidal: letrozole, anastrozole), ER downregulators (fulvestrant), select ER modulators (tamoxifen, toremifene), and steroidal aromatase inactivators (exemestane). With the recognised efficacy of CDK4/6 inhibitors, the current standard of care for first-line treatment of HR+/HER2- mBC is endocrine therapy plus a CDK4/6 inhibitor {European Society for Medical Oncology (ESMO) 2022, Gennari 2021}. For patients who develop resistance to endocrine therapy, single-agent chemotherapy is the primary treatment option for HR+/HER2- mBC. Unfortunately, clinical studies have shown that chemotherapy is associated with limited effectiveness, toxicity, and a decreased quality of life {De Laurentiis 2018, Gennari 2021} in mBC. A retrospective cohort study showed that in patients with metastatic BC, a majority of whom were HR+/HER2– mBC, who received multiple rounds of chemotherapy, median PFS was 7.6 months, 5.1 months, and 3.6 months for 1L, 2L, and 3L chemotherapy, respectively, and the median OS was 2.6 years (3.4 years in HR+/HER2- mBC patients) {Park 2015}. Due to low survival benefit, chemotherapies in later treatment lines are not the preference for patients, highlighting the need for more efficacious treatment options {Wood 2017}. Additionally, a wide range of serious side effects have been reported. Hematologic, gastrointestinal, neurologic and general disorders are the most common grade 3-5 adverse events associated with chemotherapy {Giuliano 2019}. Some chemotherapy-induced toxicities such as cardiac toxicity and peripheral neuropathy can be severe and long lasting {Al-Mahayri 2020}. Therefore, more effective, less toxic treatments in relapsed HR+/HER2- mBC are needed.

SI.2.5. Natural History of the Indicated Condition including Mortality and Morbidity

The ER and PR expression level profile of HR+/HER2- breast cancer varies with other tumor characteristics such as the histologic grade of the tumor, cell proliferation, gene expression, and type of mutations. Tumors of low histologic grade typically have greater ER and PR expression, cell proliferation rates, and a better prognosis, while tumors of higher histologic grade have less ER and PR expression, higher cell proliferation rates, and a worse prognosis {Burstein 2020}.

In early stage, HR+/HER2– tumors have a less aggressive pattern of growth versus other tumor types. In the metastatic stage, with higher tumor grade and change in biomarker status after treatment progression, HR+/HER2- tumors are more aggressive and treatment resistant which represents a treatment challenge in later treatment lines and there is a need for new, more efficacious treatment options in this setting {American Cancer Society 2020, Dunnwald 2007, Grinda 2021}. At diagnosis, HR+ BC is characterized by tumors that grow slower than HR– tumors, resulting in lower mortality risk in this stage in ER+/PR+ vs ER+/PR–, ER–/PR+, and ER–/PR– tumors, but mortality risk increases with higher grade for each ER/PR profile, with a greater elevation of mortality risk associated with HR+ vs HR– tumors {American Cancer Society 2020, Dunnwald 2007}. Relative to patients with ER+/PR+ disease, the risk of mortality is higher in patients with ER+/PR– (1.2- to 1.5-fold), ER–/PR+ (1.5- to 2.1-fold), and ER–/PR– (2.1- to 2.6-fold) {Dunnwald 2007}. The magnitude of the associated relative mortality risk

depended on ER/PR status and increased with increase in tumor grade level. Women with ER+/PR+ tumors had a 62% elevated mortality risk with each increase in tumor grade level, whereas women with ER-/PR- tumors had a 24% increase in the relative risk of breast cancer mortality with each increase in tumor grade level {Dunnwald 2007}.

Response rates in patients with HR+/HER2− metastatic breast cancer to later-line chemotherapy treatments are low. In the second-line or greater chemotherapy setting, objective response rates (ORR) range from 13% to 19.9% in patients treated with single-agent chemotherapy, including ixabepilone, capecitabine, eribulin, or vinorelbine {Cortes 2015, Jones 1995, Kaufman 2015, Perez 2010, Twelves 2016}. Reported progression free survival (PFS) range from 4.0 to 6.3 months in the second-line chemotherapy setting and 2.4 to 5.5 months in the third-line setting {Park 2015}.

The Epidemiological Strategy and Medical Economics (ESME) cohort, consisting of women in France who initiated treatment for newly diagnosed metastatic breast cancer between January 2008 and December 2016, reported a median OS of 43.3 months in HR+/HER2− patients; 50.1 months in HER2+ patients; and 14.8 months in patients with TNBC, respectively. Using a subset of patients included between 2008 and 2014, the same study reported that 43.4%, 29.8%, and 6.6% of patients received one, two or three treatments with endocrine therapy ± targeted therapy prior to initiating chemotherapy, respectively. Among these, median PFS for first-, second- and third-line endocrine therapy ± targeted therapy was 11.5 months, 5.8 months, and 5.5 months, respectively. However, these treatment effects do not sufficiently capture the impact of CDK4/6i, which was not in use during this time period.

In the Europe IRIS study, progression-free rates and survival rates were estimated among European women with locally advanced or metastatic HR+/HER2- breast cancer who received palbociclib (CDK4/6i) + an aromatase inhibitor or palbociclib + fulvestrant. At 12 months, the progression-free rate for patients treated with palbociclib + aromatase inhibitor was 88.1%, and the survival rate was 97.3%; corresponding rates for patients receiving palbociclib + fulvestrant was 79.8% and 97.5% {Mycock 2022}.

HER2-low—defined as HER2 IHC 1+ staining or IHC 2+ staining without HER2 gene amplification—has emerged lately as a potential subcategory of HER2 breast cancer. The potential prognostic impact of HER2-low breast cancer is currently unknown, with studies reporting inconsistent findings {Schettini 2021}.

SI.2.6. Important Comorbidities

In a US electronic health records database study of 396 female patients diagnosed with HR+/HER2- metastatic breast cancer (mBC) who initiated CDK 4/6 inhibitors across any line, the average age was 64 (SD 12) years, and the most frequent comorbidities were diabetes mellitus (16.7%), chronic obstructive lung disease (8%), venous thromboembolism (6%), and renal disease (5%) {Huang Y 2021}.

Findings from a nation-wide cohort of Danish women diagnosed with breast cancer from 2000-2010 indicated that premenopausal women with diabetes were more than 2.5-times more likely to have HER2-negative tumors compared to premenopausal women without diabetes. In addition to diabetes, other metabolic diseases such as obesity, hypertriglyceridemia, and hypertension have been highlighted as possible predictors for mortality and disease progression among women with HR+/HER2- breast cancer {Agresti 2016, Dong 2021}.

PART II: MODULE SII - NONCLINICAL PART OF THE SAFETY SPECIFICATION

Sacituzumab govitecan (SG), also known as IMMU-132, is an antibody drug conjugate (ADC) that comprises SN-38, a topoisomerase I inhibitor, coupled by a linker (CL2A) to the humanised monoclonal antibody hRS7 IgG1κ which binds to Trop-2.

Based on its intended use in patients with mTNBC and HR+/HER2- mBC, the nonclinical development of SG followed ICH S9 guidance. Cynomolgus monkeys were identified as the only relevant species with cross-reactivity of the target, Trop-2, with the hRS7 antibody (the binding moiety of SG). Primary pharmacology could also be tested in murine xenograft models bearing human tumors (which express human Trop-2).

Binding of the Trop-2 binding antibody portion of the ADC, hRS7 IgG, was assessed using standard tissue cross-reactivity studies in human and monkey tissues. Repeat-dose toxicity studies of up to 4 cycles (up to Day 71) and with up to 6-week recovery period were conducted in Cynomolgus monkeys. Toxicokinetic assessments comprised hRS7 antibody, free SN-38, total SN-38, as well as glucuronidated SN-38 (SN-38G). The pharmacokinetics of these analytes have been characterised in serum/blood as well as in various tissues including tumour tissue in tumour-bearing mice. Furthermore, the occurrence of anti-drug antibodies was assessed in monkeys. SN-38 was tested for mutagenicity, aneugenicity and clastogenicity. In agreement with ICH S9, neither carcinogenicity, nor effects of SG on fertility, early embryonic development, or pre- and post-natal development have been assessed.

The pharmacology of SN-38 is well known through nonclinical and clinical investigations of its prodrug, irinotecan {CAMPTOSAR 2020}. An extensive pharmacology examination was not necessary as part of the development programme of SG. SN-38 released from SG is expected to behave in a similar manner as SN-38 generated from irinotecan.

Table SII.1. Table of Key Safety Findings from Nonclinical Studies

Key Safety Findings from Nonclinical studies	Relevance to Human Usage
Toxicity	
Acute or repeat-dose toxicity studies Tumour xenograft studies in mice showed no evidence of toxicity for a dose of up to 0.5 mg SG/injection x 8 injections over 4 weeks (2.4 Nonclinical Overview; Study 022714-281; Study 120415-337). Two exploratory, non- Good Laboratory Practice (GLP)-compliant, repeat-dose toxicity studies were performed in Swiss-Webster mice (Study 100209-143; Study 122109-151). SG 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 haematological toxicity and no abnormal histology findings. Transient increases in hepatic transaminases were observed that returned to normal by the end of the study. In the latter study a MES buffer (2-[N-morpholino] ethanesulfonic acid) was substituted for the previously used NaOAc (sodium acetate) buffer; this change had no influence on the tolerability of the product.	The overall appearance of toxicological findings was essentially identical to that known from irinotecan, the pro-drug of SN-38. Main targets of toxicity were the hemolymphopoietic system, the gastrointestinal tract, and the female reproductive organs. As per the primary toxicities seen in nonclinical studies, the clinical development programme showed a similar pattern. Neutropenia occurred in 65.1% participants treated in Study IMMU-132-05 (Module SVII.3.1.1). Grade 3 and Grade 4 neutropenia were observed in 35.7% and 17.8% participants, respectively. Most cases of neutropenia were nonfebrile, nonserious, and resulted in a treatment interruption. Infections potentially associated with neutropenia occurred in 10.9% participants in the SG group, including 3.5% Grade 3 infections and 0.8% Grade 4 infections (Table SVII.7., Module SVII.3.1.1).

Key Safety Findings from Nonclinical studies	Relevance to Human Usage
Two GLP-compliant, repeat-dose toxicity studies were performed in Cynomolgus monkeys (Study SNBL.160.03; Study SNBL.160.25). SG was administered by 1-hour intravenous (IV) infusion for 2 doses (60 or 120 mg/kg) 3 days apart (Days 1 and 4) followed by a 4-week recovery period. In the second study, SG was administered at dose levels of 12.5, 25, and 50 mg/kg via a 1-hour infusion on Days 1, 8, 22, 29, 43, 50, 64, and 71 (ie, 4 treatment cycles of Days 1 and 8 per 21-day cycle). Administration was well tolerated with no unscheduled deaths throughout the study and no adverse test article-related changes noted in any of the evaluated parameters. SG administered at 50 mg/kg/dose (human equivalent dose [HED] = 16 mg/kg/dose) for 4 treatment cycles was considered the No Observed Adverse Effect Level (NOAEL). Doses ≥60 mg/kg (≥6 times the human recommended dose of 10 mg/kg based on body weight) resulted in endometrial atrophy, uterine haemorrhage, increased follicular atresia of the ovary, and atrophy of vaginal epithelial cells, whilst 120 mg/kg was associated with lethality (2.6.6. Toxicology Written Summary). 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 tract (necrosis, erosions, inflammation, fibrosis, haemorrhage, oedema). Primary toxicities were confirmed as neutropenia and gastrointestinal disturbances, which are the expected side-effects of SN-38 derived from irinotecan (2.4 Nonclinical Overview). No severe histopathological damage to Trop-2-expressing normal tissues was observed.	In Study IMMU-132-09, neutropenia occurred in 72.8% participants (Module SVII.1.2.1). Grade 3 and Grade 4 neutropenia were observed in 34.0% and 20.9% participants, respectively. Most cases of neutropenia were nonfebrile and nonserious, and approximately half resulted in a treatment interruption. Infections potentially associated with neutropenia occurred in 9.7% participants in the SG group, including 3.4% Grade 3 infections and 0.4% Grade 4 infections (Table SVII.8., Module SVII.3.1.1). “Serious infections secondary to neutropenia” is an important identified risk (Module SVII.1.2.1). Cases of diarrhoea were generally <Grade 3, nonserious, and did not lead to either a treatment interruption or dose reduction. Severe diarrhoea (Common Terminology Criteria for Adverse Events [CTCAE] severity Grade ≥3) occurred in 11.2% participants and no participants discontinued SG treatment because of severe diarrhoea in Study IMMU-132-05 (RMP Table 15.1.2.2). In Study IMMU-132-09, severe diarrhoea occurred in 10.1% participants and 0.4% participants discontinued SG treatment because of severe diarrhoea (HR+/HER2- mBC Table 14.3.2.16.2, Module SVII.1.1). Severe diarrhoea is not considered an important risk (Module SVII.1.1). Grade 1 or Grade 2 pooled nausea and vomiting occurred in 63.1% participants treated with SG in Study IMMU-132-05, whilst 2.7% pooled nausea and vomiting events were Grade 3 and 0.4% Grade 4 (Table SVII.3, Module SVII.1.1). Nausea AEs occurred more frequently than vomiting AEs in both the SG group (62.4% vs 33.3%) and TPC group (30.4% vs 16.1%), respectively (Table SVII.4, Module SVII.1.1). In the SG group, 11.2% participants experienced Grade 3 nausea AEs, 1.2% Grade 3 and 0.4% Grade 4 vomiting AEs. No Grade 4 nausea events occurred. In Study IMMU-132-09, most events of nausea and vomiting were Grade 1 or Grade 2 (HR+/HER2- mBC ISS IA2 Table 14.3.2.3.1). Nausea AEs occurred more frequently than vomiting AEs in both the SG group (58.6% vs 23.9%) and TPC group (34.9% vs 15.7%), respectively (Table SVII.4, Module SVII.1.1). In the SG group, 0.7% participants experienced Grade 3 and 0.4% Grade 4 nausea AEs, 1.1% Grade 3 and 0% Grade 4 vomiting AEs. Nausea and vomiting are not considered important risks (Module SVII.1.1). Effects on female reproductive organs were not observed in the clinical development programme.
Reproductive/developmental toxicity Based on the outcome of the genotoxicity studies (see below), and in line with ICH S9 guidance, embryo-foetal development toxicity studies were not necessary.	In the clinical development programme, pregnant women and women of childbearing potential unwilling to use highly effective contraception were excluded from participation because of the potential harm that SG could have on the foetus (Module SIV.1). There are limited data available for SG exposure in pregnant women in the clinical and post-marketing setting (Module SIV.3). Based on the nonclinical genotoxicity findings and the mechanism of action for SG (similar to that of irinotecan), embryo-foetal toxicity is a risk for SG. However, it is not considered an important risk (Module SVII.1.1).

Key Safety Findings from Nonclinical studies	Relevance to Human Usage
Genotoxicity SG contains a genotoxic component, SN-38, and targets rapidly dividing cells. SN-38 was negative for mutagenicity in a bacterial reverse mutation Ames test, both in the absence and presence of metabolic activation (Study CYP1595_R1a). As expected, and in line with the genotoxic properties of irinotecan, SN-38, the active metabolite of irinotecan, induced the formation of micronuclei in an in vitro mammalian (CHO-K1) cell micronucleus test (Study CYP1595_R1b). The lack of a consistent increase in hypodiploidy suggested that SN-38 is clastogenic, not aneugenic.	The genotoxicity results for SN-38 were not different from those reported for irinotecan, in that SN-38 was found not to be mutagenic but was clastogenic, supportive of embryo-foetal toxicity being considered a risk for SG. However, it is not considered an important risk (Module SVII.1.1).
Carcinogenicity In accordance with ICH S9, carcinogenicity studies have not been conducted with SG given the intended treatment of patients with advanced cancer.	Not applicable.
Safety pharmacology	
No designated safety pharmacology studies were performed, but clinical signs, body temperatures, respiratory rates, electrocardiograms (ECGs), heart rate and blood pressure were assessed in the repeat dose toxicity studies of SG in Cynomolgus monkeys (Study SNBL.160.03; Study SNBL.160.25). There were no treatment-related clinical findings indicating an influence on the central nervous system (CNS). There were no changes in body temperature, respiratory rate, ECG, blood pressure, or heart rate. All ECGs evaluated in the 2 Cynomolgus monkey studies were qualitatively and quantitatively normal for primates. There was no treatment-related effect on QT or corrected QT (QTc) intervals.	The nonclinical pharmacology studies of SG demonstrated strong in vivo anti-tumour efficacy of the product, thus supporting its use in patients with Trop-2 expressing cancers. Secondary and safety pharmacology studies did not reveal any findings that would indicate a concern for the continued clinical development and use in humans of SG. In the clinical development programme SG was not found to cause significant nervous system or cardiac toxicity. In Study IMMU-132-05, the most frequently reported AEs in the Nervous system disorders system organ class (SOC) in participants treated with SG (N=258) and single-agent chemotherapy (ie, treatment of physician's choice [TPC]; either eribulin, capecitabine, gemcitabine, or vinorelbine) (N= 224) were headache (17.8% vs 12.5%), dizziness (10.1% vs 7.1%) and dysgeusia (8.5% vs 2.7%) respectively (TNBC ISS Table 14.3.2.2.1). There were only 2 Grade 3 AEs relating to these preferred terms (PTs) of headache (0.8%) in participants treated with SG and 1 Grade 3 headache AE (0.4%) in a participant treated with TPC; there were no dizziness or dysgeusia AEs of Grade ≥3 severity in either group (TNBC ISS Table 14.3.2.3.1). In Study IMMU-132-09, the most frequently reported AEs in the Nervous system disorders SOC in participants treated with SG (N=268) and TPC (N=249) were headache (16.4% vs 14.5%), dizziness (8.2% vs 4.4%), dysgeusia (4.5% vs 4.8%), and neuropathy peripheral (4.5% vs 8.0%), respectively (HR+/HER2- mBC ISS IA2 Table 14.3.2.2.1). Of these PTs, there was only 1 Grade 3 AE of headache (0.4%) in a participant treated with SG and 2 Grade 3 headache AEs (0.8%) in participants treated with TPC; there was no dizziness in participants treated with SG and 1 Grade 3 dizziness AE (0.4%) in a participant treated with TPC. There were no dysgeusia AEs of Grade ≥3 severity in either group (HR+/HER2- mBC ISS IA2 Table 14.3.2.6.1).

Key Safety Findings from Nonclinical studies	Relevance to Human Usage
	In the Cardiac disorders SOC, the most frequently reported AEs in participants treated with SG and TPC in Study IMMU-132-05 were sinus tachycardia (2.3% vs 0.9%), tachycardia (1.9% vs 2.2%), and palpitations (1.9% vs 0.9%) respectively (TNBC ISS Table 14.3.2.2.1). The majority of these AEs were of Grade 1 or 2 severity, with Grade ≥3 severity AEs only reported in the TPC group including sinus tachycardia (0.4%) and tachycardia (0.4%) (TNBC ISS Table 14.3.2.3.1). In Study IMMU-132-09, the most frequently reported AEs in the Cardiac disorders SOC in participants treated with SG and TPC were tachycardia (2.2% vs 2.0%), sinus tachycardia (1.5% vs 1.2%), and palpitations (1.1% vs 1.2%), respectively (HR+/HER2- mBC ISS Table 14.3.2.2.1). The majority of these AEs were of Grade 1 or 2 severity, with Grade ≥3 severity AEs only reported in the TPC group, tachycardia (0.4%) (HR+/HER2- mBC ISS Table 14.3.2.6.1). In Study IMMU-132-05, mean and median changes from baseline over time in ventricular rate and the QT, corrected QT interval based on Bazett's formula (QTcB), corrected QT interval based on Fridericia's formula (QTcF), PR, QRS, and RR intervals over time were similar in the SG and TPC groups (TNBC ISS Table 14.3.5.2.1). A slightly higher percentage of patients in the SG group compared with the TPC group had treatment-emergent maximum QTcB (4.7% vs 1.8%) and QTcF (4.3% vs 1.8%) changes >60 msec and QTcB (4.3% vs 1.8%) values of >500 msec, respectively (TNBC ISS Table 14.3.5.2.1). However, there was no difference between the SG and TPC groups in the percentage of participants with AEs of tachycardia or arrhythmia (4.3% and 3.5%, respectively) (TNBC ISS Table 14.3.2.2.1). In Study IMMU-132-09, mean and median changes from baseline over time in ventricular rate and the QT, corrected QT interval based on Fridericia's formula (QTcF), PR, QRS, and RR intervals were minimal in the SG treatment arm (HR+/HER2- mBC ISS IA2 Table 14.3.5.1.1). Treatment-emergent maximum QTcF changes >60 msec and QTcF values of >500 msec occurred in 1.3% and 1.7% of participants in the SG group, respectively (HR+/HER2- mBC ISS IA2 Table 14.3.5.2.1). The percentage of participants with AEs of tachycardia (2.2% and 2.0%, respectively) or arrhythmia (0.4% and 0%, respectively) was similar between the SG and TPC groups (HR+/HER2- mBC ISS IA2 Table 14.3.2.2.1). A pharmacokinetic-electrocardiogram (PK-ECG) substudy of 29 patients from the SG group in Study IMMU-132-05 was conducted to assess the effects of SG on cardiac repolarisation (QTc interval) and other ECG parameters. No evidence for QTc prolongation was seen with SG in the PK ECG sub study of Study IMMU-132-05 (CSR IMMX-PMX-SN38-2457).

Key Safety Findings from Nonclinical studies	Relevance to Human Usage
Mechanisms for drug interactions	
No drug-drug interaction studies were conducted with either SG or its components **(**2.7.2 Summary of Clinical Pharmacology).	The metabolism of SG is mediated by both catabolism of the antibody into individual amino acids and metabolism of SN-38 (the small molecule moiety of SG) by uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1) in the liver to form the inactive metabolite, SN-38 glucuronide (SN-38G) (HR+/HER2- mBC 2.7.2 Summary of Clinical Pharmacology). Concomitant administration of SG with inhibitors of UGT1A1 may increase the incidence of adverse reactions due to potential increase in systemic exposure to SN-38. SG should be used with caution in patients receiving UGT1A1 inhibitors. Exposure to SN-38 may be reduced in patients concomitantly receiving UGT1A1 enzyme inducers. SG should be used with caution in patients receiving UGT1A1 inducers.
Other toxicity-related information or data	
Local tolerance Local tolerance was evaluated in the GLP-compliant monkey studies (Study SNBL.160.03; Study SNBL.160.25). Although changes were observed at the injection site, these findings were considered related to procedural trauma and not the test article, consisting of mild to moderate perivascular haemorrhage, moderate haemorrhage in the dermis and subcutis, and minimal to mild perivascular mixed cell infiltration.	In the clinical development programme local reactions were observed rarely. In Study IMMU-132-05, injection site reaction and infusion site bruising each occurred in 1 participant (0.4%) in the SG group (TNBC ISS Table 14.3.2.2.1). Injection site reaction and infusion site bruising were both of Grade 1 severity and nonserious (TNBC ISS Table 14.3.2.3.1; Table 14.3.2.5.1). In Study IMMU-132-09, injection site reaction occurred in 1 participant (0.4%) in the SG group (HR+/HER2- mBC ISS Table 14.3.2.2.1). Infusion site bruising did not occur in any participants in the SG group. Injection site reaction was Grade 1 severity and nonserious (HR+/HER2- mBC ISS Table 14.3.2.2.1; Table 14.3.2.6.1).

Conclusions from the nonclinical development programme

The nonclinical studies that evaluated the pharmacologic, pharmacokinetic, and toxicologic properties of SG support the clinical use of SG for the treatment of unresectable locally advanced or metastatic TNBC and HR+/HER2- mBC. Nonclinical findings which could have relevance for use in humans include the primary toxicities of neutropenia and gastrointestinal disturbances as seen in Cynomolgus monkeys. Based on these nonclinical findings, clinical data have confirmed the safety concerns of neutropenia and severe diarrhea. A safety concern, based on nonclinical genotoxicity findings and the mechanism of action for SG, that has relevance for human usage and has not been adequately refuted by clinical data and/or is of unknown significance is embryo-fetal toxicity.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

SIII.1. Clinical Trial Exposure

The tables in this section present exposure data to TRODELVY in participants with mTNBC and HR+/HER2- mBC from the following clinical studies:

Completed Phase 1 and 2 studies:

- Study IMMU-132-01 (NCT01631552), an uncontrolled, Phase 1/2 single-arm basket study in which SG monotherapy was evaluated in metastatic, epithelial cancers. This study included a cohort of participants with relapsed/refractory mTNBC.
  - Phase 1: a dose escalation, 3+3 design in which SG doses of 8, 10, 12, and 18 mg/kg were administered, with 2 SG doses, 8 mg/kg and 10 mg/kg, selected for further study in Phase 2.
  - Phase 2: interim analysis of efficacy and safety revealed higher response rates with a similar safety profile for the 10 mg/kg SG compared with 8 mg/kg dose and therefore the 10 mg/kg dose was selected for further study.

Completed Phase 3 studies:

- Study IMMU-132-05 (NCT02574455 and EudraCT 2017-003019-21), a confirmatory controlled Phase 3 study in mTNBC in which all participants received either a 10 mg/kg starting dose of SG or single-agent chemotherapy (ie, treatment of physician's choice [TPC]; either eribulin, capecitabine, gemcitabine, or vinorelbine).

Ongoing Phase 3 studies:

- Study IMMU-132-09 (NCT03901339 and EudraCT 2018-004201-33), Phase 3 Study of Sacituzumab Govitecan (IMMU-132) Versus Treatment of Physician's Choice (TPC) in participants with Hormonal Receptor-Positive (HR+) Human Epidermal Growth Factor Receptor 2 (HER2) Negative Metastatic Breast Cancer (mBC) who have failed at least two prior chemotherapy regimens.

The key datasets for safety evaluation in this RMP are the primary safety analysis sets for mTNBC and HR+/HER2- mBC, and the Overall Targeted mTNBC, the Overall Targeted HR+/HER2- mBC, and the Overall Target mBC pools:

- The primary safety analysis set for mTNBC (IMMU-132-05 SG) consists of 258 patients with mTNBC in Study IMMU-132-05 who received a 10 mg/kg starting dose of SG (data cutoff date 18 September 2020).

- The primary safety analysis set for HR+/HER2- mBC (IMMU-132-09 SG) consists of 268 patients with HR+/HER2- mBC in Study IMMU-132-09 who received a 10 mg/kg starting dose of SG (data cutoff date 01 July 2022).

- The Overall Targeted mTNBC pool (N=366) includes mTNBC patients who received a starting dose of 10 mg/kg SG in Study IMMU-132-01 and all patients treated with SG in Study IMMU-132-05. Pooling of these data was appropriate because of the similar design, participant selection criteria, conduct, and safety monitoring in the 2 clinical studies, and because patients who received either lower or higher starting doses of SG were excluded (data cutoff date 18 September 2020).

- The Overall Targeted HR+/HER2- mBC pool (N=322) includes participants with HR+/HER2− mBC from Study IMMU-132-01 treated with SG 10 mg/kg (N=54) and all participants from Study IMMU-132-09 treated with SG (N=268) (IMMU-132-01 final database lock date 02 April 2021; IMMU-132-09 data cutoff date 01 July 2022).

- The Overall Targeted mBC pool (N=688) includes participants with HR+/HER2− mBC (N=54) and participants with mTNBC from Study IMMU-132-01 treated with SG 10 mg/kg (N=108) and all participants from Studies IMMU-132-09 (N=268) and IMMU-132-05 (N=258) treated with SG (IMMU-132-01 final database lock date 02 April 2021; IMMU-132-05 final database lock date 25 February 2021; IMMU-132-09 data cutoff date 01 July 2022).

Exposure data are presented by duration of treatment (Table SIII.1), by number of infusions and treatment cycles (Table SIII.2), by age and gender (Table SIII.3; Table SIII.4), and by race (Table SIII.6).

Table SIII.1. SG Exposure by Duration of Treatment (mTNBC and HR+/HER2- mBC)

	Overall Targeted mTNBC (N = 366)	**Overall Targeted HR+/HER2- mBC (N = 322)**	**Overall Targeted mBC (N = 688)**
Duration of Treatment (months)[1]			
Mean (SD)	6.2 (6.07)	6.05 (6.32)	6.33 (6.82)
Median	4.9	4.16	4.63
Min, Max	0, 51	0.03, 38.44	0.03, 62.55
≥ 6 months	139 (38.0)	116 (36.0%)	255 (37.1%)
≥ 12 months	45 (12.3)	45 (14.0%)	93 (13.5%)
≥ 24 months	6 (1.6)	9 (2.8%)	22 (3.2%)
≥ 36 months	1 (0.3)	1 (0.3%)	4 (0.6%)

1 Duration of treatment (months) = (date of last dose of study drug – date of first dose of study drug + 1)/30.4375.
Max=maximum; min=minimum; SD=standard deviation; SG=sacituzumab govitecan; TNBC=triple negative breast cancer.
Source: TNBC 2.7.4 Summary of Clinical Safety Table 8; TNBC ISS Table 14.3.1.1, HR+/HER2- mBC ISS Table 14.3.1.1

Table SIII.2. SG Exposure by Number of Infusions and Cycles (mTNBC and HR+/HER2- mBC)

	Overall Targeted mTNBC (N = 366)	Overall Targeted HR+/HER2- mBC (N = 322)	Overall Targeted mBC (N = 688)
Number of Infusions Administered			
Mean (SD)	17.6 (16.52)	17.20 (17.195)	17.97 (18.492)
Median	14.0	12.00	13.00
Min, Max	1, 146	1, 103	1, 178
Number of Treatment Cycles Received[1]			
n	366	322	688
Mean (SD)	9.0 (8.31)	8.89 (8.726)	9.24 (9.356)
Median	7.0	6.00	7.00
Min, Max	1, 73	1, 52	1, 90

1 Cycles are counted if subject received at least 1 dose in that cycle
Max=maximum; min=minimum; SD=standard deviation; TNBC=triple negative breast cancer.
Source: TNBC 2.7.4 Summary of Clinical Safety Table 8; TNBC ISS Table 14.3.1.1, HR+/HER2- mBC ISS Table 14.3.1.1

Table SIII.3. SG Exposure by Age and Gender (mTNBC and HR+/HER2- mBC)

	Overall Targeted mTNBC (N = 366)	Overall Targeted HR+/HER2- mBC (N = 322)	Overall Targeted mBC (N = 688)
Age, years			
Mean (SD)	54.1 (11.12)	57 (11.4)	55 (11.3)
Median	54.0	57	55
Min, Max	27, 82	29, 86	27, 86
Age Group, n (%)			
<50 years	129 (35.2)	83 (25.8%)	212 (30.8%)
50 to 64 years	169 (46.2)	155 (48.1%)	324 (47.1%)
≥65 years	68 (18.6)	84 (26.1%)	152 (22.1%)
Gender, n (%)			
Male	3 (0.8)	1 (0.3%)	4 (0.6%)
Female	363 (99.2)	321 (99.7%)	684 (99.4%)

Denominator for percentages was big N.
SD=standard deviation; SG=sacituzumab govitecan; TNBC=triple negative breast cancer.
Age (in years) was collected on the date of first study drug dosing (Day 1).
Source: TNBC 2.7.4 Summary of Clinical Safety Table 11; TNBC ISS Table 14.1.2.1.1, HR+/HER2- mBC ISS Table 14.1.2.1.1

Table SIII.4. SG Exposure in Overall Targeted mTNBC Population by Age and Gender

	Overall Targeted mTNBC (N = 366)		
Age Group	**Males**	**Females**	**Total**
<50 years	0 (0.0)	129 (35.5)	129 (35.2)
50 to 64 years	2 (66.7)	167 (46.0)	169 (46.2)
65 to 74 years	1 (33.3)	57 (15.7)	58 (15.8)
75 to 84 years	0 (0.0)	10 (2.8)	10 (2.7)
≥85 years	0 (0.0)	0 (0.0)	0 (0.0)
Total	3 (100.0)	363 (100.0)	366 (100.0)

SG=sacituzumab govitecan; TNBC=triple negative breast cancer.
Source: TNBC ISS Table 15.1.1

Table SIII.5. SG Exposure in Overall Targeted HR+/HER2- mBC and Overall Targeted mBC Populations by Age and Gender

	Overall Targeted HR+/HER2- mBC (N = 322)			Overall Targeted mBC (N = 688)		
	Males	**Females**	**Total**	**Males**	**Females**	**Total**
<50 years	0	83 (25.9%)	83 (25.8%)	0	212 (31.0%)	212 (30.8%)
50 to 64 years	1 (100%)	154 (48.0%)	155 (48.1%)	3 (75.0%)	321 (46.9%)	324 (47.1%)
65 to 74 years	0	66 (20.6%)	66 (20.5%)	1 (25.0%)	123 (18.0%)	124 (18.0%)
75 to 84 years	0	17 (5.3%)	17 (5.3%)	0	27 (3.9%)	27 (3.9%)
≥85 years	0	1 (0.3%)	1 (0.3%)	0	1 (0.1%)	1 (0.1%)
Total	1 (100.0%)	321 (100.0%)	322 (100.0%)	4 (100.0%)	684 (100.0%)	688 (100.0%)

Denominator for percentages was big N.
Source: HR+/HER2- mBC ISS Table 14.2.1.1

Table SIII.6. SG Exposure by Race (mTNBC and HR+/HER2- mBC)

	Overall Targeted mTNBC (N = 366)	Overall Targeted HR+/HER2- mBC (N = 322)	Overall Targeted mBC (N = 688)
Race, n (%)			
White	293 (80.1)	224 (69.6)	517 (75.1)
Black or African American	33 (9.0)	8 (2.5)	41 (6.0)
Asian	14 (3.8)	12 (3.7)	26 (3.8)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
Other	26 (7.1)	10 (3.1)	36 (5.2)
Not reported	0	68 (21.1)	68 (9.9)

Denominator for percentages was big N.
SG=sacituzumab govitecan; TNBC=triple negative breast cancer, HR+/HER2- mBC=
Source: TNBC 2.7.4 Summary of Clinical Safety Table 11; TNBC ISS Table 14.1.2.1.1, HR+/HER2- mBC ISS Table 14.1.2.1.1
Not Reported = local regulators did not allow collection of race or ethnicity information

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Exclusion criteria to ensure standardisation of the study population that are common to most clinical studies are not presented, including:

Study IMMU-132-05

- Other concurrent medical or psychiatric conditions that, in the Investigator's opinion, were likely to confound study interpretation or prevent completion of study procedures and follow-up examinations
- Any anticancer therapy or any other chemotherapeutic agents for a minimum of 2 weeks before the start of SG administration
- High-dose systemic corticosteroids within 2 weeks of study entry

Study IMMU-132-09

- Any medical or other condition which, in the opinion of the Investigator, causes the participant to be medically unfit to receive sacituzumab govitecan or unsuitable for any other reason
- Treatment with chemotherapy, radiation, or small molecule targeted therapy within 2 weeks and biological therapy within 4 weeks prior to the first dose of study treatment
- Current enrollment in another clinical study or used any investigational device or drug either within 5 half-lives or 28 days prior to randomization, whichever is longer
- Existing anticancer treatment-related AEs of Grade ≥ 2 (except for alopecia and Grade 2 neuropathy) according to NCI-CTCAE v5.0
- Known hypersensitivity or intolerance to any of the study drugs or any of the excipients
- Is receiving any medication prohibited in combination with the study treatment(s) as described in the respective product labels, unless medication was stopped within 7 days prior to randomization
- Locally-advanced MBC (stage IIIc) in participants who are candidates for curative intent therapy at the time of study enrollment

Exclusion criteria related to ongoing or recent conditions or treatments that may interfere with the study results and impact the safety and efficacy assessment of SG are similarly not presented, including:

Study IMMU-132-05

- Non-melanoma skin cancer or carcinoma in situ of the cervix were eligible; patients with other prior malignancies must have had at least a 3-year disease-free interval
- Active chronic inflammatory bowel disease (ulcerative colitis, Crohn's disease) and patients with a history of bowel obstruction
- Human immunodeficiency virus (HIV), hepatitis B, or hepatitis C positive
- History of any of the following:
  - Unstable angina, myocardial infarction, or congestive heart failure present within 6 months of randomisation or a clinically significant cardiac arrhythmia (other than stable atrial fibrillation) requiring anti-arrhythmia therapy
  - Clinically significant active chronic obstructive pulmonary disease or other moderate-to-severe chronic respiratory illness present within 6 months of randomisation
  - Clinically significant bleeding, intestinal obstruction, or gastrointestinal perforation within 6 months of randomisation
- Rapid deterioration during screening prior to randomisation (eg, significant change in performance status, ≥20% decrease in serum albumin levels, unstable pain symptoms requiring modifications in analgesic management)

Study IMMU-132-09

- Previous treatment with a topoisomerase 1 inhibitor as a free form or as other formulations
- Any other malignancy that required treatment or has shown evidence of recurrence (except for non-melanoma skin cancer or histologically-confirmed complete excision of carcinoma in situ) during the 5 years prior to enrollment in this study
- Has active chronic inflammatory bowel disease (ulcerative colitis, Crohn's disease) and participants with a history of bowel obstruction
- Active hepatitis B virus (positive hepatitis B surface antigen) or active hepatitis C virus (measurable viral ribonucleic acid (RNA) load with polymerase chain reaction) infection
- History of significant cardiovascular disease, defined as:
  - Congestive heart failure greater than New York Heart Association (NYHA) Class II according to the NYHA Functional Classification
  - Unstable angina or myocardial infarction within 6 months before enrollment
  - Serious cardiac arrhythmia

- Clinically-significant ECG abnormality, including any of the following:

  — Marked Baseline prolonged QT/QTc interval (i.e., a repeated demonstration of a QTc interval > 500 ms) demonstrated on ECG at Screening. QTcF is calculated by Fridericia's formula

$$QTc_F = \frac{QT}{\sqrt[3]{\frac{RR}{(1s)}}}$$

  — History of risk factors for torsade de pointes (e.g., heart failure, hypokalemia, family history of long QT Syndrome)

- Has known active central nervous system metastases and/or carcinomatous meningitis. Participants may participate provided they have stable brain metastasis. All participants with carcinomatous meningitis are excluded regardless of clinical stability. Stable brain metastasis is defined in inclusion criterion

- Scheduled surgery during the study, other than minor surgery which would not delay study treatment

- If required per local guidelines, any participant with a blood uracil level ≥ 150 ng/mL is excluded from receiving capecitabine as TPC (Note: blood uracil level will be assessed at Screening for all participants eligible to be randomized to capecitabine as TPC)

Table SIV.1. Important Exclusion Criteria in Pivotal Studies in the Development Programme

Criterion	Reason for Exclusion	Considered to be Missing Information
Women who were pregnant or lactating, women of childbearing potential or fertile men unwilling to use highly effective contraception during study and up to 6 months after treatment discontinuation in women of child-bearing potential and 3 months in fertile males post last study drug.	Based on the nonclinical genotoxicity findings and the mechanism of action for SG (similar to that of irinotecan), embryo-foetal toxicity is an important safety concern and these patients were excluded from the clinical development programme for safety reasons, similar to the majority of investigative clinical studies.	No Rationale: Although no reproductive and developmental toxicity studies have been performed, the nonclinical genotoxicity observations for SG and the known embryotoxic and teratogenicity of irinotecan in animals indicate the active moiety of SG, SN-38, to be a potential safety hazard to the foetus. Based on its mechanism of action, SG can cause embryo-foetal toxicity but is not considered to be an important risk (Module SVII.1.1). The TRODELVY summary of product characteristics (SmPC) provides recommendations in the case of pregnancy and advises healthcare professionals to verify the pregnancy status of women of reproductive potential prior to use and that women of reproductive potential should use effective contraception during treatment with SG and for 6 months after the last dose. Male patients with female partners of reproductive potential should use effective contraception during treatment with SG and for 3 months after the last dose.

Criterion	Reason for Exclusion	Considered to be Missing Information
Gilbert's disease (Study IMMU-132-05) Known Gilbert's disease with total bilirubin >3 x institutional upper limit of normal (ULN) (Study IMMU-132-09)	Gilbert's disease is a condition where the liver does not properly process bilirubin leading to elevated levels in the bloodstream due to mutation of the UGT1A1 gene {McKusick 1986}. Reduced expression of UGT1A1 enzymes in the liver leads to reduced glucuronidation of SN-38, increasing systemic exposure to SN-38 which may increase the incidence of adverse reactions including neutropenia and diarrhoea. Patients with known Gilbert's disease were excluded from the study to avoid confounding factors that might impact the assessment of the efficacy and safety of SG.	No Rationale: Whilst the appropriate dose for patients with Gilbert's syndrome and reduced UGT1A1 activity is not known, individual patient tolerance to treatment can be taken into consideration and dose modifications introduced to manage any resultant adverse reactions such as severe neutropenia. The TRODELVY SmPC recommends that patients with known reduced UGT1A1 activity are closely monitored for adverse reactions.
Infection requiring IV antibiotic use within 1 week of randomisation (Study IMMU-132-05) Active serious infection requiring antibiotics (Study IMMU-132-09)	Nonclinical studies confirmed neutropenia as a primary toxicity of SG treatment (Part II: Module SII), and neutropenia is one of the expected side effects of SN-38 derived from irinotecan {CAMPTOSAR 2020}. Patients with pre-existing infection were excluded from study participation as administration of a neutropenia-causing agent to an infectious process can potentially lead to a worsening of the existing infection.	No Rationale: It is not expected that SG treatment will be initiated in patients with infection requiring IV antibiotic use due to the potential to worsen the infection.
Previously received irinotecan (Study IMMU-132-05)	SG is an ADC and delivers targeted cytotoxic chemotherapy to tumors through the binding of Trop-2 on the cell surface and release of the camptothecin-derived agent, SN-38. The activity of conventional irinotecan therapy, although not targeted, is based upon SN-38, which is the active metabolite of irinotecan. Patients who had previously received irinotecan and hence had been exposed to SN-38 were excluded to avoid confounding factors that might impact the assessment of the efficacy and safety of SG, which similarly provides exposure to SN-38.	No Rationale: It is not expected that there will be substantial use of SG in patients previously treated with irinotecan as very few patients with TNBC get treated with irinotecan. As the mean terminal t½ of free SN-38 is 17.4-19.7 hours, previous exposure to irinotecan is not expected to impact the safety of the patient (2.7.2 Summary of Clinical Pharmacology Table 11).
Received a live vaccine within 30 days of randomisation	Live vaccines use a weakened (or attenuated) form of the virus or bacteria causing a disease to emulate a natural infection. Since treatment with SG can compromise the immune system, there is a risk of generalised reaction to live attenuated vaccines that could be fatal. Further, live vaccines are not generally administered in patients actively receiving chemotherapy. Concomitant administration of a live vaccine is contraindicated during treatment with irinotecan and for 6 months following discontinuation of chemotherapy {CAMPTO 2018}.	No Rationale: Since live vaccines are not generally administered in patients actively receiving chemotherapy, concomitant administration of live vaccines with SG is not expected in TNBC or HR+/HER2- mBC patients.

Criterion	Reason for Exclusion	Considered to be Missing Information
Strong inhibitors or inducers of cytochrome P450 (CYP) 3A4 because of the known interaction with irinotecan (Study IMMU-132-05)	Although the irinotecan prescribing information notes that exposure to irinotecan or its active metabolite, SN-38, is reduced in adult patients concomitantly receiving the CYP3A4 enzyme-inducing anticonvulsant phenytoin and strong CYP3A4 inducers, and patients receiving concomitant ketoconazole, a strong CYP3A4 and UGT1A1 inhibitor, have increased exposure to irinotecan and its active metabolite SN-38 {CAMPTOSAR 2020}, SN-38 is primarily metabolised via UGT1A1, and an impact of CYP3A inhibitors/inducers on SN-38 exposure is not anticipated.	No Rationale: SN-38 is primarily metabolised via UGT1A1, and an impact of CYP3A inhibitors/inducers on SN-38 exposure is not anticipated. The use of CYP3A4 inhibitors/inducers is now permitted in ongoing TRODELVY clinical studies. Any adverse reactions experienced by patients treated with strong inhibitors or inducers of CYP3A4 in clinical practice will be managed by the general guidance in the TRODELVY SmPC.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged exposure.

The Overall Targeted TNBC pool (N=366) includes mTNBC patients who received a starting dose of 10 mg/kg SG in Study IMMU-132-01 and all patients treated with SG in Study IMMU-132-05. Adverse reactions with a frequency greater than 1 in 122 could be detected if there was no background incidence. The Overall Targeted HR+/HER2- mBC pool (N=322) includes participants with HR+/HER2− mBC from Study IMMU-132-01 treated with SG 10 mg/kg (N=54) and all participants from Study IMMU-132-09 treated with SG (N=268). Adverse reactions with a frequency greater than 1 in 107 could be detected if there was no background incidence.

The duration of treatment in participants treated with SG in the Overall Targeted TNBC pool is limited beyond 12 months of treatment (≥6 months [139/366, 38.0%], ≥12 months [45/366, 12.3%], ≥24 months [6/366, 1.6%], ≥36 months [1/366, 0.3%]) (Table SIII.1). The median number of treatment cycles that participants received was 7 cycles (range 1, 73) (Table SIII.2). The duration of treatment in participants treated with SG in the Overall Targeted HR+/HER2- mBC pool is also limited beyond 12 months of treatment (≥6 months [116/322, 36.0%], ≥12 months [45/322, 14.0%], ≥24 months [9/322, 2.8%], ≥36 months [1/322, 0.3%]) (Table SIII.1). The median number of treatment cycles that participants received was 6 cycles (range 1, 73) (Table SIII.2). Adverse reactions with a long latency or cumulative effects are not expected but, similar to other medicinal products, patient exposure to SG in the clinical development programme is limited.

SIV.3. Limitations in Respect to Populations Typically Underrepresented in Clinical Trial Development Programmes

Table SIV.2. Exposure of Special Populations Included or not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development programme
Breastfeeding women	
Patients with relevant comorbidities:	
Patients with hepatic impairment	In the clinical development programme patients were included if they had adequate hepatic function (bilirubin ≤1.5 x upper limit of normal [ULN]; aspartate aminotransferase [AST] and alanine aminotransferase [ALT] ≤2.5 x ULN or ≤5 x ULN if known liver metastases; and serum albumin ≥3 g/dL). Patients with Gilbert's disease were excluded from Study IMMU-132-05 and those with bilirubin ≥3 x ULN or hepatitis B/C positive were excluded from Study IMMU-132-09 (Module SIV.1). Use in patients with moderate or severe hepatic impairment is an area of missing information (Module SVII.1.3) as most participants (60.8%) in the SG treatment group in Overall Targeted mBC had normal hepatic function (bilirubin <ULN) and 39.0% had mild hepatic impairment (2.7.4 Summary of Clinical Safety Table 5; Table 14.1.2.1.1). No participants treated with SG had bilirubin > 1.5 x ULN. To further characterise this safety concern, Study IMMU-132-15 will evaluate the use of SG in patients with moderate hepatic impairment (Part III.2).
Patients with renal impairment	In the clinical development programme patients were included if they had adequate renal function (creatinine clearance of >60 mL/min; serum albumin ≥3 g/dL). In the SG treatment group in the Overall Targeted mBC population, 92.7% of participants had a renal baseline function of creatinine clearance >60 mL/min and 7.0% had 30 mL/min to <60 (HR+/HER2-mBC ISS IA2 2.7.4 Summary of Clinical Safety Table 5; Table 14.1.2.1.1). SN-38 and SN-38 G are reported to be primarily excreted through the hepatobiliary route, with lesser amounts detected in the urine. Renal elimination is known to contribute minimally to the excretion of SN-38. Population PK analyses from Studies IMMU-132-01, IMMU-132-05, and IMMU-132-09 did not identify any clinically relevant effect of mild or moderate renal impairment on SG, free SN-38, or total antibody exposure (HR+/HER2-mBC ISS IA2 2.7.2 Summary of Clinical Pharmacology Section 3.2).

Type of Special Population	Exposure
Patients with cardiovascular impairment	Patients with known history of unstable angina, myocardial infarction, or congestive heart failure present within 6 months of randomisation or clinically significant cardiac arrhythmia (other than stable atrial fibrillation) requiring anti-arrhythmia therapy were excluded from participation (Part II: Module SIV.1). In the clinical development programme SG was not found to cause significant cardiac toxicity (Part II: Module SIII).
Immunocompromised patients	HIV positive patients were excluded from participation in Study IMMU-132-05 (Part II: Module SIV.1).
Patients with a disease severity different from inclusion criteria in clinical studies	The indications for SG are for the treatment of adult patients with unresectable or mTNBC who have received at least 2 or more prior systemic therapies, including at least one of them for advanced disease and for the treatment of adult patients with unresectable or metastatic HR-positive, HER2-negative breast cancer who have received endocrine-based therapy, and at least two additional systemic therapies in the advanced setting. For mTNBC, all the participants in the clinical development programme had previously received at least 2 prior anticancer therapies. For HR+/HER2- mBC, the median number of prior systemic regimens was 7 in the Overall Targeted HR+/HER2− mBC pool and 6 in the Overall Targeted mBC pool. The median number of prior chemotherapy regimens in any setting was 4 in the Overall Targeted HR+/HER2− mBC and Overall Targeted mBC pools (HR+/HER2- mBC ISS IA2 m2.7.4 Table 6, Table 14.1.3.1).
Population with relevant different ethnic origin	SG studies mainly comprised participants who were Not Hispanic or Latino ethnicity: 88% Not Hispanic or Latino, 4% Hispanic or Latino, 4% not reported, and 3% unknown (2.7.4 Summary of Clinical Safety Table 5; Table 14.1.2.1.1). The Overall Target mBC pool had similar ethnic distribution of 86.5%, 5.1%, 4.4%, and 3.8%, respectively (HR+/HER2- mBC ISS IA2 2.7.4 Summary of Clinical Safety Table 5; Table 14.1.2.1.1). The baseline demographics of participants treated with SG in the clinical development programme by race are presented in Table SIII.6 (Part II: Module SIII). Clinical pharmacology studies concluded that race (White, Black, Asian, Other) has no effect on exposure (AUC and Cmax) to either SG, free SN-38, or total antibody (HR+/HER2- mBC ISS IA2 2.7.2 Summary of Clinical Pharmacology).

Type of Special Population	Exposure
Subpopulations carrying relevant genetic polymorphisms	Patients with reduced UGT1A1 activity (ie, individuals who are homozygous for the UGT1A1*28 allele) are at increased risk of adverse reactions following initiation of SG treatment. In the clinical development programme, there was adequate representation of patients (10.3%; 71/688) in the Overall Target mBC population who were homozygous for the UGT1A1*28 allele (HR+/HER2- mBC ISS IA2 2.7.4 Summary of Clinical Safety Table 5; Table 14.1.2.1.1). In comparison, 39.5% (272/688) and 41.4% (285/688) of patients were heterozygous for the UGT1A1*28 allele and homozygous for the wild-type allele, respectively. AEs that occurred in a higher percentage (>10%) of patients who were homozygous for the UGT1A1*28 allele compared with patients who were either heterozygous or did not have this allele were diarrhoea, anaemia, decreased appetite, cough, peripheral oedema, febrile neutropenia and thrombocytopenia (HR+/HER2- mBC ISS IA2 2.7.4 Summary of Clinical Safety Table 33; Table 14.3.2.2.1.6). The percentage of patients with ≥Grade 3 AEs was higher in patients who were homozygous for the UGT1A1*28 allele compared with patients who were either heterozygous or did not have this allele (87.3% vs 75.0% and 68.4%, respectively) (HR+/HER2- mBC ISS IA2 Table 14.3.2.1.1.6). Grade 3 or higher AEs that were reported in a higher percentage (>5%) of participants who were homozygous for the UGT1A1*28 allele compared with patients who were either heterozygous or did not have this allele were neutropenia (49.1%, 52.9%, 60.6%), diarrhea (6.7%, 12.5%, 18.3%), anemia (8.1%, 7.4%, 15.5%), leukopenia (8.8%, 12.1%, 14.1%), and febrile neutropenia (4.6%, 5.9%, 14.1%)(HR+/HER2- mBC ISS IA2 2.7.4 Summary of Clinical Safety Table 34; Table 14.3.2.6.2). There was no trend seen for SG concentration/exposure by UGT1A1 genotype and the AEs of neutropenia, diarrhoea, or vomiting (HR+/HER2-mBC ISS IA2 m2.7.4 Section 5.1.6.3, Table 14.3.2.2.1.6).

PART II: MODULE SV - POSTAUTHORISATION EXPERIENCE

SV.1. Postauthorisation Exposure

SV.1.1. Method Used to Calculate Exposure

Patient exposure to marketed Trodelvy is estimated from Gilead sales data and prescription data and is reported in PSURs.

SV.1.2. Exposure

Cumulative patient exposure to Trodelvy from the first marketing approval in the US on 22 April 2020 up to 21 April 2023 is estimated to be 21,964 patients, including 5401 patients in the EU.

PART II: MODULE SVI- ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1. Potential for Misuse for Illegal Purposes

No studies have been conducted to evaluate the abuse and dependence potential of SG. Based on its mechanism of action and safety profile in TNBC, SG is not expected to be associated with the potential for abuse or dependence. As SG is administered as an IV infusion by medical personnel and administration by the patient will not occur, the potential for abuse is minimal.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1. Identification of Safety Concerns in the Initial RMP submission

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

The risks not considered important for inclusion in the list of safety concerns are presented in Table SVII.1 followed by the justification for each risk.

Table SVII.1. Reason for Not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP

Reason	List of Risks
Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)	Hepatotoxicity
Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated	None
Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered to by prescribers (eg, actions being part of standard clinical practice in each EU member state where the product is authorised)	Nausea and vomiting
	Severe diarrhoea
	Hypersensitivity
	Drug-drug interactions with UGT1A1 inhibitors and inducers
	Anaemia
Known risks that do not impact the risk-benefit profile	None
Other reasons for considering the risks not important:	Embryo-foetal toxicity

EU = European Union

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Hepatotoxicity

Hepatotoxicity was evaluated using the Hepatic disorders standardised MedDRA query (SMQ) (broad and narrow). Hepatotoxicity AEs occurred in a similar percentage of participants in the SG group compared with the TPC control group (24.0%; 62/258; 95% CI: 49, 77 vs 22.8%; 51/224; 95% CI: 39, 65, respectively) in Study IMMU-132-05 (Table SVII.2). Likewise, treatment-related hepatotoxicity AEs were similar for participants treated with SG compared with the TPC control group (9.7%; 25/258; 95% CI: 16, 36 vs 11.6%; 26/224; 95% CI: 17, 37), respectively.

Only 5.4% cases (14/258) in the SG group were severe (≥Grade 3) and 0.8% (2/258) serious (Table SVII.2). The most frequent events (>5%) were increased AST (11.2%), increased ALT (10.5%), and increased alkaline phosphatase (7.4%) (RMP Table 15.1.3.6). No case of hepatotoxicity caused permanent discontinuation of SG treatment. Fewer cases of hepatotoxicity in the SG group than the TPC group caused a treatment interruption (0.4% vs 1.8%). Hepatotoxicity led to dose reduction and treatment interruption each in only 1 participant (0.4%) treated with SG in Study IMMU-132-05.

In the Overall Targeted mTNBC population, the overall frequency of hepatotoxicity AEs was 25.4% (93/366; 95% CI: 77,111), reflecting what was observed in SG-treated participants in Study IMMU-132-05 (Table SVII.2).

Table SVII.2. Summary of Hepatotoxicity AEs in Study IMMU-132-05, Study IMMU-132-01 and Overall Targeted mTNBC Population

	IMMU-132-05 mTNBC SG Treated (N = 258)	IMMU-132-05 mTNBC TPC (N = 224)	IMMU-132-01 mTNBC SG Treated (N = 108)	Overall Targeted mTNBC (N = 366)
Hepatotoxicity[1], n (%) [95% CI]*				
Any adverse event	62 (24.0) [49, 77]	51 (22.8) [39, 65]	31 (28.7) [22, 41]	93 (25.4) [77, 111]
Serious adverse event	2 (0.8)	1 (0.4)	0 (0.0)	2 (0.5)
Treatment-related adverse event	25 (9.7) [16, 36]	26 (11.6) [17, 37]	19 (17.6) [12, 28]	44 (12.0) [32, 58]
Action taken				
Dose reduction	1 (0.4)	4 (1.8)	0 (0.0)	1 (0.3)
Interruption	1 (0.4)	4 (1.8)	1 (0.9)	2 (0.5)
Discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Outcome[2]				
Resulted in death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not resolved	35 (13.6)	32 (14.3)	18 (16.7)	53 (14.5)
Resolved with sequelae	7 (2.7)	2 (0.9)	2 (1.9)	9 (2.5)
Resolved	47 (18.2)	32 (14.3)	20 (18.5)	67 (18.3)
Unknown	1 (0.4)	1 (0.4)	0 (0.0)	1 (0.3)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Severity (worst grade)				
Grade 1	30 (11.6)	27 (12.1)	24 (22.2)	54 (14.8)
Grade 2	18 (7.0)	11 (4.9)	3 (2.8)	21 (5.7)
Grade 3	13 (5.0)	11 (4.9)	4 (3.7)	17 (4.6)
Grade 4	1 (0.4)	2 (0.9)	0 (0.0)	1 (0.3)
Grade 5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Percentages are based on N.
1 Hepatotoxicity is the Hepatic disorders SMQ (broad and narrow).
2 Subjects are counted according to the outcomes regardless of adverse events.
* 95% CI produced by exact binomial method in terms of frequencies as applied to the respective N in each group.
CI=confidence interval; MedDRA=Medical Dictionary for Regulatory Activities; mTNBC=metastatic triple negative breast cancer; SG=sacituzumab govitecan; SMQ=standardised MedDRA query; TNBC= triple negative breast cancer; TPC=treatment of physician's choice.
Source: TNBC Table 15.1.2.6.

Changes from baseline in liver function tests in SG-treated patients were similar in Studies IMMU-132-01 and IMMU-132-05 and in the Overall Targeted mTNBC population. The percentage of SG-treated patients with a Grade 3 or Grade 4 increase in a liver function test and the worst grade on study were also similar in Studies IMMU-132-01 and IMMU-132-05 and the Overall Targeted mTNBC population (TNBC ISS Table 14.3.3.2.1.1).

Overall, 5 patients with mTNBC and 4 patients with a different metastatic epithelial cancer in Study IMMU-132-01, had AST or ALT >3x ULN with concurrent total bilirubin >2x ULN within 30 days of study drug discontinuation, and thus, met the laboratory criteria for a potential Hy's law case. All of these patients were evaluated for evidence of drug-induced liver injury, including whether or not the liver injury was primarily hepatocellular without a prominent cholestatic component and for the presence of alternative aetiologies (2.7.4 Summary of Clinical Safety Table 37). None of the patients were found to meet the criteria for drug-induced liver injury because alternative aetiologies, including progression of liver metastases, bile duct obstruction due to metastatic disease, concomitant medications, and cholecystitis, were present.

Cases of elevated liver enzymes have been reported in the postmarketing setting. Information about adverse reactions is collected continuously and regularly analyzed, including through PSUR assessment.

Hepatotoxicity is not considered an important risk of SG as the AEs observed were mainly elevated liver enzymes that were nonserious and of mild or moderate severity, and no drug induced liver toxicity cases were identified with available data. Hepatotoxicity can be managed in clinical practice through healthcare professional awareness and will continue to be monitored via routine pharmacovigilance activities.

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

- None

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered to by prescribers (eg, actions being part of standard clinical practice where the product is authorised):

- Nausea and vomiting

Adverse events of nausea and vomiting were identified using a combination of the preferred terms (PTs) nausea and vomiting (pooled nausea and vomiting).

In Study IMMU-132-05, pooled nausea and vomiting was more frequently observed in the SG treatment group compared with the TPC group (66.3% [171/258; 95% CI: 155, 186] vs 35.3% [79/224; 95% CI: 65, 94]), with the majority of cases being Grade 1 or 2 in both groups (Table SVII.3). Similarly, treatment-related pooled nausea and vomiting was more frequently observed in the SG treatment group compared with the TPC group (60.5% [156/258; 95% CI: 140, 172] vs 28.6% [64/224; 95% CI: 51, 78]). Specifically, in the SG group, 63.1% participants experienced Grade 1 or Grade 2 events, whilst 2.7% pooled nausea and vomiting events were

Grade 3 and 0.4% Grade 4. Five participants (1.9%) required a dose reduction and 5 required a dose interruption; there were no drug discontinuations. Many events (50.4%) resolved, with 1.2% resolving with sequelae and 31.4% remaining unresolved.

In the Overall Targeted mTNBC pool, pooled nausea and vomiting occurred in 62.6% (229/366) of participants (Table SVII.3). Grade 3 and Grade 4 nausea and vomiting occurred in 4.4% and 0.3% of this population, respectively, and 54.6% of the events resolved while 34.4% were not resolved.

Table SVII.3. Summary of Pooled Nausea and Vomiting AEs in Study IMMU-132-05, Study IMMU-132-01 and Overall Targeted mTNBC Population

	IMMU-132-05 mTNBC SG Treated (N = 258)	IMMU-132-05 mTNBC TPC (N = 224)	IMMU-132-01 mTNBC SG Treated (N = 108)	Overall Targeted mTNBC (N = 366)
Nausea and Vomiting[1], n (%) [95% CI]*				
Any adverse event	171 (66.3%) [155, 186]	79 (35.3%) [65, 94]	82 (75.9%) [72, 90]	253 (69.1%) [235, 270]
Serious adverse event	2 (0.8)	0 (0.0)	5 (4.6)	7 (1.9)
Treatment-related adverse event	156 (60.5%) [140, 172]	64 (28.6%) [51, 78]	73 (67.6%) [63, 82]	229 (62.6%) [210, 247]
Action taken				
Dose reduction	5 (1.9)	0 (0.0)	0 (0.0)	5 (1.4)
Interruption	5 (1.9)	0 (0.0)	3 (2.8)	8 (2.2)
Discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Outcome[2]				
Resulted in death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not resolved	81 (31.4)	33 (14.7)	45 (41.7)	126 (34.4)
Resolved with sequelae	3 (1.2)	2 (0.9)	9 (8.3)	12 (3.3)
Resolved	130 (50.4)	57 (25.4)	70 (64.8)	200 (54.6)
Unknown	1 (0.4)	1 (0.4)	0 (0.0)	1 (0.3)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Severity (worst grade)				
Grade 1	109 (42.2)	57 (25.4)	42 (38.9)	151 (41.3)
Grade 2	54 (20.9)	19 (8.5)	31 (28.7)	85 (23.2)
Grade 3	7 (2.7)	3 (1.3)	9 (8.3)	16 (4.4)
Grade 4	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.3)
Grade 5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

1 Nausea and vomiting is the combination of the preferred terms Nausea and Vomiting
2 Subjects are counted according to the outcomes regardless of adverse events. (Percentages are based on big N).
* 95% CI produced by exact binomial method in terms of frequencies as applied to the respective N in each group.
CI=confidence interval; mTNBC=metastatic triple negative breast cancer; SG=sacituzumab govitecan;
TNBC= triple negative breast cancer; TPC=treatment of physician's choice.
Source: TNBC Table 15.1.2.4

Nausea and vomiting AEs are presented separately in Table SVII.4. In Study IMMU-132-05, nausea occurred more frequently than vomiting in both the SG group (62.4% vs 33.3%) and TPC group (30.4% vs 16.1%), respectively. In the SG group, 11.2% participants experienced Grade 3 nausea AEs, 1.2% Grade 3 and 0.4% Grade 4 vomiting AEs. No Grade 4 nausea events occurred. The majority of AEs were nonserious with only 0.8% nausea and 0.8% vomiting SAEs observed in the SG group. Five participants treated with SG (1.9%) required a dose reduction and 5 required a dose interruption relating to nausea; there was also 1 (0.4%) drug discontinuation.

In the Overall Targeted mTNBC pool, nausea and vomiting AEs occurred in 64.2% (235/366) and 38.0% (139/366) of participants, respectively (Table SVII.4). In this population, Grade 3 and Grade 4 nausea events occurred in 3.8% and 0.3% of participants, and Grade 3 and Grade 4 vomiting events occurred in 2.7% and 0.3% of participants, respectively.

Table SVII.4. Nausea and Vomiting AEs in Study IMMU-132-05 and Overall Targeted mTNBC Population

MedDRA System Organ Class Preferred Term	IMMU-132-05 SG Treated (N = 258) n (%)	IMMU-132-05 TPC (N = 224) n (%)	Overall Targeted mTNBC (N = 366) n (%)
Nausea			
Adverse event	161 (62.4)	68 (30.4)	235 (64.2)
Serious adverse event	2 (0.8)	0 (0.0)	5 (1.4)
Action taken			
Dose reduction	5 (1.9)	0 (0.0)	5 (1.4)
Interruption	5 (1.9)	0 (0.0)	7 (1.9)
Discontinuation	1 (0.4)	0 (0.0)	1 (0.3)
Severity			
Grade 3	29 (11.2)	2 (0.9)	14 (3.8)
Grade 4	0 (0.0)	0 (0.0)	1 (0.3)
Vomiting			
Adverse event	86 (33.3)	36 (16.1)	139 (38.0)
Serious adverse event	2 (0.8)	0 (0.0)	7 (1.9)
Action taken			
Dose reduction	1(0.4)	0 (0.0)	1 (0.3)
Interruption	3 (1.2)	0 (0.0)	5 (1.4)
Discontinuation	0 (0.0)	0 (0.0)	0 (0.0)
Severity			
Grade 3	3 (1.2)	3 (1.3)	10 (2.7)
Grade 4	1 (0.4)	0 (0.0)	1 (0.3)

Source: Table 14.3.2.10.2.1, Table 14.3.2.10.3.1, Table 14.3.2.10.6.1, Table 14.3.2.10.7.1, Table 14.3.2.9.1.1, and Table 14.3.2.9.2.1

Cases of nausea and vomiting have been reported in the postmarketing setting. Information about adverse reactions is collected continuously and regularly analyzed, including through PSUR assessment.

The TRODELVY SmPC informs healthcare professionals that SG is emetogenic and premedication with a 2 or 3 drug combination regimen (eg, dexamethasone with either a 5 hydroxytryptamine [5-HT3] receptor antagonist or a neurokinin-1 [NK-1] receptor antagonist as well as other drugs as indicated) for prevention of chemotherapy-induced nausea and vomiting (CINV) is recommended. Guidance on dose modifications is provided for any Grade 3-4 nausea and vomiting due to treatment that is not controlled with antiemetics.

Nausea and vomiting, although observed in clinical studies and in the post-marketing setting, is not considered an important risk of SG as the AEs observed were mainly nonserious and of mild or moderate severity. The risk can be managed in clinical practice, through use of premedication and dose modifications based on severity grade if needed and will continue to be monitored via routine pharmacovigilance activities.

- Severe Diarrhoea

Sacituzumab govitecan can cause severe diarrhoea. Diarrhoea occurred in 62.5% (430/688) of breast cancer patients treated with TRODELVY, including Grade 3 diarrhoea in 10.3% (71/688) of patients. Diarrhoea led to treatment discontinuation in less than 1.0% (3/688) of patients. Diarrhoea in some cases was observed to have led to dehydration and subsequent acute kidney injury.

The benefit of SG as a treatment for patients with mTNBC or HR+/HER2- mBC outweighs the risk of severe diarrhoea. Diarrhoea can be managed in clinical practice through healthcare professional awareness of this type of reaction with oncology therapeutic agents, patient monitoring and treatment with antidiarrhoeals. Additional supportive measures (eg, fluid and electrolyte replacement) may also be employed as clinically indicated. Routine risk minimization measures are provided in the Warnings and Precautions Section 4.4 of the TRODELVY EU SmPC. Should severe diarrhoea occur, it can be managed by further SG dose reduction, interruption, or discontinuation as described in Section 4.2 of the EU SmPC. This risk will continue to be monitored via routine pharmacovigilance activities.

- Hypersensitivity

Sacituzumab govitecan can cause severe and life-threatening hypersensitivity. Grade 3 and above hypersensitivity occurred in 1.7% (12/688) of patients treated with TRODELVY. Grade 3 hypersensitivity occurred in 1.2% (3/258) and 1.5% (4/268) of participants treated with TRODELVY in Studies IMMU-132-05 and IMMU-132-09, respectively. Metastatic mBC is a serious and life-threatening condition with limited effective therapeutic options.

The benefit of SG as a treatment for patients with mBC outweighs the risk of hypersensitivity. Hypersensitivity can be managed in clinical practice through healthcare professional awareness of this type of reaction with oncology therapeutic agents, pre-infusion medication, and patient monitoring. Hypersensitivity can be further managed by dose reduction, interruption or discontinuation depending on the severity of any adverse reaction that develops. Routine risk minimization measures are provided in the Warnings and Precautions Section 4.4 of the TRODELVY EU SmPC. This risk will continue to be monitored via routine pharmacovigilance activities.

- Drug-drug interactions with UGT1A1 inhibitors and inducers

Based on the metabolism of SN-38, concomitant administration of SG with inhibitors of UGT1A1 may increase the incidence of AEs due to potential increase in systemic exposure to SN-38. Exposure to SN-38 may also be reduced in patients concomitantly receiving UGT1A1 enzyme inducers. Per the TRODELVY SmPC, SG should be used with caution in patients treated with UGT1A1 inhibitors (eg, propofol, ketoconazole, epidermal growth factor receptor [EGFR] tyrosine kinase inhibitors) and UGT1A1 inducers (eg, carbamazepine, phenytoin, rifampicin, protease inhibitors).

No cases of drug-drug interactions with UGT1A1 inhibitors and inducers were observed in the clinical development programme (Table 14.3.2.2.1) or in the post-marketing setting using the Interactions MedDRA High Level Term (HLT).

Drug-drug interactions with UGT1A1 inhibitors and inducers is not an important risk of SG as it can be managed in clinical practice, through increased awareness of the potential interactions, and will continue to be monitored using routine pharmacovigilance activities.

- Anaemia

Anaemia was evaluated using the PTs anaemia, haemoglobin decreased, and red blood cell count decreased.

Anaemia occurred in a higher percentage of participants in the SG group compared with the TPC control group (39.5% [102/258; 95% CI: 86, 118] vs 27.7% [62/224, 95% CI: 49, 76], respectively) in Study IMMU-132-05 (Table SVII.5). Similarly, treatment-related anaemia occurred in a higher percentage of participants in the SG group compared with the TPC control group (34.5% [89/258 participants; 95% CI: 74,105] vs 24.1% [54/224; 95% CI: 42, 68]). Most cases in the SG group were <Grade 3 and nonserious. Grade 3 anaemia occurred in 9.3% participants treated with SG; there were no cases of Grade 4 anaemia. No cases of anaemia caused permanent discontinuation of SG treatment. Anaemia led to dose reduction in 1.2% (3) of participants and a treatment interruption in 4.3% (11) of participants treated with SG in Study IMMU-132-05.

The percentage of SG-treated participants with anaemia was similar in Study IMMU-132-05 (39.5%) compared with the Overall Targeted mTNBC population (43.2%) (Table SVII.5).

Table SVII.5. Summary of Anaemia AEs in Study IMMU-132-05, Study IMMU-132-01 and Overall Targeted mTNBC Population

	IMMU-132-05 mTNBC SG Treated (N = 258)	IMMU-132-05 mTNBC TPC (N = 224)	IMMU-132-01 mTNBC SG Treated (N = 108)	Overall Targeted mTNBC (N = 366)
Anaemia[1], n (%) [95% CI]*				
Any adverse event	102 (39.5%) [86, 118]	62 (27.7%) [49, 76]	56 (51.9%) [45, 66]	158 (43.2%) [139, 177]
Serious adverse event	3 (1.2)	2 (0.9)	2 (1.9)	5 (1.4)
Treatment-related adverse event	89 (34.5%) [74, 105]	54 (24.1%) [42, 68]	51 (47.2%) [41, 62]	140 (38.3%) [122, 159]
Action taken				
Dose reduction	3 (1.2)	1 (0.4)	0 (0.0)	3 (0.8)
Interruption	11 (4.3)	6 (2.7)	3 (2.8)	14 (3.8)
Discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Outcome[2]				
Resulted in death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not resolved	60 (23.3)	39 (17.4)	37 (34.3)	97 (26.5)
Resolved with sequelae	5 (1.9)	1 (0.4)	7 (6.5)	12 (3.3)
Resolved	72 (27.9)	45 (20.1)	41 (38.0)	113 (30.9)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Severity (worst grade)				
Grade 1	31 (12.0)	16 (7.1)	16 (14.8)	47 (12.8)
Grade 2	47 (18.2)	33 (14.7)	27 (25.0)	74 (20.2)
Grade 3	24 (9.3)	13 (5.8)	13 (12.0)	37 (10.1)
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Percentages are based on N.
1 Anaemia is the combination of the preferred terms of Anaemia, Haemoglobin decreased, and Red blood cell count decreased.
2 Subjects are counted according to the outcomes regardless of adverse events.
* 95% CI produced by exact binomial method in terms of frequencies as applied to the respective N in each group.
CI=confidence interval; mTNBC=metastatic triple negative breast cancer; SG=sacituzumab govitecan; TNBC= triple negative breast cancer; TPC=treatment of physician's choice.
Source: TNBC Table 15.1.2.5

Median time to the first event of anaemia (29 days vs 17 days) and median time to first event of ≥Grade 3 anaemia (52.5 days vs 22.0 days) was longer in the SG group compared with the TPC group in Study IMMU-132-05. Median duration of anaemia of any grade was identical in the SG and TPC groups (15 days) in Study IMMU-132-05 and median duration of ≥Grade 3 anaemia was similar in the SG and TPC groups (5.0 days vs 6.5 days, respectively; Table SVII.6).

Median time to onset of the first event of anaemia was similar in SG-treated participants in Studies IMMU-132-01 and IMMU-132-05 (20.5 days vs 29.0 days, respectively) (TNBC ISS Table 14.3.2.10.8.1) and the Overall Targeted mTNBC population (22 days). Median time to first event of ≥Grade 3 anaemia was 52.5 days in SG-treated participants in Study IMMU-132-05 and 34.0 days in the Overall Targeted mTNBC population (Table SVII.6).

Additionally, median duration of anaemia of any grade was identical in SG treated participants in Studies IMMU-132-01 and IMMU-132-05 (15 days) (TNBC Table 14.3.2.10.9.1) and was similar in the Overall Targeted mTNBC population. Median duration of ≥Grade 3 anaemia was also similar in Study IMMU-132-05 and the Overall Targeted mTNBC population (5 days vs 7 days, respectively) (Table SVII.6).

Table SVII.6. Time to Onset and Duration of Anaemia in Study IMMU-132-05 and the Overall Targeted mTNBC Population

	IMMU-132-05 SG Treated (N = 258) n (%)	IMMU-132-05 TPC (N = 224) n (%)	Overall Targeted mTNBC (N = 366) n (%)
Time to 1st event of anaemia[1]			
n	102	62	158
Mean (SD)	51.32 (64.614)	27.74 (32.818)	49.38 (74.298)
Median	29.00	17.00	22.00
Min, Max	1.0, 335.0	1.0, 174.0	1.0, 498.0
Time to 1st anaemia of ≥grade 3[2]			
n	24	13	37
Mean (SD)	63.63 (58.867)	34.62 (30.821)	70.97 (97.276)
Median	52.50	22.00	34.00
Min, Max	4.0, 230.0	5.0, 123.0	4.0, 533.0
Duration of anaemia of any grade[3]			
n	75	46	120
Mean (SD)	30.99 (36.165)	20.52 (18.351)	27.64 (31.317)
Median	15.00	15.00	15.00
Min, Max	1.0, 172.5	1.0, 87.0	1.0, 172.5
Missing[5]	27	16	38
Duration of anaemia of ≥grade 3[4]			
n	21	12	34
Mean (SD)	6.62 (5.958)	7.75 (5.541)	6.76 (5.391)
Median	5.00	6.50	7.00
Min, Max	1.0, 26.0	2.0, 22.0	1.0, 26.0
Missing[5]	3	1	3

1 Time to onset of 1st event of AESI is defined as time from the 1st dose of study drug to the 1st event of AESI (days).
2 Time to onset of 1st event of AESI of Grade 3 or higher is defined as time from the 1st dose date to the 1st event of AESI
3 Duration of AESI of any grade (days) is calculated as the last date of AESI – date of the first onset date of AESI +1.
4 Duration of AESI of Grade 3 or higher (days) is calculated as the last date of AESI of Grade ≥ 3 – the first onset date of AESI of Grade ≥ 3 +1.
5 'Missing' refers to unknown AESI onset date or AESI end date.
AESI=adverse event of special interest; max=maximum; min=minimum; SD=standard deviation; SG=sacituzumab govitecan; TNBC=triple negative breast cancer; TPC=treatment of physician's choice.
Source: TNBC ISS Table 14.3.2.10.8.1; Table 14.3.2.10.9.1

Cases of anaemia have been reported in the postmarketing setting. Information about adverse reactions is collected continuously and regularly analyzed, including through PSUR assessment.

Anaemia is labelled in the TRODELVY SmPC as a very common (≥1/10) adverse reaction. Healthcare professionals are also advised that individuals who are homozygous for the UGT1A1*28 allele are at increased risk for anaemia, along with neutropenia and febrile neutropenia, from SG treatment. This is because SN-38 is metabolised via UGT1A1 and genetic variants of the UGT1A1 gene such as the UGT1A1*28 allele lead to reduced UGT1A1 enzyme activity. Approximately 20% of the Black or African American population, 10% of the White population, and 2% of the East Asian population are homozygous for the UGT1A1*28 allele. The TRODELVY SmPC provides guidance on dose modifications should Grade 3-4 non-neutropenic haematologic toxicities occur.

Anaemia, although observed in clinical studies and the post-marketing setting, is not an important risk for SG as it can be managed in clinical practice, through patient monitoring and dose modifications based on severity grade should anaemia occur and will continue to be monitored using routine pharmacovigilance activities.

Known risks that do not impact the risk-benefit profile

- None

Other reasons for considering the risks not important:

Known risks for therapies in the approved indications

The potential for embryo-foetal toxicity has been identified from non-clinical studies. Sacituzumab govitecan can cause teratogenicity and/or embryo-foetal lethality when administered to a pregnant woman. Routine risk minimization measures are provided in the Warnings and Precautions Section 4.4 and 4.6 of the TRODELVY EU SmPC. Pregnant women and women of childbearing potential should be informed of the potential risk to the foetus. Additionally, the pregnancy status of females of reproductive potential should be verified prior to initiation of TRODELVY. Oncology products are often foeto-toxic and care is routinely taken by clinicians to avoid pregnancy in patients exposed to potentially foeto-toxic drugs, hence routine risk management measures are sufficient. This risk will continue to be monitored via routine pharmacovigilance activities.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

SVII.1.2.1. Important Identified Risks

Important Identified Risk 1: Serious infections secondary to neutropenia

Neutropenia (neutropenia, neutrophil count decreased, and febrile neutropenia PTs) occurred in a higher percentage of participants in the SG group than in the TPC group in mTNBC Study IMMU-132-05 (65.1% vs 44.2%, respectively) and in HR+/HER2- mBC Study IMMU-132-09

(72.8% vs 55.4%, respectively). Treatment-related neutropenia occurred in 64.3% of mTNBC participants treated with SG and in 72.0% of HR+/HER2- mBC participants treated with SG (TNBC RMP Table 15.1.2.1, HR+/HER2- mBC ISS IA2 Table 14.3.2.10.1.1).

In the Overall Targeted mTNBC population, most cases of neutropenia were not febrile and were nonserious; 19 participants (7.4%) treated with SG experienced serious adverse events (SAEs). Grade 3 neutropenia occurred in 35.7% of participants with Grade 4 severity occurring in 17.8% of participants. No cases of either neutropenia or febrile neutropenia caused permanent discontinuation of SG treatment. Interruption of dose was implemented in 46.5% of participants and dose was reduced in 10.9% of participants. Overall, neutropenia was managed with dose reduction and granulocyte colony stimulating factor (G-CSF) administration (TNBC 2.7.4 Summary of Clinical Safety Section 2.1.7.1.1). The majority of neutropenia events resolved (64%) with 4.3% events not resolved and 3.9% events resolved with sequelae. A similar pattern was observed in the Overall Targeted mTNBC population (n=366), where there was no treatment discontinuation, and dose interruption and dose reduction occurred in 42.6% and 7.7% participants, respectively (Module SVII.3.1.1). Additionally, the median duration of any grade neutropenia event was 8 days and the mean duration was 10.86 days in the Overall Targeted mTNBC population (Table SVII.7; TNBC ISS Table 14.3.2.10.9.1).

Similar results were observed in the HR+/HER2- mBC population in Study IMMU-132-09 (n=268). Most cases of neutropenia were not febrile and were nonserious; 19 participants (7.1%) treated with SG experienced SAEs. Grade 3 neutropenia occurred in 34.0% of participants with Grade 4 severity occurring in 20.9% of participants. In 2 (0.7%) participants, neutropenia caused permanent discontinuation of SG treatment. No cases of febrile neutropenia caused permanent discontinuation of SG treatment. Interruption of dose was implemented in 50.4% of participants and dose was reduced in 17.9% of participants. Overall, neutropenia was managed with dose reduction and granulocyte colony stimulating factor (G-CSF) administration (HR+/HER2- mBC 2.7.4 Summary of Clinical Safety Section 2.1.6.2). A similar pattern was observed in the Overall Targeted HR+/HER2- mBC population (n=322) and the Overall Targeted mBC population (n=688), where treatment discontinuation occurred in 0.9% and 0.4% participants, respectively. Dose interruption occurred in 46.9% and 44.9% participants, respectively, and dose reduction occurred in 17.9% and 14.4% participants, respectively (Module SVII.3.1.1). Additionally, the median duration of any grade neutropenia event was 8 days and the mean duration was 10 days in the Overall Targeted HR+/HER2- mBC and Overall Targeted mBC populations (Table SVII.7; ISS IA2 Table 14.3.2.10.10.1).

Infections potentially associated with neutropenia (infection AEs from the Infections and infestations SOC that occurred within the window of 11 days of an event of neutropenia, febrile neutropenia, or neutrophil count decreased) occurred in 10.9% participants (28/258; 95% CI: 19, 39) in the SG group in Study IMMU-132-05, which was similar to that in the Overall Targeted mTNBC population (11.2% [41/366; 95% CI: 30, 54]) (Table SVII.7). The 11-day window was chosen by rounding up the mean duration of the neutropenia events in the Overall Targeted mTNBC population (TNBC ISS Table 14.3.2.10.9.1). Approximately half of the AEs were treatment-related in Study IMMU-132-05, occurring in 5.4% of participants treated with SG (14/258; 95% CI: 8, 23).

In Study IMMU-132-09, infections potentially associated with neutropenia occurred in 9.7% participants (26/268; 95% CI: 17, 37) in the SG group, which was similar to that in the Overall Targeted HR+/HER2- mBC and Overall Targeted mBC populations (9.6% [31/322; 95% CI: 21, 43] and 10.6% [73/688; 95% CI: 58, 91], respectively) (Table SVII.6). Less than half of the AEs were treatment-related in Study IMMU-132-09, occurring in 4.1% of participants treated with SG.

Serious infections potentially associated with neutropenia occurred in 2.7% of participants in mTNBC Study IMMU-132-05 (7/258) and in the Overall Targeted mTNBC population (10/366) (Table SVII.7). Grade 3 and Grade 4 infections potentially associated with neutropenia occurred in 3.5% and 0.8% of participants, respectively, treated with SG in Study IMMU-132-05 (Table SVII.7). In 1.9% of cases SG treatment was interrupted, in 0.4% the dose was reduced and in 0.8% treatment was permanently discontinued. Infections potentially associated with neutropenia resolved in the majority of cases (10.5%) and were reported as not resolved in only 2 cases (0.8%). A similar pattern of infections potentially associated with neutropenia was observed in the Overall Targeted mTNBC population (n=366) (Table SVII.7).

Serious infections potentially associated with neutropenia occurred in 3.4% of participants in HR+/HER2- mBC Study IMMU-132-09 (9/268), and in 2.8% in the Overall Targeted HR+/HER2- mBC and Overall Targeted mBC populations (9/322 and 19/688, respectively) (Table SVII.7, Table SVII.8). Grade 3 and Grade 4 infections potentially associated with neutropenia occurred in 3.4% and 0.4% of participants, respectively, treated with SG in Study IMMU-132-09 (Table SVII.7, Table SVII.8). In 1.1% of cases SG treatment was interrupted, in 0.4% the dose was reduced, and there were no cases in which treatment was permanently discontinued. Infections potentially associated with neutropenia resolved in the majority of cases (9.0%) and were reported as not resolved in only 3 cases (1.1%). A similar pattern of infections potentially associated with neutropenia was observed in the Overall Targeted HR+/HER2- mBC and Overall Targeted mBC populations (Table SVII.7, Table SVII.8).

Patients homozygous for the *28 allele of UGT1A1 compared with genotypes of *1/*1 and *1/*28 are at increased risk of neutropenia. Febrile neutropenia occurred more frequently in participants who were homozygous for the *28 allele of UGT1A1 compared with genotypes of *1/*1 and *1/*28 (17.6% vs 5.2% and 2.7%, respectively) in Study IMMU-132-05 (TNBC ISS Table 14.3.2.2.1.6). However, the overall frequency of infections in patients homozygous for the *28 allele of UGT1A1 was lower compared with genotypes of *1/*1 and *1/*28 (47.1% vs 53.1% and 54.2%, respectively).

In Study IMMU-132-09, febrile neutropenia occurred at a similar frequency in participants who were homozygous for the *28 allele of UGT1A1 compared with genotypes of *1/*1 and *1/*28 (4.0% vs 5.8% and 6.7%, respectively) (HR+/HER2- mBC ISS IA2 Table 14.3.2.2.1.6). However, the overall frequency of infections in patients homozygous for the *28 allele of UGT1A1 was lower compared with genotypes of *1/*1 and *1/*28 (36.0% vs 38.8% and 40.3%, respectively).

Nonclinical observations confirmed one of the primary toxicities as neutropenia (Part II: Module SII).

Risk-benefit impact:

SG can cause severe or life-threatening neutropenia, which predisposes patients to serious infections. However, TNBC is often associated with visceral metastases and mTNBC is incurable, with a median survival of approximately 13.3 months {Kassam 2009}. Treatment options are limited. HR+/HER2- mBC is also often associated with visceral metastases and after resistance to multiple endocrine and targeted therapies, chemotherapy is often the only available treatment option (Part II: Module SI).

The benefit of SG as an effective treatment for patients with previously treated mTNBC or HR+/HER2- mBC outweighs the important identified risk of serious infections secondary to neutropenia, which can be managed in clinical practice through healthcare professional awareness of this type of reaction with oncology therapeutic agents, patient monitoring, SG dose modification, G-CSF administration, and antibiotics.

The TRODELVY SmPC informs healthcare professionals of the dose modifications to implement based on occurrence of severe neutropenic adverse reactions, which specify administration of G-CSF, 25% dose reduction, 50% dose reduction or discontinuation of treatment at first, second, third or fourth occurrences, respectively. SG treatment should not be administered if absolute neutrophil count is below 1500/mm^3 on Day 1 of any cycle or neutrophil count is below 1000/mm^3 on Day 8 of any cycle, or if there is neutropenic fever.

SVII.1.2.2. Important Potential Risks

None

SVII.1.3. Missing Information

Missing information 1: Use in patients with moderate or severe hepatic impairment

Use in patients with moderate or severe hepatic impairment is an area of missing information based on the limited exposure in this population in the clinical development programme (Table SIV.2, Module SIV.3).

Risk-benefit impact:

The benefit of SG treatment for patients with mTNBC and HR+/HER2- mBC, both life-threatening conditions with limited treatment options, outweighs the use of SG in patients with moderate or severe hepatic impairment, an area of missing information that has yet to be characterised in humans.

The TRODELVY SmPC informs healthcare professionals that no adjustment to the starting dose is required when administering SG to patients with mild hepatic impairment (bilirubin ≤1.5x ULN and AST/ALT < 3x ULN). In the Overall Targeted mBC population, 39.0% (268/688) of participants had mild hepatic impairment and 60.8% (418/688) of participants had normal hepatic function (bilirubin or AST ≤ULN) (HR+/HER2- mBC ISS IA2 Table 14.3.1.1.4).

The safety of SG in patients with moderate or severe hepatic impairment has not been established. SG has not been studied in patients with serum bilirubin >1.5x ULN, or AST or ALT >3x ULN in patients without liver metastases, or AST or ALT >5x ULN, in patients with liver metastases. The use of SG should be avoided in these patients.

An open-label non-randomised, dose-escalation study to determine an appropriate starting dose in patients with moderate hepatic impairment is being conducted to further characterise use in patients with moderate hepatic impairment (Study IMMU-132-15; Part III.2).

Missing information 2: Immunogenicity

Immunogenicity is an area of missing information based on insufficient data available at the time of the data lock point of this report concerning the potential development of antidrug antibodies (ADAs) and neutralizing antibodies.

Risk-benefit impact:

The benefit of SG treatment for patients with mTNBC and HR+/HER2- mBC, both life-threatening conditions with limited treatment options, outweighs the risk of potential development of immunogenicity to SG, an area of missing information that has yet to be fully characterised.

As with all therapeutic proteins, there is potential for immunogenicity with SG. Possible outcomes of development of ADAs are decreased efficacy, altered pharmacokinetics of the treatment drug, and adverse effects such as those attributable to the development of a strong immune response. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay used. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease.

The TRODELVY SmPC informs healthcare professionals that across clinical studies in patients treated with sacituzumab govitecan, 9 (1.1%) of 785 patients developed antibodies to SG; 6 of these patients (0.8% of all patients treated with SG) had neutralizing antibodies (NAbs) against SG.

In Study IMMU-132-09, no participants had ADAs to SG at baseline or treatment emergent ADAs to SG. In Studies IMMU-132-01, IMMU-132-05, IMMU-132-06, and IMMU-132-09 across multiple solid tumors, 9 of 785 participants evaluable for ADA incidence (1.1%) had treatment-emergent ADAs to SG. Six of the 9 participants with treatment emergent ADAs also had positive NAb assessments.

Overall, the clinical immunogenicity data evaluated demonstrate no discernible impact of ADAs on the efficacy, safety, or PK of SG, indicating that the presence of ADAs to SG does not affect the safety or efficacy of SG in patients with mTNBC, HR+/HER− mBC, or mUC at the intended 10-mg/kg dose on Days 1 and 8 of a 21-day cycle. Given the low incidence of treatment-emergent ADAs (1.1%), no formal analysis could be performed to assess the impact of ADAs on the efficacy of SG and a quantitative assessment of the impact of ADAs on SG or total antibody exposure could not be performed in the population PK analyses.

No cases suggestive of immunogenicity (eg, Neutralising antibodies, Neutralising antibodies negative, Neutralising antibodies positive PTs) have been observed in the post-marketing setting.

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

No new safety concerns have been identified since the submission of the last approved RMP v3.0. The important identified risks (severe diarrhoea, hypersensitivity) and important potential risk (embryo-foetal toxicity) are removed from the list of important risks in this updated RMP (see Part II: Module SVII.1).

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

SVII.3.1.1. Important Identified Risks

Important Identified Risk 1: Serious infections secondary to neutropenia

Potential mechanisms:

Neutropenia is characterised by a decline in absolute neutrophil counts precipitated by exposure to cytotoxic chemotherapy agents such as SG. The active moiety of SG is a topoisomerase I inhibitor, inducing single-stranded DNA breaks during replication, and able to directly damage myeloid cells. In cancer patients treated with cytotoxic agents, neutropenia occurs as a result of decreased neutrophil production, accelerated utilisation, or a combination of both. Drug-induced neutropenia is mainly related to a direct inhibition of bone marrow precursors {Fontanella 2014}. Serious infections can occur secondary to neutropenia due to the resulting deficient immune response.

Evidence source and strength of evidence:

In the clinical studies 65.6% of 366 patients in the Overall Targeted TNBC population treated with SG had neutropenia and in 51.6% patients the neutropenia was severe. The dose of SG was interrupted in 42.6% patients and reduced in 7.7% patients. However, no patients had to discontinue SG permanently because of neutropenia. In the Overall Targeted HR+/HER2- mBC population, 71.4% of 322 patients treated with SG had neutropenia and in 51.9% of patients the neutropenia was severe. The dose of SG was interrupted in 46.3% of patients and reduced in 15.7% of patients in the Overall Targeted HR+/HER2- mBC population; 3 (0.9%) participants discontinued SG treatment due to neutropenia. Similar results were seen in the Overall Targeted mBC population (HR+/HER2- mBC ISS IA2 Tables 14.3.2.9.2.1, 14.3.2.9.1.1, 14.3.2.9.3.1).

Infections potentially associated with neutropenia occurred in 11.2% of 366 patients in the Overall Targeted mTNBC population and in 9.6% of 322 patients in the Overall Targeted HR+/HER2- mBC population. Serious infections potentially associated with neutropenia occurred in 2.7% of 366 patients in the Overall Targeted TNBC population and in 2.8% of 322 patients in the Overall Targeted HR+/HER2- mBC population.

Neutropenia was one of the main toxicities seen in animal studies.

Clinical studies can provide an estimation of the frequency and nature of a side effect that is expected to occur in clinical practice. Findings from studies in animals may be relevant for humans and in the absence of data in humans suggest a potential safety concern that awaits clinical confirmation.

Characterisation of the risk:

Events of neutropenia were evaluated using the PTs of neutropenia, neutrophil count decreased, and febrile neutropenia.

Neutropenia occurred in 65.1% participants (168/258; 95% CI: 152, 183) in the SG group in Study IMMU-132-05, which was similar to that in the Overall Targeted mTNBC population (65.6% [240/366; 95% CI: 221, 258]) (RMP Table 15.1.2.1). The majority of AEs were treatment related. Treatment-related neutropenia occurred similarly in Study IMMU-132-05 and the Overall Targeted mTNBC population in 64.3% participants (166/258; 95% CI: 150, 181) and 65.0% participants (238/366; 95% CI: 219, 256), respectively, with serious AEs occurring in 7.4% and 7.7% participants, respectively (RMP Table 15.1.2.1).

Neutropenia occurred in 70.5% participants (189/268) in the SG group in Study IMMU-132-09, which was similar to that in the Overall Target HR+/HER2- mBC population (71.4% [230/322]) and Overall Target mBC population (67.6% [465/688]) (ISS Table 14.3.2.2.1). The majority of AEs were treatment related. Treatment-related neutropenia occurred similarly in Study IMMU-132-09 (70.1% [188/268]), Overall Target HR+/HER2- mBC population (71.1% [229/322]) and the Overall Target mBC population (67.2% [462/688]), with serious AEs occurring in 3.0%, 2.8%, and 2.6%, respectively (HR+/HER2- mBC ISS IA2 Tables 14.3.2.5.1.1, 14.3.2.10.4.1.1, 14.3.2.10.3.1).

Median time to onset of the first event of neutropenia was similar in SG-treated participants in Studies IMMU-132-01 and IMMU-132-05 (13.5 days vs 15.5 days; Table 14.3.2.10.8.1) and the Overall Targeted mTNBC population (15 days). Median time to first event of ≥Grade 3 neutropenia was also similar in SG-treated participants in Studies IMMU-132-01 and IMMU-132-05 (16 days vs 20 days; Table 14.3.2.10.8.1) and the Overall Targeted mTNBC population (20 days).

Median time to onset of the first event of neutropenia was similar in SG-treated participants in Study IMMU-132-09 and Overall Targeted HR+/HER2- mBC population (19 days in both) and the Overall Targeted mBC population (16 days) (ISS Table 14.3.2.10.9.1). Median time to first event of ≥Grade 3 neutropenia was also similar in SG-treated participants in Study IMMU-132-09 and Overall Target HR+/HER2- population (16 days) and the Overall Target mBC population (19 days) (ISS Table 14.3.2.10.9.1).

Additionally, median duration of neutropenia was similar in SG-treated participants in Studies IMMU-132-01 and IMMU-132-05 (8.75 days vs 8.0 days) and the Overall Targeted mTNBC population (8.0 days; TNBC ISS Table 14.3.2.10.9.1). Mean duration of neutropenia of any grade in SG-treated participants in Studies IMMU-132-01, IMMU-132-05, and in the Overall Targeted mTNBC pool was 13.3 days, 9.84 days, and 10.86 days, respectively. Median duration of ≥Grade 3 neutropenia was also similar in Studies IMMU-132-01 and IMMU-132-05 (7.25 days vs 7.0 days; Table 14.3.2.10.9.1) and the Overall Targeted mTNBC population (7.0 days). Mean duration of ≥Grade 3 neutropenia was similar in Studies IMMU-132-01 and IMMU-132-05 (7.90 days vs 8.49 days) and the Overall Targeted mTNBC population (8.34 days; TNBC ISS Table 14.3.2.10.9.1).

Treatment emergent infection AEs from the Infections and infestations SOC that occurred within the window of 11 days of an event of neutropenia, febrile neutropenia, or neutrophil count decreased were identified as being potentially associated with neutropenia. The 11-day window was chosen by rounding up the mean duration of the neutropenia events in the Overall Target mTNBC population (TNBC ISS Table 14.3.2.10.9.1) and in the Overall Targeted HR+/HER2- mBC and Overall Targeted mBC populations (ISS Table 14.3.2.16.1). The frequency, seriousness, outcome and severity of these infection AEs are presented in Table SVII.7 and Table SVII.8 (HR+/HER2- mBC).

While 65.1% participants (168/258; 95% CI: 152, 183) experienced neutropenia in the SG group in Study IMMU-132-05, infections potentially associated with neutropenia occurred in only 10.9% participants (28/258; 95% CI: 19, 39), which was similar to that in the Overall Targeted mTNBC population (65.6% [240/366; 95% CI: 221, 258] compared to 11.2% [41/366; 95% CI: 30, 54]) (Table SVII.7). The frequency of infections potentially associated with neutropenia in Study IMMU-132-05 (10.9%) was also similar to the frequency of all treatment-related infections in Study IMMU-132-05 (11.6% of participants; TNBC ISS Table 14.3.2.10.4.1.1).

Serious infections potentially associated with neutropenia occurred in 2.7% of participants in Study IMMU-132-05 and in the Overall Targeted mTNBC population (Table SVII.7).

Table SVII.7. Frequency, Seriousness, Outcome and Severity of Treatment Emergent Infections Potentially Secondary to Neutropenia in mTNBC

	IMMU-132-05 mTNBC SG Treated (N = 258)	IMMU-132-05 mTNBC TPC (N = 224)	IMMU-132-01 mTNBC SG Treated (N = 108)	Overall Targeted mTNBC (N = 366)
Infection[1], n(%) [95% CI]*				
Any adverse event	28 (10.9%) [19, 39]	16 (7.1%) [9, 25]	13 (12.0%) [7, 21]	41 (11.2%) [30, 54]
Serious adverse event	7 (2.7)	3 (1.3)	3 (2.8)	10 (2.7)
Treatment-related adverse events	14 (5.4%) [8, 23]	5 (2.2%) [2, 11]	3 (2.8%) [1, 9]	17 (4.6%) [10, 27]
Action taken				
Dose reduction	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.3)
Interruption	5 (1.9)	2 (0.9)	2 (1.9)	7 (1.9)
Discontinuation	2 (0.8)	0 (0.0)	0 (0.0)	2 (0.5)

	IMMU-132-05 mTNBC SG Treated (N = 258)	IMMU-132-05 mTNBC TPC (N = 224)	IMMU-132-01 mTNBC SG Treated (N = 108)	Overall Targeted mTNBC (N = 366)
Outcome[2]				
Resulted in death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not resolved	2 (0.8)	3 (1.3)	3 (2.8)	5 (1.4)
Resolved with sequelae	0 (0.0)	1 (0.4)	1 (0.9)	1 (0.3)
Resolved	27 (10.5)	12 (5.4)	11 (10.2)	38 (10.4)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Severity (worst grade)				
Grade 1	8 (3.1)	5 (2.2)	3 (2.8)	11 (3.0)
Grade 2	9 (3.5)	8 (3.6)	6 (5.6)	15 (4.1)
Grade 3	9 (3.5)	1 (0.4)	4 (3.7)	13 (3.6)
Grade 4	2 (0.8)	2 (0.9)	0 (0.0)	2 (0.5)
Grade 5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Percentages are based on N.
1 Infection is the SOC of Infections and infestations that occurred within the window of 11 days of an event of neutropenia, febrile neutropenia, or neutrophil count decreased.
2 Subjects are counted according to the outcomes regardless of adverse events.
* 95% CI produced by exact binomial method in terms of frequencies as applied to the respective N in each group.
CI=confidence interval; mTNBC=metastatic triple negative breast cancer; SG=sacituzumab govitecan; TNBC= triple negative breast cancer; TPC=treatment of physician's choice.
Source: TNBC Table 15.1.2.7.

While 70.5% of participants (189/268) experienced neutropenia in the SG group in Study IMMU-132-09, infections potentially associated with neutropenia occurred in only 9.7% participants (26/268; 95% CI: 17, 37), which was similar to that in the Overall Targeted HR+/HER2- mBC population (71.4% [230/322] compared to 9.6% [31/322; 95% CI: 21, 43]) and Overall Targeted mBC population (67.6% [465/688]) compared to 10.6% [73/688; 95% CI: 58, 91) (Table SVII.7). The frequency of infections potentially associated with neutropenia in Study IMMU-132-09 (4.1%) was also similar to the frequency of all treatment-related infections in Overall Target HR+/HER2- mBC and Overall Targeted mBC populations (3.7% and 4.2%, respectively) (HR+/HER2- mBC Table 14.3.2.10.4.1.1).

Serious infections potentially associated with neutropenia occurred in 3.4% of participants in Study IMMU-132-09 and in 2.8% of participants in both the Overall Target HR+/HER2- and Overall Targeted mBC populations (Table SVII.8).

Table SVII.8. Frequency, Seriousness, Outcome and Severity of Treatment Emergent Infections Potentially Secondary to Neutropenia in HR+/HER2- mBC

	IMMU-132-09 SG Treated (N=268)	IMMU-132-09 TPC (N=249)	Overall Targeted HR+/HER2- mBC (N=322)	Overall Targeted mBC (N=688)
Infection[1], n(%) [95% CI]*				
Any adverse event	26 (9.7%) [17, 37]	12 (4.8%) [6, 21]	31 (9.6%) [21, 43]	73 (10.6%) [58, 91]
Serious	9 (3.4%)	1 (0.4%)	9 (2.8%)	19 (2.8%)
Treatment-Related Adverse Events	11 (4.1%) [6, 19]	4 (1.6%) [1, 10]	12 (3.7%) [6, 21]	29 (4.2%) [20, 41]
Action Taken				
Dose Reduction	1 (0.4%)	0	1/268 (0.4%)	2/526 (0.4%)
Interruption	3 (1.1%)	1 (0.4%)	3 (0.9%)	10 (1.5%)
Discontinuation	0	0	0	2 (0.3%)
Outcome [1]				
Resulted in Death	0	0	0	0
Not Resolved	3 (1.1%)	2 (0.8%)	3 (0.9%)	8 (1.2%)
Resolved with Sequelae	0	0	1 (0.3%)	2 (0.3%)
Resolved	24 (9.0%)	10 (4.0%)	29 (9.0%)	68 (9.9%)
Unknown	0	1 (0.4%)	0	0
Severity (Worst Grade)				
Grade1	5 (1.9%)	0	6 (1.9%)	17 (2.5%)
Grade2	11 (4.1%)	10 (4.0%)	15 (4.7%)	31 (4.5%)
Grade3	9 (3.4%)	1 (0.4%)	9 (2.8%)	22 (3.2%)
Grade4	1 (0.4%)	1 (0.4%)	1 (0.3%)	3 (0.4%)
Grade5	0	0	0	0

Percentages are based on N.
1 Infection is the SOC of Infections and infestations that occurred within the window of 11 days of an event of neutropenia, febrile neutropenia, or neutrophil count decreased.
2 Subjects are counted according to the outcomes regardless of adverse events.
* 95% CI produced by exact binomial method in terms of frequencies as applied to the respective N in each group.
CI=confidence interval; SG=sacituzumab govitecan; HR+/HER2- mBC=hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer, TPC=treatment of physician's choice.
Source: HR+/HER2- mBC Table 14.3.2.16.1.

The most frequently reported (>1 patient) serious infections potentially associated with neutropenia events in Study IMMU-132-05 and in the Overall Targeted mTNBC population were pneumonia (3 [1.2%] and 5 [1.4%] patients, respectively) and sepsis (2 [0.8%] and 2 [0.5%] patients, respectively) (Table SVII.9). All 5 pneumonia cases in the Overall Targeted mTNBC population were Grade 3 (TNBC Listing 16.2.7.1). SG treatment was interrupted in 2 cases, and in 1 case each, the dose was decreased, the dose was withdrawn, and no action was taken. All 5 events resolved. Both sepsis events were Grade 4. In one case, SG was withdrawn, and the event resolved. In the other case, SG was interrupted, and the event had not resolved by the data cut-off date of this report.

Table SVII.9. Treatment Emergent Serious Infections Potentially Secondary to Neutropenia by System Organ Class and Preferred Term in mTNBC

	IMMU-132-05 mTNBC SG Treated (N=258)	IMMU-132-05 mTNBC TPC (N=224)	IMMU-132-01 mTNBC SG Treated (N=108)	Overall Targeted mTNBC (N=366)
Number of subjects treated	258	224	108	366
Infections Frequency (all Serious TEAEs)	7 (2.7%)	3 (1.3%)	3 (2.8%)	10 (2.7%)
Infections and infestations	7 (2.7%)	3 (1.3%)	3 (2.8%)	10 (2.7%)
Pneumonia	3 (1.2%)	1 (0.4%)	2 (1.9%)	5 (1.4%)
Sepsis	2 (0.8%)	1 (0.4%)	0	2 (0.5%)
Cellulitis	1 (0.4%)	0	0	1 (0.3%)
Clostridium difficile infection	0	0	1 (0.9%)	1 (0.3%)
Device related infection	1 (0.4%)	0	0	1 (0.3%)
Diverticulitis	1 (0.4%)	0	0	1 (0.3%)
Corynebacterium infection	0	1 (0.4%)	0	0

Percentages are based on N.
A subject with two or more adverse events in the same system organ class (or with the same preferred term) is counted only once for that system organ class (or preferred term).
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 23.0.
Note: Infection is the SOC of Infections and infestations that occurred within the window of 11 days of an event of neutropenia, febrile neutropenia, or neutrophil count decreased.
Document Source: TNBC Ad Hoc Table 10881.1

The most frequently reported (>1 patient) serious infections potentially associated with neutropenia events in patients treated with SG in Study IMMU-132-09 and in the Overall Targeted HR+/HER2- mBC population were pneumonia (0 and 5 [0.7%] patients, respectively) and sepsis (2 [0.7%] and 4 [0.6%] patients, respectively) (Table SVII.10).

Table SVII.10. Treatment Emergent Serious Infections Potentially Secondary to Neutropenia by System Organ Class and Preferred Term in HR+/HER2- mBC

	IMMU-132-09 SG Treated (N=268)	IMMU-132-09 TPC (N=249)	Overall Targeted HR+/HER2- mBC (N=322)	Overall Targeted mBC (N=688)
Number of Subjects Treated	268	249	322	688
Infections Frequency (all Serious TEAEs)	9 (3.4%)	1 (0.4%)	9 (2.8%)	19 (2.8%)
Infections and infestations	9 (3.4%)	1 (0.4%)	9 (2.8%)	19 (2.8%)
Sepsis	2 (0.7%)	0	2 (0.6%)	4 (0.6%)
Pneumonia	0	0	0	5 (0.7%)
Clostridium difficile infection	1 (0.4%)	0	1 (0.3%)	2 (0.3%)
Urinary tract infection	1 (0.4%)	1 (0.4%)	1 (0.3%)	1 (0.1%)
COVID-19	1 (0.4%)	0	1 (0.3%)	1 (0.1%)
COVID-19 pneumonia	1 (0.4%)	0	1 (0.3%)	1 (0.1%)
Escherichia bacteraemia	1 (0.4%)	0	1 (0.3%)	1 (0.1%)
Urosepsis	1 (0.4%)	0	1 (0.3%)	1 (0.1%)
Vascular device infection	1 (0.4%)	0	1 (0.3%)	1 (0.1%)
Wound infection	1 (0.4%)	0	1 (0.3%)	1 (0.1%)
Cellulitis	0	0	0	1 (0.1%)
Device related infection	0	0	0	1 (0.1%)
Diverticulitis	0	0	0	1 (0.1%)

Percentages are based on N.
A subject with two or more adverse events in the same system organ class (or with the same preferred term) is counted only once for that system organ class (or preferred term).
Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.0.
Note: Infection is the SOC of Infections and infestations that occurred within the window of 11 days of an event of neutropenia, febrile neutropenia, or neutrophil count decreased.
SG=sacituzumab govitecan; HR+/HER2- mBC=hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer, TPC=treatment of physician's choice.
Document Source: HR+/HER2- mBC Ad Hoc Table 11015.2.1

Cases of neutropenia and infections secondary to neutropenia have been reported in the postmarketing setting. Information about adverse reactions is collected continuously and regularly analyzed, including through PSUR assessment.

Nonclinical studies confirmed that neutropenia was one of the primary toxicities in Cynomolgus monkeys, which is an expected effect of the active moiety SN-38 (Part II: Module SII).

Risk factors and risk groups:

Risk factors for neutropenia caused by cancer chemotherapies include increasing age, abnormal liver enzyme laboratory values, female gender, underweight, radiation therapy to the bone marrow, type of prior chemotherapy, and type of current treatment {Fontanella 2014}.

When SG is metabolised in the body, the active metabolite SN-38 is inactivated by an enzyme called uridine 5'-diphospho (UDP)-glucuronosyltransferase (UGT). Patients with reduced activity of this enzyme, such as patients who are homozygous for the *28 allele of UGT1A1, who are treated with SG have an increased risk of neutropenia.

An increased risk of serious infections can occur secondary to neutropenia due to the resulting deficient immune response.

Preventability:

It is standard practice to monitor haematological variables in patients undergoing chemotherapy. Use of G-CSF before a neutropenic event occurred, dose delays, and dose reductions are protective against Grade 4 chemotherapy-induced neutropenia {Schwenkglenks 2011}.

The TRODELVY SmPC advises healthcare professionals that fatal infections in the setting of neutropenia have been observed in clinical studies with SG. It also advises that SG treatment should not be administered if the absolute neutrophil count is below 1500/mm^3 on Day 1 of any cycle or neutrophil count below 1000/mm^3 on Day 8 of any cycle. SG should also not be administered in case of neutropenic fever. Dose modifications may be introduced according to the TRODELVY SmPC for Grade 4 neutropenia ≥7 days, Grade 3 febrile neutropenia (absolute neutrophil count <1000/mm^3 and fever ≥38.5^{o}C), or Grade 3-4 neutropenia which delays dosing by 2 or 3 weeks for recovery to ≤Grade 1 at time of scheduled treatment. Treatment may need to be modified by administration of G-CSF, a 25% dose reduction, a 50% dose reduction, or discontinuation after the first, second, third, or fourth occurrence of the severe neutropenic reaction, respectively. If Grade 3-4 neutropenia delays dosing beyond 3 weeks for recovery to ≤Grade 1, treatment must be discontinued.

In addition, healthcare professionals are advised to closely monitor patients with known reduced UGT1A1 activity (eg, individuals who are homozygous for the UGT1A1*28 allele) for adverse reactions as these patients are potentially at increased risk for neutropenia and febrile neutropenia (and anaemia), and therefore, serious infection.

Impact on the risk-benefit balance of the product:

SG can cause severe or life-threatening neutropenia. However, mTNBC and HR+/HER2- mBC are serious and life-threatening conditions with limited effective therapeutic options.

The benefit of SG as a treatment for patients with mTNBC or HR+/HER2- mBC outweighs the important identified risk of serious infections secondary to neutropenia that can be managed in clinical practice through healthcare professional awareness of this type of reaction with oncology therapeutic agents, patient monitoring, antibiotics, and SG dose reduction, interruption or discontinuation should severe neutropenia occur.

Public health impact:

The impact on public health is anticipated to be low since monitoring for neutropenia is standard clinical practice in patients undergoing chemotherapy and neutropenia can be adequately managed with close monitoring, dose interruptions or delays, and established supportive care measures, including G-CSF.

SVII.3.1.2. Important Potential Risks

There are no important potential risks for TRODELVY.

SVII.3.2. Presentation of the Missing Information

Table SVII.11. Missing Information

Missing Information:	Evidence Source
Use in patients with moderate or severe hepatic impairment	In the clinical development programme participants with Gilbert's disease were excluded from Study IMMU-132-05 and those with bilirubin ≥3 x ULN or hepatitis B/C positive were excluded from Study IMMU-132-09 (TNBC Module SIV.1). In addition, most participants (98.1%) in the SG treatment group in Study IMMU-132-05 had normal hepatic function (Table SIV.2; TNBC Module SIV.3). Most participants (99.3%) had normal hepatic function or mild hepatic impairment (HR+/HER2- mBC ISS IA2 Table 14.3.1.1.4). No conclusions can be drawn about either exposure (TNBC ISS Table 14.3.1.1.4) or AEs by baseline hepatic function (TNBC ISS Table 14.3.2.1.1.4; Table 14.3.2.2.1.4). Hence, use in patients with moderate or severe hepatic impairment is an area of missing information. Cases of use of SG in patients with moderate or severe hepatic impairment have been reported in the post-marketing setting; no safety issues have been identified from the review of these cases. Population in need of further characterisation: To further characterise this population, Study IMMU-132-15 will evaluate the use of SG in patients with moderate hepatic impairment (Part III.2). Patients with advanced or metastatic solid tumors and moderate hepatic function defined according to the National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria (ie, 1.5× ULN <total bilirubin <3.0× ULN) will be enrolled and will receive SG IV infusion over 3 hours on Day 1 and Day 8. Serial blood samples will be collected on Day 1 and Day 8 up to 7 days after dosing for pharmacokinetic (PK) assessments and safety will be evaluated throughout the study.
Immunogenicity	The risk of immunogenicity has not been fully established due to overall low incidences of treatment emergent ADAs to SG. A previous analysis of immunogenicity of SG in serum samples from 106 patients with mTNBC in Study IMMU-132-01 was evaluated using an ECL-based immunoassay to test for anti-SG antibodies. Anti SG antibodies developed in 2% (2/106) of patients. However, this analysis of the potential effect of drug tolerance on the detection of ADA indicated that the total hRS7 IgG drug tolerance of the prior ADA assay (≤ 25 µg/mL) was inadequate. To better characterise the potential for immunogenicity with SG, two new assays for the detection of ADAs and NAbs for SG were used to determine the impact of immunogenicity on PK, safety, and efficacy. Immunogenicity of SG or its components was assessed in clinical studies by evaluating and characterizing ADA response with a competitive radioimmunoassay (RIA) which transitioned to a 3-tiered approach (screening, confirmation, and titer) using an enzyme-linked immunosorbent assay (ELISA) to detect and semiquantitate ADAs. A competitive ligand-based electrochemiluminescence (ECL) NAb assay method was also developed and validated to evaluate the ability of ADAs to interfere with the activity of SG or its components. The results are discussed in detail in the Trodelvy Integrated Summary of Immunogenicity (ISI) and a summary of the results is provided below. Samples for treatment-emergent ADA assessments were evaluable for 785 participants who received at least 1 dose of SG 10 mg/kg across 4 clinical studies (Studies IMMU-132-01, IMMU-132-05, IMMU-132-06, and IMMU-132-09). Overall,

Missing Information:	Evidence Source
	9/785 participants (1.1%) from Studies IMMU-132-01, IMMU-132-05, and IMMU-132-06 experienced treatment-emergent ADAs to SG. No participant from Study IMMU-132-09 had ADAs to SG at baseline or treatment-emergent ADAs to SG. Among participants with treatment-emergent ADA samples, the onset of ADA was typically observed at their last visit (ISI Table 10). Six of the 9 participants with treatment-emergent ADAs had positive NAb assessments. Overall, the incidence of ADAs was very low across the SG clinical program. All 9 participants (1.1%) with treatment-emergent ADAs received a starting dose of 10 mg/kg SG. None of these participants experienced a treatment-emergent SAE that was considered related to SG or a treatment-emergent AE (TEAE) that led to premature discontinuation of study drug or death (ISI Table 16). Two (2) participants (0.2%) with treatment-emergent ADAs experienced a total of 4 TEAEs (1 participant in IMMU-132-05 and 1 participant in IMMU-132-06) in the Hypersensitivity+ SMQs (Hypersensitivity SMQ [broad and narrow] and Anaphylactic Reaction SMQ [broad and narrow] with onset dates on the day of or 1 day after study drug administration). All of these events were Grade 1-2 and nonserious, and none of them began in the setting of positive ADA results (ISI Table 17). All but one event resolved by the data cut-off data. No participants experienced TEAEs in the Immune-mediated AEs SMQ (Immune-mediated/Autoimmune Disorders SMQ [narrow]). Overall, safety was similar between participants with or without ADAs to SG across individual studies and pooled populations and there was no clear impact of ADA on safety. Pharmacokinetic data were available for 8 of 9 participants with treatment-emergent ADA responses. SG exposures in ADA-positive participants were within the range of exposures observed in the ADA-negative participants. Due to the very low incidence of treatment-emergent ADAs (1.1%), a quantitative assessment of the impact of ADA on SG or total antibody exposure could not be performed in the population PK analyses. The efficacy endpoint of Best Overall Response (BOR) per Independent Review Assessment was stable disease for 3 ADA-positive participants, partial response for 1 ADA-positive participant, progressive disease for 1 ADA-positive participant, and either not evaluable per RECIST 1.1 criteria or not assessed by independent review for 4 ADA-positive participants. Of these 4 participants, 3 participants (from Studies IMMU-132-05 and IMMU-132-06) had a BOR of progressive disease by investigator assessment. For the remaining participant in Study IMMU-132-01, neither independent review nor investigator assessment of BOR was available. Given the small number of participants with positive ADA responses to SG, no formal analysis was performed to assess the impact of ADAs on the efficacy of SG. Overall, there was no clear impact of ADA on efficacy. Overall, the clinical immunogenicity data evaluated demonstrate no discernible impact of ADAs on the efficacy, safety, or PK of SG, indicating that the presence of ADAs to SG does not affect the safety or efficacy of SG in patients with mTNBC, HR+/HER− mBC, or mUC at the intended 10-mg/kg dose on Days 1 and 8 of a 21-day cycle. In the post-marketing setting, no cases suggestive of immunogenicity (eg, PTs Neutralising antibodies, Neutralising antibodies negative, Neutralising antibodies positive) were observed as of the data cut-off date of this report. Population in need of further characterization: To further characterise the potential for immunogenicity with SG, the impact of ADAs on PK, efficacy, and safety of SG will continue to be monitored in ongoing clinical studies.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1. Summary of Safety Concerns

Important Identified Risks	Serious infections secondary to neutropenia
Important Potential Risks	None
Missing Information	Use in patients with moderate or severe hepatic impairment
	Immunogenicity

PART III: PHARMACOVIGILANCE PLAN

III.1. Routine Pharmacovigilance Activities

Routine Pharmacovigilance Activities Beyond Adverse Drug Reactions Reporting and Signal Detection:

None.

Other Forms of Routine Pharmacovigilance Activities

There are no other forms of routine pharmacovigilance activities for any of the safety concerns.

III.2. Additional Pharmacovigilance Activities

Table Part III.1. Ongoing and Planned Additional Pharmacovigilance Activities

Study IMMU-132-15A Phase 1, Open-Label, Dose-Escalation Study to Determine an Appropriate Starting Dose of Sacituzumab Govitecan in Subjects with Advanced or Metastatic Solid Tumour and Moderate Liver Impairment	
Rationale and Study Objectives	*Primary Objectives:* • To identify the safe starting dose of SG in subjects with solid tumour and moderate hepatic impairment • To evaluate the PK of SG in subjects with solid tumour and moderate hepatic impairment • To evaluate the PK of free SN-38 in subjects with solid tumour and moderate hepatic impairment • To evaluate the PK of SN-38G in subjects with solid tumour and moderate hepatic impairment • To evaluate the PK of total SN-38 in subjects with solid tumour and moderate hepatic impairment • To assess the occurrences of human antibodies against SG in subjects with solid tumour and moderate hepatic impairment.
Study Design	A Phase 1, multi-centre, open-label, dose-escalation study of SG in adult subjects with advanced or metastatic solid tumour and moderate hepatic impairment or normal hepatic function. Eligible subjects will receive SG IV infusion over 3 hours on Day 1 and Day 8. Subjects with moderate hepatic impairment will undergo dose escalation following a 3+3 design. The starting SG dose will be 5 mg/kg. If the starting dose is not acceptably tolerated, a lower dose of SG may need to be evaluated. SG doses to be studied will be 5, 7.5, and 10 mg/kg. Dose escalation will only occur if it is deemed to be acceptable after review of safety data up to Day 21. Once the recommended dose is determined, additional subjects with moderate hepatic impairment will be added for a total of 8 subjects receiving the recommended dose. In addition, 8 subjects with normal hepatic function will receive SG 10 mg/kg. Serial blood samples will be collected on Day 1 and Day 8 for up to 7 days after dosing for PK assessments. Safety will be evaluated throughout the study. Subjects will be confined in the study centre from the evening of Day 1 to Day 4 and Day 8 to Day 11. Subjects will report to the study centre on the other days for study procedures. Subjects will exit the study on Day 22. At the completion of the study, subjects who are deriving benefit from SG may continue to receive treatment in an extension study (Study IMMU-132-14). Otherwise, subjects will exit the study on Day 22 and may be followed up further for safety evaluation at the Investigator's discretion.

Study IMMU-132-15A Phase 1, Open-Label, Dose-Escalation Study to Determine an Appropriate Starting Dose of Sacituzumab Govitecan in Subjects with Advanced or Metastatic Solid Tumour and Moderate Liver Impairment	
Study Population	A sample size of up to 20 adult subjects with moderate hepatic impairment defined according to NCI-ODWG criteria (ie, 1.5× ULN <total bilirubin <3.0× ULN) and 8 subjects with normal hepatic function (total bilirubin ≤ULN and AST ≤3.0× ULN) will be enrolled. Subjects will be male or female at least 18 years of age with histologically confirmed advanced or metastatic solid tumour that is measurable or non-measurable and an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2. In addition, subjects must have adequate haematologic counts without transfusional or growth factor support within 2 weeks of study drug initiation (haemoglobin ≥9 g/dL, absolute neutrophil count ≥1,500/mm3, and platelets ≥100,000/ μL), and creatinine clearance ≥30 mL/min as assessed by the Cockcroft-Gault equation.
Milestones	Protocol finalised: 30 Oct 2020; First subject enrolled: Apr 2021; Last subject completed: Dec 2026; CSR Filing: Jun 2027

III.3. Summary Table of Additional Pharmacovigilance Activities

Table Part III.2. Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
Study IMMU-132-15 A Phase 1, Open-Label, Dose-Escalation Study to Determine an Appropriate Starting Dose of Sacituzumab Govitecan in Subjects with Advanced or Metastatic Solid Tumour and Moderate Liver Impairment Ongoing	To identify the safe starting dose of SG in subjects with solid tumour and moderate hepatic impairment. To evaluate the PK of SG, free SN-38, total SN-38, and SN-38G in subjects with solid tumour and moderate hepatic impairment. To assess the occurrences of human antibodies against SG in subjects with solid tumour and moderate hepatic impairment.	Use in patients with moderate or severe hepatic impairment	Protocol finalised	30-Oct-2020
			First subject enrolled	Apr-2021
			Last subject completed	Dec-2026
			CSR filing	Jun-2027

CSR= clinical study report; SG=sacituzumab govitecan; PK=pharmacokinetics

PART IV:
PLANS FOR POSTAUTHORISATION EFFICACY STUDIES

There are no planned or ongoing postauthorisation efficacy studies.

PART V:
RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

V.1. Routine Risk Minimisation Measures

The routine risk minimisation measures for TRODELVY in the EU comprise of the SmPC, the package leaflet (PL), and the legal status of the product. TRODELVY is subject to restricted medical prescription, whereby therapy should only be prescribed and administered by a healthcare professional experienced in the use of anti-cancer therapies (SmPC Section 4.2). The routine risk minimisation recommendations provided by the SmPC and PL are described further by safety concern in Table Part V.1. The legal status can be considered a general measure applicable to all individual safety concerns.

Table Part V.1. Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Serious infections secondary to neutropenia (Important identified risk)	Routine risk communication: • Adverse reaction in SmPC section 4.8 • Side effect in package leaflet (PL) section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Guidance for dose modifications based on severity and occurrence of neutropenia in SmPC section 4.2 — Warning that SG can cause severe or life-threatening neutropenia, fatal infections in the setting of neutropenia have been observed in clinical studies, and recommendations to monitor patients' blood counts during treatment and for when not to administer TRODELVY in SmPC section 4.4 • Warning that UGT1A1*28 allele homozygous patients are at increased risk for neutropenia and febrile neutropenia in SmPC section 4.4 • Guidance for treating severe neutropenia relating to overdose in SmPC section 4.9 • Warning for the patient to seek urgent medical attention for the symptoms of neutropenia or infections and that the patient's doctor may adjust the amount of TRODELVY given or withhold treatment if the patient's blood samples show severe neutropenia in PL section 2 Other routine risk minimisation measures beyond the Product Information: • Restricted medical prescription
Use in patients with moderate or severe hepatic impairment (Missing information)	Routine risk communication: • Information that the exposure of SG is similar in patients with mild hepatic impairment to patients with normal hepatic function in SmPC Section 5.2 • Information that SG exposure is unknown in patients with moderate or severe hepatic impairment and that SN-38 exposure may be elevated in such patients due to decreased hepatic UGT1A1 activity in SmPC Section 5.2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Guidance that no dose adjustment is necessary in patients with mild hepatic impairment in SmPC Section 4.2 • Guidance that the safety of TRODELVY in patients with moderate or severe hepatic impairment has not been established and that the use of TRODELVY should be avoided in these patients in SmPC Section 4.2 • Guidance for the patient to talk to their doctor or nurse before they are given TRODELVY if they have liver problems in PL Section 2 Other routine risk minimisation measures beyond the Product Information: • Restricted medical prescription
Immunogenicity (Missing information)	Routine risk communication: • Information that across clinical studies in patients treated with SG, 9 (1.1%) of 785 patients developed antibodies to SG; 6 of these patients (0.8% of all patients treated with SG) had NAbs against SG in SmPC section 4.8 Other routine risk minimisation measures beyond the Product Information: • Restricted medical prescription

V.2. Additional Risk Minimisation Measures

Routine risk minimization activities as described in Part V are sufficient to manage the safety concerns of the medicinal product.

V.3. Summary of Risk Minimisation Measures

Table Part V.2. Summary Table of Pharmacovigilance and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important identified risk		
Serious infections secondary to neutropenia	Routine risk minimisation measures: • Dose modifications based on severity and occurrence in SmPC section 4.2 • Warnings of severe or life-threatening neutropenia, including fatal infections in the setting of neutropenia observed in clinical studies, in SmPC section 4.4 • Warning for UGT1A1*28 allele homozygous patients in SmPC section 4.4 • Adverse reaction in SmPC section 4.8 • Guidance for treating severe neutropenia relating to overdose in SmPC section 4.9 • Warning in PL section 2 • Side effect in PL section 4 • Restricted medical prescription Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: None
Important potential risk(s)		
None		
Missing information		
Use in patients with moderate or severe hepatic impairment	Routine risk minimisation measures: • Guidance that no dose adjustment is necessary for mild hepatic impairment in SmPC Section 4.2 • Guidance that TRODELVY should be avoided in patients with moderate or severe hepatic impairment in SmPC Section 4.2 • Information on SG exposure in patients with hepatic impairment in SmPC Section 5.2 • Guidance for the patient to talk to their doctor or nurse if they have liver problems in PL Section 2 • Restricted medical prescription Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study IMMU-132-15
Immunogenicity	Routine risk minimisation measures: • Available clinical data on SG immunogenicity SG SmPC section 4.8 • Restricted medical prescription Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR TRODELVY (SACITUZUMAB GOVITECAN)

This is a summary of the risk management plan (RMP) for TRODELVY. The RMP details important risks of TRODELVY, how these risks can be minimized, and how more information will be obtained about TRODELVY's risks and uncertainties (missing information).

TRODELVY's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how TRODELVY should be used.

This summary of the RMP for TRODELVY should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of TRODELVY's RMP.

I. The Medicine and What Is It Used For

TRODELVY is authorized as a monotherapy for the treatment of adult patients with unresectable or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, including at least one of them for advanced disease and for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-negative breast cancer who have received endocrine-based therapy, and at least two additional systemic therapies in the advanced setting (see SmPC for the full indication). It contains sacituzumab govitecan as the active substance and it is given as an intravenous infusion.

Further information about the evaluation of TRODELVY's benefits can be found in TRODELVY's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage <link to the EPAR summary landing page>.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of TRODELVY, together with measures to minimize such risks and the proposed studies for learning more about TRODELVY's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;

- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the public (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including periodic safety update report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of TRODELVY is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of TRODELVY are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of TRODELVY. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine)

Table Part VI.1. List of Important Risks and Missing Information

Important Identified Risks	Serious infections secondary to neutropenia
Important Potential Risks	None
Missing Information	Use in patients with moderate or severe hepatic impairment
	Immunogenicity

II.B. Summary of Important Risks

TRODELVY has been assigned the legal status of a medicine subject to medical prescription in the European Union (EU), whereby therapy should only be prescribed and administered by a healthcare professional experienced in the use of anti-cancer therapies (as described in Section 4.2 of the SmPC).

Table Part VI.2. Summary of Important Risks and Missing Information

Important identified risk	**Serious infections secondary to neutropenia**
Evidence for linking the risk to the medicine	In the clinical studies 67.6% of 688 patients had neutropenia and in 50.7% of patients the neutropenia was severe. The dose of sacituzumab govitecan (SG) was interrupted in 44.2% and reduced in 12.4% of patients. Three patients (0.4%) discontinued SG because of neutropenia. Infections potentially associated with neutropenia occurred in 10.6% of 688 patients in the Overall Targeted metastatic breast cancer (mBC) population. Serious infections potentially associated with neutropenia occurred in 2.8% of 688 patients. The dose of SG was interrupted in 1.5% of patients, reduced in 0.4% of patients, and was discontinued in 0.3% of patients. Neutropenia was one of the main toxicities seen in animal studies. Clinical studies can provide an estimation of the frequency and nature of a side effect that is expected to occur in clinical practice. Findings from studies in animals may be relevant for humans and in the absence of data in humans suggest a potential safety concern that awaits clinical confirmation.
Risk factors and risk groups	Risk factors for neutropenia caused by cancer chemotherapies include increasing age, abnormal liver enzyme laboratory values, female gender, underweight, radiation therapy to the bone marrow, type of prior chemotherapy, and type of current treatment {Fontanella 2014}. When SG is metabolised in the body, the active metabolite SN-38 is inactivated by an enzyme called uridine 5'-diphospho (UDP)-glucuronosyltransferase (UGT). Patients with reduced activity of this enzyme, such as patients who are homozygous for the *28 allele of UGT1A1, who are treated with SG have an increased risk of neutropenia and accordingly, an increased risk of serious infection.
Risk minimisation measures	Routine risk minimisation measures: • Dose modifications based on severity and occurrence in SmPC section 4.2 • Warnings of severe or life-threatening neutropenia, including fatal infections in the setting of neutropenia observed in clinical studies, in SmPC section 4.4 • Warning for UGT1A1*28 allele homozygous patients in SmPC section 4.4 • Adverse reaction in SmPC section 4.8 • Guidance for treating severe neutropenia relating to overdose in SmPC section 4.9 • Warning in PL section 2 • Side effect in PL section 4 • Restricted medical prescription Additional risk minimisation measures: • None
Missing information	**Use in patients with moderate or severe hepatic impairment**
Risk minimisation measures	Routine risk minimisation measures: • Guidance that no dose adjustment is necessary for mild hepatic impairment in SmPC Section 4.2 • Guidance that TRODELVY should be avoided in patients with moderate or severe hepatic impairment in SmPC Section 4.2 • Information on SG exposure in patients with hepatic impairment in SmPC Section 5.2 • Guidance for the patient to talk to their doctor or nurse if they have liver problems in PL Section 2 • Restricted medical prescription Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study IMMU-132-15 See Section II.C of this summary for an overview of the postauthorisation development plan.
Missing information	**Immunogenicity**
Risk minimisation measures	Routine risk minimisation measures: • Available clinical data on SG immunogenicity in SmPC section 4.8 • Restricted medical prescription Additional risk minimisation measures: • None

II.C. Postauthorisation Development Plan

II.C.1. Studies Which Are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorization or specific obligation of TRODELVY.

II.C.2. Other Studies in Postauthorisation Development Plan

Table Part VI.3. Other Studies in Postauthorization Development Plan

Short Study Name	Purpose of the Study
Study IMMU-132-15 A Phase 1, Open-Label, Dose-Escalation Study to Determine an Appropriate Starting Dose of Sacituzumab Govitecan in Subjects with Advanced or Metastatic Solid Tumour and Moderate Liver Impairment	The purpose of this study is: To identify the safe starting dose of TRODELVY in subjects with solid tumour and moderate hepatic impairment. To evaluate the pharmacokinetics of TRODELVY, free SN-38, total SN-38, and SN-38G in subjects with solid tumour and moderate hepatic impairment. To assess the occurrences of human antibodies against TRODELVY in subjects with solid tumour and moderate hepatic impairment.

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PART VII: ANNEXES

Table of Contents

Annex 1. EudraVigilance Interface

This XML file is submitted electronically and can be provided on request.

Annex 2. Tabulation Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program

Annex 3. Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Plan

Annex 4. Specific Adverse Drug Reaction Follow-up Forms

None.

Annex 5. Protocols for Proposed and Ongoing Studies in RMP Part IV

None.

Annex 6. Details of proposed additional risk minimisation measures (if applicable)

None.

Annex 7. Other Supporting Data (Including Referenced Material)

The following information is included in this annex:

Referenced material (Refer to REFERENCES)

Annex 8. Summary of Changes to the Risk Management Plan over Time

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2. ELECTRONIC SIGNATURES

[redacted]

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
Eva Vanengelen	QPPV eSigned	11-Mar-2024 16:26:40
[redacted]	Patient Safety eSigned	11-Mar-2024 21:21:05
[redacted]	Global Development Lead (GDL) eSigned	12-Mar-2024 01:18:48

Annex 2. Tabulation Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program

Table 1. Planned and Ongoing Studies

Study	Summary of Objectives	Safety Concern addressed	Protocol link Milestones
Planned studies			
None			
Ongoing studies			
Study IMMU-132-15 A Phase 1, Open-Label, Dose-Escalation Study to Determine an Appropriate Starting Dose of Sacituzumab Govitecan in Subjects with Advanced or Metastatic Solid Tumour and Moderate Liver Impairment Ongoing Category 3	To identify the safe starting dose of SG in subjects with solid tumour and moderate hepatic impairment. To evaluate the PK of SG, free SN-38, total SN-38, and SN-38G in subjects with solid tumour and moderate hepatic impairment. To assess the occurrences of human antibodies against SG in subjects with solid tumour and moderate hepatic impairment.	Use in patients with moderate or severe hepatic impairment	Study IMMU-132-15 Protocol finalised: 30 Oct 2020 First subject enrolled: Apr 2021 Last subject completed: Dec 2026 CSR filing: Jun 2027

CSR=clinical study report; SG=sacituzumab govitecan; PK=pharmacokinetics

Table 2. Completed Studies

Study	Summary of Objectives	Safety Concern addressed	Date of Final Study Report submission Link to report
None			

Annex 3. Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Plan

Protocols for the studies included in the table below are provided in this annex.

Table 1. Overview of Included Protocols

Study Number and Title	Version of Protocol	Date of Protocol Version
Part A: Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP		
None	Not applicable	Not applicable
Part B: Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP		
None	Not applicable	Not applicable
Part C: Previously agreed protocols for ongoing studies and final protocols not reviewed by the competent authority.		
Approved protocols:		
None	Not applicable	Not applicable
Final protocols not reviewed or not approved:		
Study IMMU-132-15	Amendment 3	16-Jun-2021

The following studies included in the pharmacovigilance plan are planned and protocols are not currently available:

Not applicable

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1, Open-Label, Dose-Escalation Study to Determine an Appropriate Starting Dose of Sacituzumab Govitecan in Subjects With Advanced or Metastatic Solid Tumor and Moderate Liver Impairment
Sponsor:	Immunomedics, Inc. 300 The American Road Morris Plains, NJ 07950
IND Number:	122694
ClinicalTrials.gov Identifier:	NCT04617522
Protocol ID:	IMMU-132-15
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List
Protocol Version/Date:	Original: 30 October 2020 Amendment 1: 22 December 2020 Amendment 2: 23 February 2021 Amendment 3: 16 June 2021

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, sites located in the European Economic Area, the United Kingdom, and Switzerland are not included under the investigational new drug application and are considered noninvestigational new drug application sites.

SUMMARY OF CHANGES

Amendment 3

The major changes incorporated in this protocol (Amendment 3, dated 16 June 2021) relative to the prior approved version (Amendment 2, dated 23 February 2021) are summarized below. Editorial and formatting changes are not included in this summary.

Section	Change in Amendment 3	Rationale for Change
Protocol Synopsis – Study Centers	Updated the number of planned study centers from "2 to 3" to "approximately 7"	Increased the number of planned study centers to meet enrollment targets
Protocol Synopsis – Study Design Section 3.1 Overall Study Design Section 7.5 Administration	Clarified the timing of infusions on Day 1 and Day 8 to align with the sacituzumab govitecan Pharmacy Manual and package insert	Clarification
Protocol Synopsis – Study Design Section 3.1 Overall Study Design	Added language to include review of available pharmacokinetic (PK) data during the dose escalation review at each dose group	Added review of PK data, if available, during dose escalation review
Protocol Synopsis – Study Design Section 3.1 Overall Study Design Section 4.4 Study Procedures (Table 2 Schedule of Assessments)	Clarified that the serial PK blood samples on Day 1 and Day 8 are required and will be collected through 7 days after dosing Updated footnotes 13 and 14 in Table 2 to align with body of protocol	Clarification
Protocol Synopsis – Study Design, Duration of Treatment Section 3.1 Overall Study Design Section 3.4 Thirty-Day Safety Follow-Up Section 3.5 Definition of End of Study	Clarified the timing when subjects may continue to the rollover study (IMMU-132-14), at the end of treatment visit. In addition, all subjects must complete an end of study visit approximately 30 days after the last dose of study drug.	Clarification
Protocol Synopsis – Diagnosis and Main Criteria for Inclusion; Main Criteria for Exclusion Section 4.4 Study Procedures (Table 2: Schedule of Assessments) Section 5.1 Subject Inclusion Criteria Section 5.2. Subject Exclusion Criteria	Clarified that eligibility for participation in the study will be based on subjects meeting all inclusion criteria and no exclusion criteria at Screening. Table 2 Schedule of Assessments and footnote 2 have been updated to align with language in Sections 5.1 and 5.2 regarding eligibility.	Clarification

Section	Change in Amendment 3	Rationale for Change
Protocol Synopsis – Diagnosis and Main Criteria for Inclusion (Inclusion Criteria 7, 8, 9) Section 5.1 Subject Inclusion Criteria (Inclusion Criteria 7, 8, 9)	Revised the contraception language for males and females. Parts of Inclusion Criteria 8 and 9 were combined with Inclusion Criterion 7.	Revised contraception language to align with contraception requirements in other Trodelvy studies
Protocol Synopsis - Main Criteria for Exclusion (Exclusion Criterion 6) Section 5.2 Subject Exclusion Criteria (Exclusion Criterion 6)	Replaced “study drug” with “investigational drug”	Clarification
Protocol Synopsis - Main Criteria for Exclusion (Exclusion Criterion 12) Section 5.2 Subject Exclusion Criteria (Exclusion Criterion 12)	Clarified the intent of Exclusion Criterion 12, replaced “have active cardiac disease” with “history of cardiac disease”. Clarified part C of Exclusion Criterion 12, added “documented” left ventricular ejection fraction of < 40%.	Clarification
Protocol Synopsis - Main Criteria for Exclusion (Exclusion Criterion 16) Section 5.2 Subject Exclusion Criteria (Exclusion Criterion 16)	Replaced “uncontrolled” with “undetectable” in Exclusion Criterion 16: “Have known history of human immunodeficiency virus-1/2 with undectable viral load and on medications that may interfere with study drug metabolism.”	Clarification based on FDA feedback for IMMU-132-13
Protocol Synopsis - Main Criteria for Exclusion (Exclusion Criterion 17) Section 5.2 Subject Exclusion Criteria (Exclusion Criterion 17)	Clarified the requirements for hepatitis B virus and hepatitis C virus testing	Clarification
Protocol Synopsis – Objectives, Criteria for Evaluation (Immunogenicity), Statistical Methods Section 2.1 Primary Objectives Section 2.2.3 Immunogenicity End Points	Updated the objective and end point criteria to report the number of subjects who have antibodies against sacituzumab govitecan	Updated the immunogenicity end point to be more quantitative Updated the objective to align with the end point
Protocol Synopsis – Criteria for Evaluation (Pharmacokinetics) Section 2.2.2 Pharmacokinetic End Points	Clarified the definition of AUC extrapolated to be “between AUC_{last} and AUC_{inf}” and to align with master abbreviations list	Clarification
Protocol Synopsis – Criteria for Evaluation (Statistical Methods)	Clarified that “Serum concentrations of sacituzumab govitecan, free SN-38, SN-38G, and total SN-38 will be summarized over each	Clarification

Section	Change in Amendment 3	Rationale for Change
12.3.1. Pharmacokinetic Analyses	scheduled sampling time by dosing day (Day 1, Day 8)…"; removed reference to Day 22	
Section 1.3 Clinical Experience	Provided current information about sacituzumab govitecan	Provided current information
Section 4.1. Informed Consent	Removed the following language: "In the case where the subject decides to stop all protocol procedures and decides to withdraw consent from treatment, in order to continue follow-up for long-term survival, the subject may be required to sign an additional informed consent form (ICF)."	Subjects are not being followed for long term survival
Section 4.2 Screening	Clarified language to allow rescreen of a previously screen failed subject once at the discretion of the principal investigator and with approval from sponsor medical monitor Clarified language regarding repeat of screening labs Added language to note a unique subject number will be assigned at the time of consent at screening. In addition, a unique number will be assigned when a subject rescreens.	Clarification for rescreening and repeat labs Clarification for unique subject numbers
Section 4.2.2 Subject Replacement	Added section to provide details regarding subject replacement	Added section for subject replacement
Section 4.4 Study Procedures (Table 2 Schedule of Assessments)	Added windows for End of Treatment/Early Termination (Day 22 ± 1) and End of Study/30 Day Safety Follow-up (Day 30 ± 1)	Updated schedule of assessments to align with updated assessments throughout protocol Added windows for Day 22 and Day 30 to allow flexibility for study visits
Section 4.4 Study Procedures (Table 2 Schedule of Assessments) Section 11.1.7.6 Pregnancy Testing Section 11.1.7.7 Follicle-Stimulating Hormone (FSH)	Revised serum and urine pregnancy and follicle-stimulating hormone (FSH) testing requirements in Table 2 and Appendix 5 Updated Section 11.1.7.6 name from "Pregnancy Screen" to "Pregnancy Testing"	Revised pregnancy testing and FSH requirements to align with other Trodelvy studies
Section 6.3 Definition of Dose-Limiting Toxicity	Clarified the definition of dose-limiting toxicity to specify treatment related TEAEs are considered DLTs, and revised the dose-limiting toxicity criteria for neutropenia from ≥ Grade 3 to ≥ Grade 4 Added language to section 6.3: "Subjects who experience a DLT may continue dosing with dose adjustment per toxicity management guidelines as per section 6.5.3 at the discretion	Updated to align with other early phase Trodelvy studies (eg, IMMU-132-01) given Trodelvy's known and manageable effect on neutrophil count Clarified the definition of DLT to specify treatment related TEAEs and provided

Section	Change in Amendment 3	Rationale for Change
	of the investigator and sponsor as long as they are able to receive a minimum dose of 5 mg/kg."	dose reduction guidelines for subjects who experience a DLT
Section 6.5.2. Management of Sacituzumab Govitecan Toxicities	Removed the following language: "If found to have the 1/28 or 28/28 polymorphism, data should be recorded in the eCRF with dosing adjusted per institutional standards." Added the following language: "All efforts to avoid dose reduction should be taken to address toxicity prior to initiation of dose reduction. Instructions for dose reduction and discontinuation of sacituzumab govitecan for treatment related toxicities are provided in Section 6.5.3."	UGT1A1 results are not captured in eCRF. Added language to ensure toxicity is addressed prior to initiation of dose reduction.
Section 6.5.3 Dose Reduction and Discontinuation (as per Package Insert)	Added section to provide guidance for dose reduction and discontinuation as per package insert	Added section to align dose reduction and discontinuation across other Trodelvy studies
Section 6.6.1 COVID-19 Vaccine	Added section regarding COVID-19 vaccine	Incorporated COVID-19 vaccine guidance from Protocol Clarification Letter #1 (dated 05 March 2021)
Section 7.5 Administration	Clarified the administration procedures for sacituzumab govitecan	Clarification
Section 7.7.2. Receipt of Study Drug	Removed reference to IWRS	Not applicable to study
Section 9. Assessment of Pharmacokinetics (Table 4: Pharmacokinetic Sampling Time Points)	Added windows for PK time points in Table 4	Added windows for PK time points to allow flexibility
Section 10.1 Sample Storage	Added section to provide sample storage duration for PK and antidrug antibody sampling	Added sample storage duration for PK and antidrug antibody sampling
Section 11.2.1.3 Special Situation Reports	Added section for special situations reports including 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	Added section to align special situations reports with other Trodelvy studies
Section 11.2.2.1 Reporting Period for Adverse Events and Special Situation Reports Section 11.2.2.2 Adverse Event Collection and Documentation	Added the following text regarding special situation reporting: Section 11.2.2.1: "All study drug SSRs that occur from study drug initiation and throughout the duration of the study, including	Added reporting period and reporting process for special situations to align with other Trodelvy studies

Section	Change in Amendment 3	Rationale for Change
	the post treatment follow-up visit, must be reported to the sponsor." Section 11.2.2.2: "All study drug SSRs that occur from study drug initiation and throughout the duration of the study, including the post treatment follow-up visit, must be reported to the sponsor."… "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 11.2.5."	
Section 11.2.4 Reporting Exposure During Pregnancy	Updated section regarding exposure during pregnancy	Updated section to align with other Trodelvy studies
Section 12.2 Populations for Analyses	Updated "and total SN-38" to "or total SN-38"	Corrected the definition
Section 12.3 Statistical Analyses	Added CV% to the summary statistics	Added one more statistic
Section 12.3.2 Safety Analyses	Added the definitions of treatment-emergent adverse events and treatment-emergent laboratory abnormalities	Clarification
Section 12.3.3 Immunogenicity	Updated "Occurrence of positive human antibodies…" to "Number of subjects with antibodies…"	Aligned with the endpoint
Section 13.1 Study Monitoring	Removed the word "onsite" review of subject's eCRFs to allow flexibility with the monitoring methods performed during the pandemic	Allow additional monitoring methods (e,g remote monitoring visits) during the pandemic
Appendix 4. Pandemic Risk Assessment and Mitigation Plan	Added Appendix for pandemic assess risk mitigation plan	Added section to assess risk and outline mitigation plan during a pandemic
Appendix 5. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements	Added section to provide standard contraception requirements for females and males	Updated contraception requirements to align with other Trodelvy studies

PROTOCOL SYNOPSIS

Immunomedics, Inc.
300 The American Road
Morris Plains, NJ 07950

Name of Sponsor/Company: Immunomedics, Inc.

Name of Study Drug: sacituzumab govitecan

Name of Active Ingredient: Sacituzumab govitecan (IMMU-132) is an antibody-drug conjugate composed of hRS7, a humanized immunoglobulin G1 κ monoclonal antibody that binds to trophoblast cell-surface antigen-2; SN-38, a camptothecin analog that inhibits topoisomerase I; and CL2A, a pH-sensitive linker that couples SN-38 to hRS7.

Protocol Number: IMMU-132-15	**Phase:** 1	**Country:** United States

Title of Study: A Phase 1, Open-Label, Dose-Escalation Study to Determine an Appropriate Starting Dose of Sacituzumab Govitecan in Subjects With Advanced or Metastatic Solid Tumor and Moderate Liver Impairment

Study Centers: Approximately 7 study centers

Phase of Development: 1

Objectives:

- To identify the safe starting dose of sacituzumab govitecan in subjects with solid tumor and moderate hepatic impairment
- To evaluate the pharmacokinetics (PK) of sacituzumab govitecan in subjects with solid tumor and moderate hepatic impairment
- To evaluate the PK of free SN-38 in subjects with solid tumor and moderate hepatic impairment
- To evaluate the PK of SN-38 glucuronide (SN-38G) in subjects with solid tumor and moderate hepatic impairment
- To evaluate the PK of total SN-38 in subjects with solid tumor and moderate hepatic impairment
- To assess the number of subjects with antibodies against sacituzumab govitecan with solid tumor and moderate hepatic impairment

Study Design:

This is a Phase 1, multicenter, open-label, dose-escalation study of sacituzumab govitecan in adult subjects with advanced or metastatic solid tumor and moderate hepatic impairment or normal hepatic function. Up to 20 subjects with moderate hepatic impairment defined according to the National Cancer Institute Organ Dysfunction Working Group criteria (ie, 1.5 × upper limit of normal [ULN] < total bilirubin < 3.0 × ULN) and 8 subjects with normal hepatic function will be enrolled. Eligible subjects will receive sacituzumab govitecan intravenous (IV) infusion on Day 1 and Day 8. Subjects will be administered the first infusion on Day 1 over 3 hours. The second infusion on Day 8 will be administered over 1 to 2 hours if the prior infusion was tolerated.

Subjects with moderate hepatic impairment will undergo dose escalation following a 3+3 study design. Dose escalation will occur if fewer than 33% of subjects within the dosing group experienced a dose-limiting toxicity. The starting sacituzumab govitecan dose will be 5 mg/kg. If the starting dose is not acceptably tolerated, a lower dose of sacituzumab govitecan may need to be evaluated. Sacituzumab govitecan doses to be studied will be 5, 7.5, and 10 mg/kg. Dose escalation will only occur if deemed acceptable after review of safety data up to Day 22 and available PK data. Once the recommended dose is determined, additional subjects with moderate hepatic impairment will be added, for a total of 8 subjects receiving the recommended dose. In addition, 8 subjects with normal hepatic function will receive sacituzumab govitecan 10 mg/kg.

Serial blood samples will be collected on Day 1 and Day 8 (dosing days) through 7 days after dosing for PK assessments. Safety will be evaluated throughout the study. Subjects may be confined in the study center from the evening of Day 1 to Day 4 and Day 8 to Day 11 at the discretion of the investigator. Subjects will report to the study center on the study days for study procedures. Subjects will exit the study on Day 38. At the completion of study treatment (end of treatment [EOT]), subjects who are deriving benefit from sacituzumab govitecan may continue to receive treatment in a rollover study (IMMU-132-14). All subjects must complete an End-of-Study visit approximately 30 days after the last dose of the study drug.

Sample Size Justification:

A sample size of up to 20 adult subjects with moderate hepatic impairment with solid tumor and 8 adult subjects with normal hepatic function with solid tumor is deemed sufficient to evaluate the PK and safety profiles of sacituzumab govitecan when administered to subjects with moderate hepatic impairment.

Number of Subjects (planned): Up to 20 adult subjects with moderate hepatic impairment with solid tumor and 8 adult subjects with normal hepatic function with solid tumor.

Diagnosis and Main Criteria for Inclusion:

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

Inclusion criteria for all subjects:

1) Male or female subjects ≥ 18 years of age, at the time of signing the informed consent form.
2) Histologically confirmed advanced or metastatic solid tumor that is measurable or non-measurable.
3) Eastern Cooperative Oncology Group performance status score of 0, 1, or 2.
4) Adequate hematologic counts without transfusional or growth factor support within 2 weeks of study drug initiation (hemoglobin ≥ 9 g/dL, absolute neutrophil count ≥ 1,500/mm^3, and platelets ≥ 100,000/μL).
5) Creatinine clearance ≥ 30 mL/min as assessed by the Cockcroft-Gault equation.
6) Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form.
7) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception as described in Appendix 5.

Additional inclusion criteria for subjects with normal hepatic function:

8) In acceptable health as determined by a responsible and experienced physician, based on a medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.
9) Normal hepatic function (total bilirubin ≤ ULN and aspartate aminotransferase [AST] ≤ 3.0 × ULN).

Additional inclusion criteria for subjects with moderate hepatic impairment:

10) Moderate hepatic impairment (1.5 × ULN < total bilirubin < 3.0 × ULN and any level of AST).
11) For subjects with hepatic encephalopathy, the condition does not, in the investigator's opinion, interfere with the subject's ability to provide an appropriate informed consent.

Main Criteria for Exclusion:

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

Exclusion criteria for all subjects:

1) Women who are pregnant or lactating.
2) Unwillingness or inability to follow the procedures outlined in the protocol.
3) Have poor venous access.
4) Donated or lost 500 mL or more of blood volume (including plasmapheresis) or plans to donate blood during the study.
5) Have a history of sensitivity to any of the study medications, or components thereof, or a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates their participation.
6) Received investigational drug within 4 weeks prior to Day 1.
7) Have had a prior anticancer biologic agent within 4 weeks prior to Day 1 visit or have had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to Day 1 and who have not recovered (ie, ≤ Grade 2) from adverse events (AEs) at the time of study entry. Subjects participating in observational studies are eligible.
8) Had prior treatment with irinotecan within 4 weeks prior to Day 1.
9) Have not recovered (ie, ≤ Grade 1) from AEs due to a previously administered agent.

   Note: Subjects with ≤ Grade 2 neuropathy or 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 therapy.
10) Have an active second malignancy.

    Note: Subjects with a history of malignancy that has been completely treated, with no evidence of active cancer for 3 years prior to enrollment, or subjects with surgically cured tumors with a low risk of recurrence are allowed to enroll.
11) Have known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they have stable CNS disease for at least 4 weeks prior to the first dose of the study drug and all neurologic symptoms have returned to baseline, have no evidence of new or enlarging brain metastases, and are taking ≤ 20 mg/day of prednisone or its equivalent. All subjects with carcinomatous meningitis are excluded regardless of clinical stability.

12) History of cardiac disease, defined as follows:
    a) Myocardial infarction or unstable angina pectoris within 6 months of Day 1.
    b) History of serious ventricular arrhythmia (ie, ventricular tachycardia or ventricular fibrillation), high-grade atrioventricular block, or other cardiac arrhythmias requiring antiarrhythmic medications (except for atrial fibrillation that is well controlled with antiarrhythmic medication); history of QT interval prolongation.
    c) New York Heart Association Class III or greater congestive heart failure or documented left ventricular ejection fraction of < 40%.
13) Have active chronic inflammatory bowel disease (ulcerative colitis or Crohn's disease) or gastrointestinal perforation within 6 months of enrollment.
14) Have active serious infection requiring IV antibiotics (contact medical monitor for clarification).
15) 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.
16) Have known history of human immunodeficiency virus-1/2 with undectable viral load and on medications that may interfere with study drug metabolism.
17) Have active hepatitis B virus (HBV) or hepatitis C virus (HCV) by confirming with hepatitis B surface antigen and hepatitis C antibody. In subjects with a history of HBV or HCV, subjects with a detectable viral load confirmed by polymerase chain reaction test will be excluded.
18) Have a history of regular alcohol consumption within 6 months of the study defined as an average weekly intake of > 14 drinks for males or > 7 drinks for females. One drink is equivalent to 12 g of alcohol, 12 ounces (360 mL) of beer, 5 ounces (150 mL) of wine, or 1.5 ounces (45 mL) of 80-proof distilled spirits.
19) High-dose systemic corticosteroids (≥ 20 mg of prednisone or its equivalent) are not allowed within 2 weeks prior to Day 1. However, inhaled, intranasal, intra-articular, and topical steroids are allowed.
20) Use of strong inhibitor or inducer of UGT1A1.
21) Have a history of Gilbert's disease.

<u>Additional exclusion criteria for subjects with normal hepatic function</u>:

22) Have pre-existing condition interfering with hepatic and/or renal function that could interfere with the metabolism and/or excretion of the study drug.

Additional exclusion criteria for subjects with moderate hepatic impairment:

23) Had a clinical exacerbation of liver disease within the 2-week period before administration of study drug (ie, abdominal pain, nausea, vomiting, anorexia, or fever).

24) Had clinically demonstrable, tense ascites.

25) Had evidence of acute viral hepatitis within 1 month prior to administration of study drug.

26) Have evidence of hepatorenal syndrome.

27) Subjects with transjugular intrahepatic portosystemic shunt placement.

28) Have active Stage 3 or 4 encephalopathy.

Study Drug, Dosage, and Mode of Administration: sacituzumab govitecan: 5, 7.5, and 10 mg/kg once weekly as IV infusion

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Duration of Treatment: A total of 2 doses are administered on Day 1 and Day 8. The end of study visit is approximately 30 days after the last dose of study drug (Day 38). At the completion of study treatment (EOT), subjects who are deriving benefit from sacituzumab govitecan may continue to receive treatment in a rollover study (IMMU-132-14).

Reference Therapy, Dosage, and Mode of Administration: Not applicable

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Criteria for Evaluation

Efficacy: Not applicable

Safety:

- Number of subjects experiencing treatment-emergent AEs
- Clinical laboratory tests
- Vital signs
- Electrocardiogram (ECG)

Pharmacokinetics:

Primary PK end points

- Maximum observed serum concentration (C_{max}) of sacituzumab govitecan, free SN-38, SN-38G, and total SN-38 following dosing on Day 1 and Day 8
- Area under the serum concentration-time curve from time 0 to time of the last quantifiable concentration ($AUC_{0\text{-}last}$) of sacituzumab govitecan, free SN-38, SN-38G, and total SN-38 following dosing on Day 1 and Day 8
- Area under the serum concentration-time curve from time 0 to 168 hours ($AUC_{0\text{-}168}$) of sacituzumab govitecan, free SN-38, SN-38G, and total SN-38 following dosing on Day 1 and Day 8

Additional PK end points

- Area under the serum concentration-time curve from time 0 extrapolated to infinity ($AUC_{0\text{-}inf}$) of sacituzumab govitecan, free SN-38, SN-38G, and total SN-38 following dosing on Day 1 and Day 8
- Percentage of AUC extrapolated between AUC_{last} and AUC_{inf} ($\%AUC_{exp}$) of sacituzumab govitecan, free SN-38, SN-38, and total SN-38 following dosing on Day 1 and Day 8
- Time to maximum observed serum concentration (T_{max}) of sacituzumab govitecan, free SN-38, SN-38G, and total SN-38 following dosing on Day 1 and Day 8
- Total body clearance of sacituzumab govitecan following dosing on Day 1 and Day 8
- Total volume of distribution during the terminal phase (V_z) of sacituzumab govitecan following dosing on Day 1 and Day 8
- Terminal elimination rate constant (λ_z) of sacituzumab govitecan, free SN-38, SN-38G, and total SN-38 following dosing on Day 1 and Day 8
- Terminal elimination half-life ($t_{1/2}$) of sacituzumab govitecan, free SN-38, SN-38G, and total SN-38 following dosing on Day 1 and Day 8
- Accumulation ratio based on C_{max} of sacituzumab govitecan, free SN-38, SN-38G, and total SN-38 following dosing on Day 1 and Day 8
- Accumulation ratio based on $AUC_{0\text{-}168}$ of sacituzumab govitecan, free SN-38, SN-38G, and total SN-38 following dosing on Day 1 and Day 8

Immunogenicity:

- Number of subjects with antibodies against sacituzumab govitecan

Statistical Methods:

Any subject who has received at least a single dose of sacituzumab govitecan will be included for safety and immunogenicity analyses. Any subject who has at least 1 measurable serum concentration of sacituzumab govitecan, free SN-38, SN-38G, and total SN-38 will be included in the PK analysis.

Serum concentrations of sacituzumab govitecan, free SN-38, SN-38G, and total SN-38 will be summarized over each scheduled sampling time by dosing day (Day 1, Day 8) for each dose level and subject population (normal hepatic function and moderate hepatic impairment) using descriptive statistics. Serum PK parameters of sacituzumab govitecan, free SN-38, SN-38G, and total SN-38 will be derived by noncompartmental methods and summarized by dosing day (Day 1 and Day 8) for each dose level and subject population using descriptive statistics. Individual concentration and PK parameter data will be listed. Graphical presentation will also be used to present the concentration-time profiles and PK parameters as appropriate.

An analysis of variance (ANOVA) will be performed on natural logarithms of $AUC_{0\text{-last}}$, $AUC_{0\text{-}168}$, and C_{max} for sacituzumab govitecan, free SN-38, SN-38G, and total SN-38, with subject population as a fixed effect. Dose-normalized parameters will be used if the doses are different between the 2 subject populations. Within the ANOVA framework, the ratio of the geometric means and the corresponding 90% confidence interval of the ratio between the moderate hepatic impairment and the normal hepatic function populations will be estimated.

All safety analyses will be summarized by dose level and subject population (normal hepatic function and moderate hepatic impairment). Treatment-emergent AEs and serious AEs, laboratory test results, vital signs, and ECG results will be summarized. Safety data will be summarized using descriptive statistics. Individual data will be listed.

Number of subjects with antibodies against sacituzumab govitecan will be summarized by dose level and subject population (normal hepatic function and moderate hepatic impairment). Individual data will be listed.

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LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS

The following abbreviations are used in this study protocol.

$\%AUC_{exp}$	percentage of AUC extrapolated between AUC_{last} and AUC_{inf}
%CV	percentage coefficient of variation
λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the log concentration of drug versus time curve of the drug
ADA	antidrug antibody
AE	adverse event
ANC	absolute neutrophil count
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC_{0-168}	Partial area under the serum concentration-time curve from time 0 to 168 hours
CFR	Code of Federal Regulations
CL	Clearance
CNS	central nervous system
C_{max}	maximum observed serum concentration of drug
CRF	case report form
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOS	end of study
EOT	end of treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	informed consent form
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IEC	Independent Ethics Committee
IgG1	immunoglobulin G1
IND	Investigational New Drug
IRB	Institutional Review Board
IV	intravenous(ly)
mAb	monoclonal antibody
MTD	maximum tolerated dose

mTNBC	metastatic triple-negative breast cancer
n	number of subjects with available data
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NSCLC	non-small cell lung cancer
PI	principal investigator
PK	pharmacokinetic(s)
PO	orally
SAE	serious adverse event
SN-38G	SN-38 glucuronide
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
T_{max}	time (observed time point) of C_{max}
TNBC	triple-negative breast cancer
Trop-2	trophoblast cell-surface antigen-2
UGT1A1	UDP-glucuronosyltransferase 1A1
ULN	upper limit of normal
US	United States
V_z	volume of distribution
WBC	white blood cell

1. INTRODUCTION

1.1. Mechanism of Action of Sacituzumab Govitecan

Sacituzumab govitecan (Company Code: IMMU-132) is a trophoblast cell-surface antigen-2 (Trop-2)-directed antibody-drug conjugate that comprises SN-38, a topoisomerase I inhibitor and active metabolite of irinotecan, coupled by a linker (CL2A) to the humanized monoclonal antibody (mAb) hRS7 immunoglobulin G1 (IgG1)κ, which binds to Trop-2. Trop-2 is a transmembrane calcium signal transducer glycoprotein of the Tumor Associated Calcium Signal Transducer 2 (TACSTD2) 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 damage leads to cell death. The hydrolysable linker may permit release of SN-38 in the acidic microenvironment of the tumor without Trop-2 binding.

1.2. Nonclinical Experience

1.2.1. Pharmacology

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

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

1.2.2. 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 1,500 mg/kg) caused minimal loss (< 10%) in body weight. There were no evidence of hematological toxicity and no abnormal histology findings. Transient increases in hepatic transaminases that returned to normal by the end of the study were observed.

In cynomolgus monkeys, sacituzumab govitecan administered 50 mg/kg/dose (human equivalent dose = 16 mg/kg/dose) for 4 treatment cycles (Day 1 and Day 8 of a 21-day cycle) was considered a no-observable- adverse- effect level, 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 and 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 fertility, early embryonic development, or pre- and postnatal development have been assessed. However, SN-38 is a camptothecin analog 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.

1.3. Clinical Experience

Sacituzumab govitecan received accelerated approval in the US for use in metastatic triple-negative breast cancer (mTNBC) based on results from the Phase 1/2 Study IMMU-132-01, and subsequently received full approval based on results from the Phase 3 confirmatory Study IMMU-132-05. Sacituzumab govitecan received accelerated approval for use in metastatic urothelial cancer based on results from the Phase 2 Study IMMU-132-06 and is currently being studied in patients with metastatic urothelial cancer in the confirmatory Study IMMU-132-13. Sacituzumab govitecan is also currently being studied in metastatic breast cancer (IMMU-132-09) and various epithelial cancers (IMMU-132-11). The ongoing Study IMMU-132-14 is being planned as a rollover study from Study IMMU-132-15.

The largest experience to date is a Phase 1/2 study (IMMU-132-01) titled "Phase 1/2 Study of IMMU-132 (hRS7-SN38 Antibody Drug Conjugate) in Epithelial Cancers." Five hundred twenty subjects were enrolled in this study regardless of Trop-2 expression and were treated with sacituzumab govitecan monotherapy. Doses of 8 to 18 mg/kg were tested with the 10-mg/kg dose selected for further investigation.

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

1.3.1. Pharmacokinetics

1.3.1.1. Pharmacokinetics

The serum pharmacokinetics (PK) of sacituzumab govitecan and free SN-38 were evaluated in a Phase 3 Study IMMU-132-05 in a population of mTNBC subjects who received sacituzumab govitecan as a single agent at a dose of 10 mg/kg. Sacituzumab govitecan and free SN-38 had a maximum observed serum concentration (C_{max}) (%CV) of 240,000 ng/mL (22.2%) and 90.6 ng/mL (65%) respectively, and area under the serum concentration-time curve from time 0 to 168 hours (AUC_{0-168}) (%CV) of 5,340,000 h□ng/mL (23.7%) and 2,730 h□ng/mL (41.1%), respectively.

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

1.3.1.2. Distribution

Based on population PK analysis, central volume of distribution of sacituzumab govitecan is 2.96 L.

1.3.1.3. **Elimination**

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

1.3.1.4. Metabolism

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

1.3.1.5. Excretion

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

1.3.2. Immunogenicity

As with all therapeutic proteins, there is a potential for an immune response to sacituzumab govitecan. None of the subjects with treatment-emergent adverse events (TEAEs) and subjects who were confirmed antidrug antibody (ADA) positive had infusion reactions or adverse events (AEs) suggestive of immunogenicity.

1.3.3. Rationale for Dose Regimen

The total body clearance (CL) of sacituzumab govitecan is mediated by both catabolism of the antibody and metabolism of the released payload, SN-38. The distribution and CL of the antibody portion of sacituzumab govitecan are likely to be similar to those other IgG1 antibodies and are influenced by target (Trop-2)-mediated uptake on antigen-expressing cells, pinocytosis, and neonatal Fc receptor negative-mediated CL mechanisms in vivo. SN-38 is primarily eliminated from the body via the hepatic route. Sacituzumab govitecan has been studied in subjects with mild hepatic impairment but not in subjects with moderate hepatic impairment. Thus, a study to identify a safe starting dose of sacituzumab govitecan is being studied.

In the Phase 1 part of Study IMMU-132-01, dose escalation was performed with doses ranging from 8 to 18 mg/kg. 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. A sacituzumab govitecan dose of 10 mg/kg was found to be safe and efficacious and is the recommended starting dose for subjects with normal hepatic function and mild hepatic impairment. Additional information regarding the safety and efficacy of sacituzumab govitecan can be found in the investigator's brochure.

In the planned study, subjects with moderate hepatic impairment will receive an initial dose of 5 mg/kg sacituzumab govitecan prior to dose escalation to 7.5 mg/kg and 10 mg/kg sacituzumab govitecan. Dose escalation following 3+3 study design is applied to minimize the potential AEs related to increased exposure in the event that hepatic impairment affects PK. Subjects with normal hepatic function will receive 10 mg/kg sacituzumab govitecan as the control group for comparison with subjects with moderate hepatic impairment. A multiple-dose study will provide opportunities to evaluate the potential delayed safety and tolerability effects of sacituzumab govitecan.

1.3.4. Summary of Sacituzumab Govitecan Safety Data

The safety profile of sacituzumab govitecan has been characterized in 408 subjects with mTNBC and other malignancies who had received prior systemic therapeutic regimen for advanced disease in Study IMMU-132-01. In a subset of 108 subjects with mTNBC who had received at least 2 prior treatments for metastatic disease in Study IMMU-132-01, the median treatment duration in these 108 subjects was 5.1 months (range: 0-51 months). Sacituzumab govitecan was administered as an intravenous (IV) infusion once weekly on Days 1 and 8 of 21-day treatment cycles at doses up to 10 mg/kg until disease progression or unacceptable toxicity.

The most frequent AEs were GI (nausea, vomiting, and diarrhea) and myelosuppressive (neutropenia) AEs. Nausea occurred in 69% (74/108) of patients with mTNBC and 69% (281/408) of all patients treated with sacituzumab govitecan. Grade 3 nausea occurred in 6% (7/108) and 5% (22/408) of these populations, respectively. Vomiting occurred in 49% (53/108) of patients with mTNBC and 45% (183/408) of all patients treated with sacituzumab govitecan. Grade 3 vomiting occurred in 6% (7/108) and 4% (16/408) of these patients, respectively. Diarrhea occurred in 63% (68/108) of patients with mTNBC and 62% (254/408) of all patients treated with sacituzumab govitecan. In each population, events of Grade 3-4 occurred in 9%

(10/108) of mTNBC patients and 9% (36/408) of all patients treated with sacituzumab govitecan. Out of 408 patients, 4 (< 1%) discontinued treatment because of diarrhea. Neutropenic colitis was observed in 2% (2/108) of patients in the mTNBC cohort and 1% of all patients treated with sacituzumab govitecan.

Febrile neutropenia occurred in 6% (24/408) of patients treated with sacituzumab govitecan, including 8% (9/108) of patients with mTNBC after at least 2 prior therapies. Less than 1% (1/408) of patients had febrile neutropenia leading to permanent discontinuation. The incidence of Grade 1 to 4 neutropenia was 64% in patients with mTNBC (n=108). In all patients treated with sacituzumab govitecan (n = 408), the incidence of Grade 1 to 4 neutropenia was 54%; Grade 4 neutropenia occurred in 13%. Less than 1% (2/408) of patients permanently discontinued treatment due to neutropenia.

Hypersensitivity reactions within 24 hours of dosing occurred in 37% (151/408) of patients treated with sacituzumab govitecan. Grade 3 to 4 hypersensitivity occurred in 1% (6/408) of patients treated with sacituzumab govitecan. The incidence of hypersensitivity reactions leading to permanent discontinuation of sacituzumab govitecan was 1% (3/408).

Of the 108 subjects with mTNBC, sacituzumab govitecan was permanently discontinued for adverse reactions in 2% of patients. Adverse reactions leading to discontinuation were anaphylaxis, anorexia/fatigue, headache (each < 1%, 1 patient for each event). Forty-five percent (45%) of patients experienced an adverse reaction leading to treatment interruption. The most common adverse reaction leading to treatment interruption was neutropenia (33%). Adverse reactions leading to dose reduction occurred in 33% of patients treated with sacituzumab govitecan, with 24% having 1 dose reduction and 9% with 2 dose reductions. The most common adverse reaction leading to dose reductions was neutropenia/febrile neutropenia.

The analysis of immunogenicity of sacituzumab govitecan in serum samples from 106 patients with mTNBC was evaluated using an electrochemiluminescence-based immunoassay to test for anti-sacituzumab govitecan-hziy antibodies. Detection of the antisacituzumab govitecan-hziy antibodies was done using a 3-tier approach: screen, confirm, and titer. Persistent antisacituzumab govitecan-hziy antibodies developed in 2% (2/106) of patients.

As noted previously (Section 1.3.1.4), SN-38 is metabolized by UGT1A1. Subjects who are homozygous for the UGT1A1*28 allele may be at increased risk for neutropenia and diarrhea {CAMPTOSAR 2020}. In 84% (343/408) of patients who received sacituzumab govitecan (up to 10 mg/kg on Days 1 and 8 of a 21-day cycle) and had retrospective UGT1A1 genotype results available, the incidence of Grade 4 neutropenia was 26% (10/39) in patients homozygous for the UGT1A1*28 allele, 13% (20/155) in patients heterozygous for the UGT1A1*28 allele and 11% (16/149) in patients homozygous for the wild-type allele.

2. STUDY OBJECTIVES AND END POINTS

2.1. Primary Objectives

The primary objectives of the study are as follows:

- To identify the safe starting dose of sacituzumab govitecan in subjects with solid tumor and moderate hepatic impairment
- To evaluate the PK of sacituzumab govitecan in subjects with solid tumor and moderate hepatic impairment
- To evaluate the PK of free SN-38 in subjects with solid tumor and moderate hepatic impairment
- To evaluate the PK of SN-38G in subjects with solid tumor and moderate hepatic impairment
- To evaluate the PK of total SN-38 in subjects with solid tumor and moderate hepatic impairment
- To assess the number of subjects with antibodies against sacituzumab govitecan in subjects with solid tumor and moderate hepatic impairment

2.2. End Points

2.2.1. Safety End Points

The safety end points include the following:

- Number of subjects experiencing TEAEs
- Clinical laboratory tests
- Vital signs
- Electrocardiogram (ECG)

2.2.2. Pharmacokinetic End Points

The following PK parameters will be evaluated as primary PK end points:

- C_{max} of sacituzumab govitecan, free SN-38, SN-38G, and total SN-38 following dosing on Day 1 and Day 8
- Area under the serum concentration-time curve from time 0 to time of the last quantifiable concentration ($AUC_{0\text{-}last}$) of sacituzumab govitecan, free SN-38, SN-38G, and total SN-38 following dosing on Day 1 and Day 8
- $AUC_{0\text{-}168}$ of sacituzumab govitecan, free SN-38, SN-38G, and total SN-38 following dosing on Day 1 and Day 8

The following PK parameters will be evaluated as additional PK end points:

- Area under the serum concentration-time curve from time 0 extrapolated to infinity ($AUC_{0\text{-}inf}$) of sacituzumab govitecan, free SN-38, SN-38G, and total SN-38 following dosing on Day 1 and Day 8
- Percentage of AUC extrapolated between AUC_{last} and AUC_{inf} ($\%AUC_{exp}$) of sacituzumab govitecan, free SN-38, SN-38, and total SN-38 following dosing on Day 1 and Day 8
- Time to maximum observed serum concentration (T_{max}) of sacituzumab govitecan, free SN-38, SN-38G, and total SN-38 following dosing on Day 1 and Day 8
- CL of sacituzumab govitecan following dosing on Day 1 and Day 8
- Total volume of distribution during the terminal phase (V_z) of sacituzumab govitecan following dosing on Day 1 and Day 8
- Terminal elimination rate constant (λ_z) of sacituzumab govitecan, free SN-38, SN-38G, and total SN-38 following dosing on Day 1 and Day 8
- Terminal elimination half-life ($t_{1/2}$) of sacituzumab govitecan, free SN-38, SN-38G, and total SN-38 following dosing on Day 1 and Day 8
- Accumulation ratio based on C_{max} of sacituzumab govitecan, free SN-38, SN-38G, and total SN-38 following dosing on Day 1 and Day 8
- Accumulation ratio based on $AUC_{0\text{-}168}$ of sacituzumab govitecan, free SN-38, SN-38G, and total SN-38 following dosing on Day 1 and Day 8

2.2.3. Immunogenicity End Points

- Number of subjects with antibodies against sacituzumab govitecan

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This is a Phase 1, multicenter, open-label, dose-escalation study of sacituzumab govitecan in adult subjects with advanced or metastatic solid tumor and moderate hepatic impairment or normal hepatic function. Up to 20 subjects with moderate hepatic function defined according to the National Cancer Institute Organ Dysfunction Working Group criteria (ie, 1.5 × upper limit of normal [ULN] < total bilirubin < 3.0 × ULN) and 8 subjects with normal hepatic function will be enrolled. Eligible subjects will receive sacituzumab govitecan IV infusion on Day 1 and Day 8. Subjects will be administered the first infusion on Day 1 over 3 hours. The second infusion on Day 8 will be administered over 1 to 2 hours if the prior infusion was tolerated.

Subjects with moderate hepatic impairment will undergo dose escalation following a 3+3 study design. Dose escalation will occur if fewer than 33% of subjects within the dosing group experienced a dose-limiting toxicity (DLT). The starting sacituzumab govitecan dose will be 5 mg/kg. If the starting dose is not acceptably tolerated, a lower dose of sacituzumab govitecan may need to be evaluated. Sacituzumab govitecan doses to be studied will be 5, 7.5, and 10 mg/kg. Dose escalation will only occur if deemed acceptable after review of safety data up to Day 22 and available PK data. Once the recommended dose is determined, additional subjects with moderate hepatic impairment will be added, for a total of 8 subjects receiving the recommended dose. In addition, 8 subjects with normal hepatic function will receive sacituzumab govitecan 10 mg/kg.

Serial blood samples will be collected on Day 1 and Day 8 (dosing days) through 7 days after dosing for PK assessments. Safety will be evaluated throughout the study. Subjects may be confined in the study center from the evening of Day 1 to Day 4 and Day 8 to Day 11 at the discretion of the investigator. Subjects will report to the study center on the study days for study procedures. Subjects will exit the study on Day 38. At the completion of study treatment (end of treatment [EOT]), subjects who are deriving benefit from sacituzumab govitecan may continue to receive treatment in a rollover study (IMMU-132-14). All subjects must complete an end of study (EOS) visit approximately 30 days after the last dose of the study drug.

Study design schematic is provided in Table 1.

Table 1. Schematic of Study Design

Screening Period	Treatment Period	End of Treatment (EOT)	EOS/30-Day Safety Follow-up
Days -28 to -1	Dosing: Day 1 and Day 8 PK: 0 to 168 hours after each dosing Safety: Day 1 to Day 22 for dose escalation	Day 22 ± 1	Day 38 ± 1

EOS = end of study; PK = pharmacokinetics

3.2. Number of Subjects

A sample size of up to 20 adult subjects with moderate hepatic impairment with solid tumor and 8 subjects with normal hepatic function with solid tumor is deemed sufficient to evaluate the PK and safety profiles of sacituzumab govitecan when administered to subjects with moderate hepatic impairment. Subjects who do not complete the study may be replaced at the discretion of the sponsor.

3.3. Treatment Assignment

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

3.4. Thirty-Day Safety Follow-Up

All subjects must complete an EOS visit approximately 30 days after the last dose of the study drug, including subjects who discontinue treatment (see Section 5.3). This follow-up assessment may be done by telephone or visit and will include documentation of any AEs and concomitant medications.

3.5. Definition of End of Study

End of study for a subject occurs when there is a death event, withdrawal of consent, lost to follow-up, or sponsor termination of the study (see Section 5.4).

End of the study occurs after all events are collected for the primary analysis with appropriate follow-up as designated.

At the completion of study treatment (EOT), subjects who are deriving benefit from sacituzumab govitecan may continue to receive treatment in a rollover study (IMMU-132-14).

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 standard of care may be utilized for screening purposes if obtained with the subject's consent. The investigator 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 ICF must be signed, dated, and witnessed with a copy given to the subject. The consenting process must be well documented by each study center.

4.2. Screening

Subjects must complete all screening procedures within 28 days of signing the ICF. Standard-of-care procedures performed before obtaining informed consent may be utilized for screening if the subject agrees. Absolutely no waivers for subject eligibility will be offered or permitted.

Sites are permitted to rescreen a previously screen failed subject once for the study, at the discretion of principal investigator (PI) and with approval from the sponsor medical monitor. Screening labs may be repeated during the screening period at the discretion of the PI.

At screening, study subjects will be assigned a screening number at the time of consent. Once a subject number has been assigned to a subject, it will not be reassigned to another subject. Subjects who rescreen will be assigned a new unique subject number.

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. All subjects who have signed an ICF and were deemed ineligible will be recorded with the reason for ineligibility on the appropriate electronic case report form (eCRF). 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 (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes demography, informed consent date, screen failure details, eligibility criteria, study discontinuation date, AEs, and any serious adverse event (SAE).

4.2.2. Subject Replacement

Subjects who do not complete the study may be replaced at the discretion of the sponsor. Replacement subjects will not be enrolled for subjects who discontinue the study due to study drug-related AEs.

4.3. Randomization and Blinding

Not applicable.

4.4. Study Procedures

Enrollment occurs upon completion of all screening procedures within the screening window, signing of the ICF, and upon approval of the eligibility form by the sponsor or the sponsor's designee. Clear documentation as to the reason the subject was not dosed should be provided on the relevant eCRF.

For PK parameters, please refer to Section 9.

For safety parameters, please refer to Section 11.

For all other evaluations, please refer to Section 10.

Table 2. Schedule of Assessments

Period	Screening	Treatment											End of Treatment/ET	EOS/30-Day Safety FU
Day	−28 to −1	1 (include baseline[1])	2	3	4	5-7	8	9	10	11	12-15	16-21	22 ± 1	38 ± 1
Informed consent	X													
Inclusion and exclusion criteria[2]	X													
Demography	X													
Medical/surgical history	X													
Prior anticancer therapy	X													
Prior radiation therapy	X													
ECOG	X	X											X	
Vital signs[3]	X	X					X						X	
Serum pregnancy test[4]	X													
Urine pregnancy test[4]		X												
FSH[4]	X													
Physical exam	X	X											X	
Height	X													
Weight[5]	X	X					X						X	
ECG[6]		X					X							
Hematology[7]	X	X					X						X	
Chemistry[8]	X	X					X						X	
PT/INR, PTT[9]	X													

Period	Screening	Treatment											End of Treatment/ET	EOS/30-Day Safety FU
Day	**−28 to −1**	**1 (include baseline[1])**	**2**	**3**	**4**	**5-7**	**8**	**9**	**10**	**11**	**12-15**	**16-21**	**22 ± 1**	**38 ± 1**
LDH and uric acid[10]	X													
Urinalysis[11]	X													
Hepatitis B surface antigen, hepatitis C antibody test	X													
Blood sample for UGT1A1 genotyping[12]		X												
Sacituzumab govitecan administration[18]		X					X							
PK sampling[13]		X	X	X	X	X	X	X	X	X	X		X	
ADA blood sampling[14]		X											X	
Provide meals[15]		X	X	X	X		X	X	X	X				
Confinement[16]		X	X	X	X		X	X	X	X				
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X

ADA = antidrug antibody; AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOS = end of study; EOT = end of treatment; ET = early termination; FU = follow-up; INR = international normalized ratio; LDH = lactate dehydrogenase; PK = pharmacokinetic(s); PT = prothrombin time; PTT = partial thromboplastin time; SAE = serious adverse event; UGT1A1 = UDP-glucuronosyltransferase 1A1; WBC = white blood cell

1 Baseline study procedures may occur within 3 days of dosing on Day 1.
2 Confirmation of subject eligibility will be based on screening criteria.
3 Vital signs include heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature. Vitals should be collected after the subject has been resting for at least 5 minutes.
4 In female patients of childbearing potential, the Cycle 1 Day 1 urine pregnancy test does not need to be conducted if the screening pregnancy test was performed within 3 days before study treatment administration.
FSH testing will be conducted as needed per Appendix 5 for determination of childbearing potential.
5 If weight fluctuates more than 10% between Day 8 and Day 1, discuss with the sponsor before dosing.

6 Twelve-lead ECG will be obtained prior to infusion on Day 1 and at 3 hours after the start of infusion on Day 1 and Day 8. Abnormal findings should be evaluated as clinically indicated, including repeated ECGs. Electrocardiograms may be done at other time points during the study if clinically indicated.
7 CBC with platelets and WBC differential with absolute cell counts will be obtained prior to infusion. 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.
8 Serum chemistries include glucose, creatinine (estimated glomerular filtration rate), BUN or urea, total bilirubin, AST, ALT, ALP, serum albumin, total protein, sodium, potassium, calcium, chloride, bicarbonate, magnesium, and phosphorus.
9 PT/INR and PTT at screening and as clinically indicated.
10 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.
11 Urinalysis will be performed locally on a freshly voided, clean sample by dipstick for protein, glucose, blood, pH, and ketones.
12 Blood samples for UGT1A1 is preferred to be collected prior to dosing on Day 1. However, it can be collected at any time if it was not collected prior to dosing on Day 1.
13 PK sampling will be collected on Day 1 and Day 8 through 168 hours after each infusion as detailed in Table 4. PK collection on Day 22 (EOT) should be collected within ± 5 minutes from the ADA sample as detailed in Table 4. Refer to Table 4 for PK windows.
14 Blood sampling for ADA will be collected prior to dosing on Day 1. Blood sampling for ADA will be collected on Day 22 (prior to subjects enrolling in a rollover study, if applicable). Refer to Sections 9 and 10.
15 Breakfast, lunch, dinner, and a snack will be provided to subjects who are confined at the study center.
16 Subjects may be confined to the study center on 2 occasions (Day 1 to Day 4 and Day 8 to Day 11) at the investigator's discretion.
17 End of Treatment/EOT (Day 22) and EOS/30-Day Safety Follow-up (Day 38) have a ± 1-day window
18 Refer to Section 7.5 for administration instructions.

5. SELECTION AND WITHDRAWAL OF SUBJECTS

5.1. Subject Inclusion Criteria

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

Inclusion criteria for all subjects:

1) Male or female subjects ≥ 18 years of age, at the time of signing the ICF.

2) Histologically confirmed advanced or metastatic solid tumor that is measurable or nonmeasurable.

3) Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2.

4) Adequate hematologic counts without transfusional or growth factor support within 2 weeks of study drug initiation (hemoglobin ≥ 9 g/dL, absolute neutrophil count [ANC] ≥ 1,500/mm^3, and platelets ≥ 100,000/μL).

5) Creatinine clearance ≥ 30 mL/min as assessed by the Cockcroft-Gault equation.

6) Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form.

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

Additional inclusion criteria for subjects with normal hepatic function:

8) In acceptable health as determined by a responsible and experienced physician, based on a medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.

9) Normal hepatic function (total bilirubin ≤ ULN and aspartate aminotransferase [AST] ≤ 3.0 × ULN).

Additional inclusion criteria for subjects with moderate hepatic impairment:

10) Moderate hepatic impairment (1.5 × ULN < total bilirubin < 3.0 × ULN and any level of AST).

11) For subjects with hepatic encephalopathy, the condition does not, in the investigator's opinion, interfere with the subject's ability to provide an appropriate informed consent.

5.2. Subject Exclusion Criteria

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

Exclusion criteria for all subjects:

1) Women who are pregnant or lactating.

2) Unwillingness or inability to follow the procedures outlined in the protocol.

3) Have poor venous access.

4) Donated or lost 500 mL or more blood volume (including plasmapheresis) or plans to donate blood during the study.

5) Have a history of sensitivity to any of the study medications, or components thereof, or a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates their participation.

6) Received investigational drug within 4 weeks prior to Day 1.

7) Have had a prior anticancer biologic agent within 4 weeks prior to Day 1 visit or have had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to Day 1 and who have not recovered (ie, ≤ Grade 2) from AEs at the time of study entry. Subjects participating in observational studies are eligible.

8) Had prior treatment with irinotecan within 4 weeks prior to Day 1.

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

   Note: Subjects with ≤ Grade 2 neuropathy or 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 therapy.

10) Have an active second malignancy.

    Note: Subjects with a history of malignancy that has been completely treated, 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.

11) Have known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they have stable CNS disease for at least 4 weeks prior to the first dose of the study drug and all neurologic symptoms have returned to baseline, have no evidence of new or enlarging brain metastases, and are taking ≤ 20 mg/day of prednisone or its equivalent. All subjects with carcinomatous meningitis are excluded regardless of clinical stability.

12) History of cardiac disease, defined as follows:

    a) Myocardial infarction or unstable angina pectoris within 6 months of Day 1.

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

    c) New York Heart Association Class III or greater congestive heart failure or documented left ventricular ejection fraction of < 40%.

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

14) Have active serious infection requiring IV antibiotics (contact medical monitor for clarification).

15) 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.

16) Have known history of human immunodeficiency virus-1/2 with undetectable viral load and on medications that may interfere with study drug metabolism.

17) Have active hepatitis B virus (HBV) or hepatitis C virus (HCV) by confirming with hepatitis B surface antigen and hepatitis C antibody. In subjects with a history of HBV or HCV, subjects with a detectable viral load confirmed by polymerase chain reaction test will be excluded.

18) Have a history of regular alcohol consumption within 6 months of the study defined as an average weekly intake of > 14 drinks for males or > 7 drinks for females. One drink is equivalent to 12 g of alcohol, 12 ounces (360 mL) of beer, 5 ounces (150 mL) of wine, or 1.5 ounces (45 mL) of 80 proof distilled spirits.

19) High-dose systemic corticosteroids (≥ 20 mg of prednisone or its equivalent) are not allowed within 2 weeks prior to Day 1. However, inhaled, intranasal, intra-articular, and topical steroids are allowed.

20) Use of strong inhibitor or inducer of UGT1A1.

21) Have a history of Gilbert's disease.

<u>Additional exclusion criteria for subjects with normal hepatic function</u>:

22) Have pre-existing condition interfering with hepatic and/or renal function that could interfere with the metabolism and/or excretion of the study drug.

Additional exclusion criteria for subjects with moderate hepatic impairment:

23) Had a clinical exacerbation of liver disease within the 2-week period before administration of study drug (ie, abdominal pain, nausea, vomiting, anorexia, or fever).

24) Had clinically demonstrable, tense ascites.

25) Had evidence of acute viral hepatitis within 1 month prior to administration of study drug.

26) Have evidence of hepatorenal syndrome.

27) Subjects with transjugular intrahepatic portosystemic shunt placement.

28) Have active Stage 3 or 4 encephalopathy.

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 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 antitumor therapy, including any investigational agent.

5) Pregnancy.

6) Subject noncompliance.

5.4. Criteria for Study Discontinuation

Subjects will be discontinued from the study under any of the following conditions:

1) Death.

2) Withdrawal of consent from the study.

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

4) The sponsor terminates the study.

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 catabolite of sacituzumab govitecan.

6.2. Study Drug, Dosage, and Mode of Administration

Sacituzumab govitecan will be administered as an IV infusion on Day 1 and Day 8 of the study. The starting dose will be 5 mg/kg. The dose may be escalated to 7.5 mg/kg and then to 10 mg/kg based on safety evaluation. There will be no intrasubject dose escalation in the study.

6.3. Definition of Dose-Limiting Toxicity

The following treatment related TEAEs are considered DLTs:

- Any ≥ Grade 3 nonhematologic toxicity (excluding alopecia, hypophosphatemia [if resolved with supplementation therapy], and liver abnormalities) that does not recover after 72 hours with maximal therapy.
- ≥ Grade 4 neutropenia or Grade ≥3 neutropenic fever.
- Grade 4 thrombocytopenia.
- ≥ Grade 3 nausea and vomiting if they occur despite maximal (5-HT antagonist and corticosteroid) antiemetic therapy and if hydration is required for > 24 hours.
- ≥ Grade 3 diarrhea despite subject compliance with loperamide therapy and maximal medical therapy.
- ≥ Grade 3 elevation of prothrombin time or a partial thromboplastin time that is associated with clinically significant bleeding (eg, CNS and GI).
- Any other TEAEs that the investigator may consider a significant safety concern.
- In subjects with biliary stents, elevations of total bilirubin and AST that are due to obstructed biliary stents or cholangitis not accompanied by neutropenia will not be considered as a DLT.

Subjects who experience a DLT may continue dosing with dose adjustment per toxicity management guidelines as per Section 6.5.3 at the discretion of the investigator and sponsor as long as they are able to receive a minimum dose of 5 mg/kg.

6.4. Dose-Escalation Scheme

Subjects are considered evaluable for toxicity when they have received 1 cycle of treatment (single dose of sacituzumab govitecan on Day 1 and Day 8) and have experienced either DLT or without DLT. Dose escalation will occur if fewer than 33% of subjects within the dosing group experienced a DLT. The starting dose of sacituzumab govitecan will be 5 mg/kg. After review of safety data, dose escalation will proceed to the next higher dose level as follows:

1) If 0 of 3 subjects experiences DLT, dose escalation will proceed to the next higher dose level, at which 3 subjects will be enrolled.

2) If 1 of 3 subjects experiences DLT, 3 more subjects will be enrolled at that same dose level. Escalation will continue if 1 of 6 subjects experiences DLT.

3) If 2 or more subjects in any dose level experience DLT, dosing will stop, and the previous dose level will be considered the MTD.

6.5. Treatment of Sacituzumab Govitecan-Associated Toxicities

Instructions for the infusion of sacituzumab govitecan are provided in Section 7.5. The following sections provide guidance for sacituzumab govitecan administration and management of treatment-related toxicities. Toxicities should be managed in accordance with standard institutional practices and accepted treatment guidelines.

6.5.1. Preventative Medications

Infusion-Related Reactions: Premedication for prevention of infusion-related reactions with antipyretics and H1 and H2 blockers should be administered before each sacituzumab govitecan infusion. Corticosteroids (hydrocortisone 50 mg or equivalent orally [PO] or IV) may be administered prior to subsequent infusions. Additional details of recommended treatment of infusion-related reactions are described in Section 6.5.2.1.

Nausea and Vomiting: Sacituzumab govitecan is considered to be moderately emetogenic. Premedication with a 2-drug antiemetic regimen is recommended. If nausea and vomiting are persistent, a 3-drug regimen may be used, including a 5-HT3 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 6.5.2.2.

6.5.2. Management of Sacituzumab Govitecan Toxicities

National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 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 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 polymorphisms due to increased episodes of diarrhea or neutropenia should have their polymorphism assessed.

All efforts to avoid dose reduction should be taken to address toxicity prior to initiation of dose reduction. Instructions for dose modification and discontinuation of sacituzumab govitecan for treatment related toxicities are provided in Section 6.5.3.

6.5.2.1. Infusion-Related Reactions

Infusion-related reactions are defined as symptoms that occur during and within the first 6 hours after the infusion of sacituzumab govitecan and can occur at any cycle. Symptoms can include fever, chills, rigors, arthralgias, myalgias, urticaria, pruritus, rash, diaphoresis, hypotension, dizziness, syncope, hypertension, dyspnea, cough, and wheezing, as well as severe hypersensitivity reactions including anaphylactic reactions. Infusion-related reactions should be treated in accordance with best clinical practices and standard institutional guidelines. Because of the potential for life-threatening infusion-related reactions, sacituzumab govitecan should only be administered in a setting where appropriately trained medical staff, emergency equipment, and medications are available in the event that resuscitation is required. NCI-CTCAE Version 5.0 is used to grade the severity of all infusion-related AEs. Premedication for the prevention of infusion-related reactions is described in Section 6.5.1.

Grade 3 and Grade 4 Events

Grade 3 and Grade 4 infusion-related reactions can include severe or clinically significant cardiopulmonary events and severe allergic reactions such as symptomatic bronchospasm and anaphylactic reactions. Grade 3 infusion-related reactions are defined as those which are prolonged and do not improve with symptomatic treatment and/or brief interruption of treatment, reactions that recur following treatment, and reactions that require hospitalization. Grade 4 reactions include potentially life-threatening reactions, requiring urgent intervention. Severe allergic and anaphylactic reactions should be treated in accordance with best clinical practices and standard institutional guidelines. If Grade 3 or Grade 4 infusion-related reactions occur, sacituzumab govitecan should be permanently discontinued.

Grade 2 Events

Grade 2 infusion-related reactions are defined as those that require infusion interruption and respond to symptomatic treatment; prophylactic medications are indicated for ≤ 24 hours. For Grade 2 infusion-related reactions, the infusion should be interrupted until symptoms resolve. After symptoms resolved, the infusion should be resumed at a slower infusion rate, as determined appropriate by the managing physician. Recommended infusion rates are provided in the Pharmacy Manual. For recurrent Grade 2 infusion-related reactions that fail to recover within 6 hours despite optimal management, sacituzumab govitecan should be permanently discontinued.

6.5.2.2. 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.

Nausea and Vomiting

Instructions for the use of premedications for prophylactic treatment of nausea and vomiting and anticipatory nausea are provided in Section 6.5.1. Do not hold the dose of sacituzumab govitecan for Grade 3 nausea unless Grade 3 nausea persists despite maximal optimal medical management. Manage this toxicity per standard institutional guidelines.

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 Grade 1 or Grade 2 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. If diarrhea is not resolved after 24 hours, consider adding diphenoxylate/atropine and/or opium tincture, as clinically indicated.

Add octreotide 100 to 150 mcg subcutaneously 3 times per day if diarrhea persists. For Grade 3 or Grade 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, and salivation) can receive appropriate premedication (eg, atropine) for subsequent treatments.

6.5.2.3. Neutropenia

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

- Day 1: ANC $\geq$ 1,500/mm^3
- Day 8: ANC $\geq$ 1,000/mm^3

The routine prophylactic use of growth factors is not required; however, prophylactic administration may be considered and should comply with American Society of Clinical Oncology guidelines for use of growth factors. They may be used in subjects who have experienced febrile neutropenia or Grade 3 or Grade 4 neutropenia following previous infusions. Growth factors may also be administered in the setting of neutropenia in subjects at high risk of poor clinical outcomes, including those with prolonged neutropenia, ANC $<$ 1000/mm^3, febrile neutropenia, and serious infections.

6.5.2.4. Overdose

Overdose is defined as administration of more than 10% higher dose 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 11.2.2.

6.5.3. Dose Reductions and Discontinuation (as per Package Insert)

Table 3 summarizes recommendations for sacituzumab govitecan dose reductions and discontinuations for treatment-related toxicities.

Sacituzumab govitecan dose reductions and interruptions will be managed based on toxicity severity. Leukopenia or lymphopenia in the absence of neutropenia does not require dose modification. The sacituzumab govitecan dose must not be reescalated following a dose reduction.

Table 3. Recommended Dose Modification Schedule for Sacituzumab Govitecan

Adverse Reaction	Occurrence	Dose Modification or Action
Severe neutropenia		
Grade 4 neutropenia ≥ 7 days, OR Grade 3 febrile neutropenia (absolute neutrophil count < 1000/mm^3 and fever ≥ 38.5 °C), OR At time of scheduled treatment, Grade 3 or 4 neutropenia that delays dosing by 2 or 3 weeks for recovery to ≤ Grade 1	First	25% dose reduction and administer G-CSF
	Second	50% dose reduction
	Third	Discontinue Treatment
At time of scheduled treatment, Grade 3 or 4 neutropenia that delays dosing beyond 3 weeks for recovery to ≤ Grade 1	First	Discontinue treatment
Severe nonneutropenic toxicity		
Grade 4 nonhematologic toxicity of any duration, OR Any Grade 3 or 4 nausea, vomiting, or diarrhea due to treatment that is not controlled with antiemetics and antidiarrheal agents OR Other Grade 3 or 4 nonhematologic toxicity persisting > 48 hours despite optimal medical management, OR At time of scheduled treatment, Grade 3 or 4 nonneutropenic hematologic or nonhematologic toxicity that delays dose 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 or 4 nonneutropenic hematologic or nonhematologic toxicity that does not recover to ≤ Grade 1 within 3 weeks	First	Discontinue treatment
Infusion-Related Toxicities		
Grade 2 infusion-related reactions that fail to recover within 6 hours, despite optimal management	Recurrent	Discontinue treatment
Grade 3 or 4 infusion-related reaction	First	Discontinue treatment

G-CSF = granulocyte-colony stimulating factor; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events
Refer to Section 11.2.2.3 for the NCI-CTCAE severity grading details.

6.6. Concomitant Medications

Medications initiated prior to the first dose of the study drug will be recorded as prior medications, with medications initiated following receipt of the first dose of the study drug until 30 days after treatment discontinuation being 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 documented with rationale for prophylactic intent.

No anticancer therapies, aside from the study drug (sacituzumab govitecan), are permitted during this study. However, palliative and/or supportive medications, such as pain medications, bone-modifying medications (bisphosphonates or denosumab), antiemetics or antidiarrheal medications, transfusions, and growth factor support, are allowed at the investigator's discretion. Palliative radiotherapy is permitted, but the presence of new or worsening metastases will be considered progression. Palliative radiation of a target lesion will render that target lesion and subsequent tumor assessments "not evaluable" and should be avoided.

High-dose systemic corticosteroids (≥ 20 mg of prednisone or its equivalent) are not allowed within 2 weeks of the first dose of the study drug.

6.6.1. COVID-19 Vaccine

There is no prohibition on virus attenuated or RNA vaccine administration while the subjects are on trial nor will vaccination prevent enrollment on the study. The sponsor does not have substantial safety data regarding the concurrent administration of the COVID-19 vaccine and sacituzumab govitecan. COVID-19 vaccine clinical trials did not include subjects who were receiving chemotherapy, so the safety profile in these subjects is unknown.

Subjects should be offered the 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. The institutional guidelines should always be followed. The administration of specific COVID-19 vaccine must be documented in the clinical database as well as any side effects related to the vaccine. The study visits should continue as planned, if possible and clinically appropriate if vaccination occurs while the subject is on the study.

6.7. Drug Interactions

No formal drug-drug interaction studies with sacituzumab govitecan have been conducted. SN-38 is metabolized via human UGT1A1. Concomitant administration of strong 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.

6.7.1. Strong UGT1A1 Enzyme Inhibitors

Coadministration of sacituzumab govitecan with strong inhibitors of UGT1A1 (eg, atazanavir, gemfibrozil, or indinavir) may increase systemic exposure to the active metabolite, SN-38. Do not administer strong UGT1A1 enzyme inhibitors with sacituzumab govitecan.

6.7.2. Strong UGT1A1 Enzyme Inducers

Exposure to SN-38 may be substantially reduced in subjects concomitantly receiving UGT1A1 enzyme inducers. Do not administer strong UGT1A1 enzyme inducers with sacituzumab govitecan.

6.8. Treatment Compliance

Sacituzumab govitecan will be administered at scheduled study centers under the supervision of the investigator or subinvestigator(s). The study pharmacist will maintain records of study drug receipt, preparation, and dispensing, including the applicable lot numbers, subject's weight, and total drug administered in milligrams. Any discrepancy between the calculated dose and the 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

Sacituzumab govitecan 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 study drug is 10 mg/mL. The pH of the reconstituted solution is approximately 6.5.

7.2. Study Drug Packaging and Labeling

Vials of sacituzumab govitecan are intended for clinical use only, and the label includes the study name or code, name of the study drug, lot number, and strength. Additional information regarding study drug packaging and labeling is presented in the Pharmacy Manual.

7.3. Study Drug Storage

Sacituzumab govitecan is photosensitive and should be protected from light during storage, transport, and administration.

All vials of sacituzumab govitecan must be stored under refrigeration (2 °C to 8 °C) and protected from light in locked location that can be accessed only by the study pharmacist, the PI, or other duly authorized persons until administered to the subject. Additional information regarding study drug storage is presented in the Pharmacy Manual.

7.4. Study Drug Preparation

Dose preparation must be documented according to institutional guidelines, and all records must be kept in the study file.

The study pharmacist is required to follow the appropriate steps regarding the reconstitution and dilution of the study drug per the Pharmacy Manual.

7.5. Administration

Sacituzumab govitecan is a cytotoxic drug. Follow applicable special handling and disposal procedures.

- Use the diluted solution in the infusion bag immediately. If not used immediately, the infusion bag containing sacituzumab govitecan solution can be stored refrigerated 2 °C to 8 °C for up to 4 hours. After refrigeration, administer diluted solution within 4 hours (including infusion time).

- Administer sacituzumab govitecan as an IV infusion.

- Administer the first infusion on Day 1 over 3 hours. Administer the second infusion on Day 8 over 1 to 2 hours if the prior infusion was tolerated. Observe subjects during each infusion and for at least 30 minutes after infusion, for signs or symptoms of infusion-related reactions.

- Protect the infusion bag from light.

- An infusion pump may be used.

- Confirm compatibility with polypropylene infusion bags.

- Compatibility with in-line filters and other ancillary infusion equipment has not been studied.

- Do not mix study drug or administer as an infusion with other medicinal products.

- Upon completion of the infusion, flush IV line with 20 mL 0.9% Sodium Chloride Injection, United States Pharmacopeia.

7.6. Study Drug Accountability

The study drug must be stored in a locked location that can be accessed only by the study pharmacist, the PI, or another duly authorized study/study center personnel.

The study drug must not be used outside of the context of this protocol. Under no circumstances should the investigator or other study center personnel supply study drug to other investigators, subjects, or study centers or allow supplies to be used other than as directed by this protocol without prior written authorization from Immunomedics, Inc. (Immunomedics).

Records documenting receipt, use, return, loss, or other disposition of the study drug must be kept to ensure adequate accountability of study drug. A complete drug accountability record should be maintained at the site. In all cases, information describing study medication supplies and their disposition, subject-by-subject, must be provided and signed by the investigator (or the study pharmacist or other person who dispensed the drug) and collected by the Immunomedics Study Contact or designee. Requisite data include relevant dates, quantities, batches or code numbers, and subject identification for subjects who received the study drug.

7.7. Study Drug Handling and Disposal

7.7.1. Study Drug Shipment

The study drug will be shipped at refrigerated temperature in an insulated shipper, protected from light, and with a temperature-monitoring device. The shipper must be opened immediately upon receipt. Each shipment will include a set of instructions for execution upon receipt.

7.7.2. Receipt of Study Drug

All study drug should be inspected upon receipt as indicated on the Packing List. Follow instructions on the Packing List to complete any necessary forms and report issues or product complaints as directed in the Pharmacy Manual. Study centers must retain all study drug vials affected and may not perform any additional testing on the vials in question.

The study pharmacist, the PI, or the designee must confirm that appropriate conditions have been maintained during transit and that any discrepancies are reported per guidance found in the Pharmacy Manual.

- Do not destroy the study drug, but place in quarantine at 2 °C to 8 °C, protected from light.
- Complete the "Product Inspection Form" (refer to the Pharmacy Manual, Appendix 1).
- Contact the Immunomedics Study Contact, ComplaintManagement@immunomedics.com with a summary of the finding (including lot number and expiration date) and photos of the vial(s)/materials effected.
- When summarizing, it is important to only report what is seen without drawing conclusions.
- The study center will be contacted promptly with further instructions after review by Immunomedics, Inc.
- Specific instructions as to the disposition of the vial(s)/study materials will be provided by the sponsor or its designee (ie, approval to use study drug instructions to return the product[s] or to destroy the study drug).

7.7.3. Study Drug Disposal

At the end of study, or if instructed to do so during the study, the study drug may be destroyed at the study center as dictated by the appropriate standard operating procedures at the study centers. The study drug may not be destroyed until it has been reconciled and written confirmation has been received from the Immunomedics Study Contact or designee. Used study drug vials may be destroyed prior to study drug reconciliation at the end of study if required by the study center's standard operating procedures.

Destruction of study drug must be documented.

If local destruction is not possible, the study drug may be returned as per the agreed upon process. Return of the study drug must be documented. The Immunomedics Study Contact or designee assigned to your study center will assist with the return of the study drug once it has been deemed appropriate by Immunomedics.

8. ASSESSMENT OF EFFICACY

Not applicable.

9. ASSESSMENT OF PHARMACOKINETICS

Blood samples will be collected in all subjects at selected time points for the determination of serum concentrations of free SN-38, total SN-38, and SN-38G. Sacituzumab govitecan serum concentrations will be calculated based on levels of free SN-38, total SN-38, and SN-38G measured concentrations. Free SN-38, SN-38G, and total SN-38 will be quantified by using validated assays at a laboratory selected by the sponsor.

The PK sampling scheme is detailed in Table 4. The infusion history (start time and end time) and actual collection date and time of PK samples will be recorded. Blood draws will be conducted in the arm opposite a subject's IV infusion. In the case that only a single arm is available, blood may be drawn as distal to the site for IV infusion as feasible, and the site of blood draw should be documented.

Details regarding the preparation, handling, and shipping of samples are provided in the Study Manual.

Table 4. Pharmacokinetic Sampling Time Points

Matrix	Study Day	Collection Time Point	Collection Window
Blood (PK)	Day 1 Day 8	Preinfusion	Within 30 minutes prior to infusion
		Immediately prior to the end of infusion	± 5 minutes from the end of infusion
		1 h postinfusion	± 5 minutes
		3 h postinfusion	± 15 minutes
		6 h postinfusion	± 30 minutes
		12 h postinfusion	± 1 h
		24 h postinfusion	± 2 h
		48 h postinfusion	± 4 h
		72 h postinfusion	± 6 h
		96 h postinfusion	± 6 h
		120 h postinfusion	± 6 h
		144 h postinfusion	± 6 h
		168 h postinfusion	± 6 h
Blood (PK)	Day 22 ± 1	At the same time as the ADA collection	± 5 minutes from the ADA collection

ADA = antidrug antibody; PK = pharmacokinetic(s)

Serum PK parameters will be derived using a noncompartmental analysis from concentration-time data for all evaluable subjects. The PK parameters to be calculated are listed in Section 2.2.2. Additional PK parameters may be derived, if deemed appropriate.

10. OTHER EVALUATIONS

UGT1A1 genotype will be evaluated from a whole blood sample by the sponsor's designee. Subject eligibility will not be determined based on the results of this testing.

Immunogenicity will be evaluated from a serum sample for human ADA using a validated assay. ADA sample will be collected predose on Day 1 and during the EOT visit on Day 22.

10.1. Sample Storage

At the end of this study, PK and ADA samples may be retained in storage by sponsor for a period up to 15 years.

11. ASSESSMENT OF SAFETY

11.1. Safety Parameters

11.1.1. Demographic/Medical History

Basic demographic and baseline characteristics will be collected as indicated in Table 2. In addition to the evaluation of a subject's medical/surgical history in terms of study eligibility, all relevant medical conditions will be documented on the appropriate eCRF. Events that occur after signing of ICF but prior to initiation of the 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, dates of diagnosis, prior surgeries/treatments received for cancer, treatment administration, intent of administered regimen (neoadjuvant, adjuvant, or metastatic), best response achieved, and date of progression.

11.1.2. Vital Signs

Vital signs will include heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature and will be taken as indicated in Table 2 after the subject has been resting for at least 5 minutes. If the subject experiences an infusion-related reaction, then additional vital signs will be recorded every 15 minutes to resolution on the eCRF.

11.1.3. Weight and Height

Weight and height will be measured as indicated in Table 2. If weight fluctuates more than 10% between Day 8 and Day 1, discuss with the sponsor before dosing.

11.1.4. Physical Examination

Complete physical examinations will be performed as in indicated in Table 2. Clinically targeted physical examinations will be performed at study visits during the treatment phase. Only clinically significant abnormalities will be recorded on the appropriate eCRF.

11.1.5. Electrocardiogram

For all subjects, local 12-lead ECGs will be taken as indicated in Table 2. Abnormal findings should be evaluated as clinically indicated, including repeated ECGs. Electrocardiograms may be done at other time points during the study if clinically indicated. Electrocardiograms are to be performed at rest in the semi-recumbent or supine position. Clinically significant abnormal findings should be noted, and the appropriate clinical work-up should be initiated until the condition has stabilized.

11.1.6. ECOG Performance Status

ECOG performance status will be assessed as indicated in Table 2.

11.1.7. Laboratory Assessments

All clinical laboratory samples for safety will be collected and analyzed by the study center'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 2. 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 24 to 48 hours to confirm abnormality and followed until resolution. The panels of laboratory tests to be performed are shown in the succeeding sections.

11.1.7.1. Hematology

Hemoglobin, white blood cell (WBC) count and differential (with ANC), and platelet count will be performed as indicated in Table 2. ANC levels must be confirmed prior to each dose as described in Section 6.5.2.3.

11.1.7.2. Coagulation

Prothrombin time or international normalized ratio and partial thromboplastin time will be obtained as indicated in Table 2.

11.1.7.3. Blood Chemistry

Total protein, albumin, total bilirubin, alkaline phosphatase, alanine aminotransferase, AST, creatinine (estimated glomerular filtration rate) using a validated model (Appendix 2), creatinine, blood urea nitrogen or urea, glucose, sodium, potassium, magnesium, chloride, bicarbonate, calcium, and phosphorus will be obtained as indicated in Table 2.

11.1.7.4. Lactate Dehydrogenase and Uric Acid

Lactate dehydrogenase and uric acid will only be required as indicated in Table 2.

11.1.7.5. 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 as indicated in Table 2 and as clinically indicated with details regarding protein, casts, WBC and red blood cell counts, and bacteria recorded. Only abnormal results will be captured on the eCRF.

11.1.7.6. Pregnancy Testing

In female patients of childbearing potential, pregnancy testing will be performed according to the Schedule of Assessments (Table 2) and as presented in Appendix 5.

11.1.7.7. Follicle-Stimulating Hormone (FSH)

FSH testing will be conducted as needed per Appendix 5 for determination of childbearing potential.

11.2. 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.

11.2.1. Safety Reporting Definitions

11.2.1.1. 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 study drug.

AEs may include worsening or exacerbation of the disease under study, worsening or exacerbation of pre-existing conditions or events, intercurrent illnesses, or drug interactions. Any standard-of-care assessments that show abnormalities should be recorded as an AE. Anticipated fluctuations of pre-existing conditions that do not represent a clinically significant exacerbation or worsening is not considered AEs.

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.

11.2.1.2. Serious Adverse Events

An 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 was 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.

An SAE does not include the following:

- Progression of disease (see Section 11.2.2.6)
- Hospitalization for a routine clinical procedure as stipulated by the protocol
- Preplanned treatments or surgical procedures requiring hospitalization (The conditions should be documented as appropriate in the eCRF.)
- Hospitalization for nonmedical reasons (ie, social admissions or hospitalizations for social, convenience, or respite care)

11.2.1.3. 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 health care professional, patient, or consumer. Medication errors may be classified as a medication error without an AE, which includes situations of missed dose, medication error with an AE, intercepted medication error, or potential medication error.

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

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

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

11.2.2. Adverse Event and Special Situation Reporting

11.2.2.1. 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 11.2.5. The safety reporting period begins when the subject signs the ICF and continues until 30 days after the last dose of the study drug or initiation of alternative therapy. During the period after the informed consent has been obtained and before the first dose of the study drug, only SAEs caused by a protocol-mandated intervention (eg, biopsy) should be reported. After the first dose of the study drug until 30 days after the last dose of the study drug, all AEs must be recorded. Any SAE that occurs after the safety reporting period and is assessed as possibly related to the study drug must be reported according to the instructions in Section 11.2.5.

All study drug SSRs that occur from study drug initiation and throughout the duration of the study, including the post treatment follow-up visit, must be reported to the sponsor.

11.2.2.2. 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 case report form (CRF). AEs should be elicited by asking the subject a nonleading 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 11.2.1.1 and Section 11.2.2.5).

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 11.2.5). 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 test 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 11.2.2.2 and 11.2.5.

Serious Adverse Event Reporting Process

Serious AEs 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 11.2.5. 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 the 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 11.2.5.

11.2.2.3. Assessment of Adverse Event Severity

The severity of AEs will be graded using NCI-CTCAE Version 5.0. For each SAE, the highest severity grade should be reported. If an NCI-CTCAE criterion does not exist, the investigator should assess the severity according to the criteria in Table 5.

Table 5. Grading for AEs Not Listed in NCI-CTCAE

NCI-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 ADLs[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

ADL = activities of daily living; AE = adverse event; 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 refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not being bedridden.
3 These events should be assessed to determine if they meet the definition of SAEs.

11.2.2.4. Assessment of Adverse Event Causality

The investigator's causality assessment is required for all AEs including both nonserious 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 by the underlying disease, comorbidities, or concomitant medications.

- Unlikely related: a temporal relationship to drug administration that 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.

11.2.2.5. Adverse Events Based on Abnormal Test Findings

An abnormal test finding that meets any one of the following criteria 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, 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 11.2.5)

- 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 result, 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 11.2.1.2) should be reported as such.

11.2.2.6. Disease Progression

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

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

In most cases, disease progression will be based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) criteria. If disease progression is based on the subject's symptoms, every effort should be made to document progression using objective criteria.

11.2.3. 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 the study drug. Deaths that occur more than 30 days after the last dose of the study drug are to be reported if they are assessed by the investigator as related to the 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 11.2.5.

Deaths related to progression of the underlying disease during the study will not be reported as an SAE (see Section 11.2.2.6) 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.

11.2.4. Reporting Exposure During Pregnancy

Pregnancy occurring in a female subject after initiation of study drug and throughout the study (including the post study drug follow-up period) or 6 months after the last study drug dose, whichever is longer, should be reported to the sponsor on the Pregnancy Form within 24 hours of the investigator becoming aware of the event.

Pregnancy occurring in female partners of male subjects after initiation of study drug and throughout the study (including the poststudy drug follow-up period) or 3 months after the last study drug dose, whichever is longer, should be reported to the sponsor within 24 hours of becoming aware of the event.

The investigator should counsel the subject and, in the case of a male subject, the subject's partner, regarding the risks of continuing with the pregnancy and the possible effects on the fetus.

If the female partner of a male subject becomes pregnant, the investigator should obtain informed consent of the pregnant partner prior to monitoring the pregnancy, so that information regarding the pregnancy outcome can be reported to the sponsor.

Information regarding the pregnancy should include estimated date of conception, duration of study drug exposure (or number of days/months after treatment discontinuation) as of the estimated conception date, expected delivery date, date of the last menstrual period, all concomitant medications (including recreational drug use such as alcohol, tobacco, and illicit drugs), and other maternal medical conditions.

The investigator should make every effort to follow up with the subject (or female partner of a male subject) through the resolution of the pregnancy (ie, delivery or pregnancy termination). If the pregnancy results in abortion (spontaneous or induced) or premature birth or if the infant is born with a congenital anomaly, these events are considered SAEs and should be reported as described in Section 11.2.5. The outcome of all pregnancies must be reported to the sponsor, even for normal births. The condition of the infant at birth should be reported, including any anomalies, and the infant should be followed up until 3 months of age and any illnesses should be reported.

All information regarding the pregnancy in a female subject or a female partner of a male subject and the infant should be reported on the Pregnancy Form.

11.2.5. 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 11.2.2.2); 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 forms for email instructions.

Fax: Refer to the SAE Form Completion Guidelines for country-specific fax numbers.

11.2.6. 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 Council for Harmonisation (ICH) guidelines.

11.2.7. 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 IRB/IECs in accordance with all applicable regulations and guidance documents.

12. STATISTICS

12.1. Sample Size Determination

A sample size of up to 20 subjects with moderate hepatic impairment and 8 subjects with normal hepatic function is deemed sufficient to evaluate the PK and safety profiles of sacituzumab govitecan when administered to subjects with moderate hepatic impairment. Subjects who do not complete the study, withdraw inform consent, or died prior to completing 1 cycle of treatment may be replaced at the sponsor's discretion. Replaced subjects will begin the study as a new subject.

12.2. Populations for Analyses

Safety Population: All subjects who received at least 1 dose of study medication. The Safety Population will be used for all safety analyses.

PK Population: All subjects who received the study drug and have at least 1 measurable serum concentration of sacituzumab govitecan, free SN-38, SN-38G, or total SN-38.

12.3. Statistical Analyses

Corresponding to the primary and secondary objectives, the primary and secondary analyses, including definitions of primary and secondary end points, populations for analysis, and statistical methods, are described in this section. Additional details will be included in the statistical analysis plan. Summary statistics for continuous variables will include the number of subjects with available data (n), mean, standard deviation, CV%, median, and range (minimum and maximum). Categorical variables will be presented as frequency counts and percentages. Data listings will be created to support tables and figures.

12.3.1. Pharmacokinetic Analyses

Serum concentrations of sacituzumab govitecan, free SN-38, SN-38G, and total SN-38 will be summarized over each scheduled sampling time by dosing day (Day 1, Day 8) for each dose level and subject population (normal hepatic function and moderate hepatic impairment) using descriptive statistics. Serum PK parameters of sacituzumab govitecan, free SN-38, SN-38G, and total SN-38 will be derived by noncompartmental methods and summarized by dosing day (Day 1 and Day 8) for each dose level and subject population using descriptive statistics. Individual concentration and PK parameter data will be listed.

Scatter plots will be used to present the concentration-time profiles. Box plots will be used to present the PK parameters. Additional graphical presentation may also be used to present the data as appropriate.

An analysis of variance (ANOVA) will be performed on natural logarithms of $AUC_{0\text{-last}}$, $AUC_{0\text{-}168}$, and C_{max} for sacituzumab govitecan, free SN-38, SN-38G, and total SN-38, with subject population as a fixed effect. Dose-normalized parameters will be used if the doses are different between the 2 subject populations. Within the ANOVA framework, the ratio of the geometric means and the corresponding 90% confidence interval of the ratio between the moderate hepatic impairment and the normal hepatic function populations will be estimated.

12.3.2. Safety Analyses

Safety analyses will be based on the Safety Population. All safety analyses will be summarized by dose level and subject population (normal hepatic function and moderate hepatic impairment). Treatment-emergent AEs and SAEs, clinical laboratory test results, vital signs, and ECG results will be summarized. Safety data will be summarized using descriptive statistics. Categorical variables will be summarized by number and percentage. Continuous variables will be summarized using n, mean, standard deviation, median, upper and lower quartiles, and range (minimum and maximum), unless otherwise specified. Individual data will be listed.

Treatment-emergent adverse events (TEAEs) are defined as one or both of the following:

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

Treatment-emergent laboratory abnormalities are defined as values that increase at least one toxicity grade from baseline at any time post-baseline up to and including the date of last dose of study drug plus 30 days.

12.3.3. Immunogenicity

Number of subjects with antibodies against sacituzumab govitecan will be summarized by dose level and subject population (normal hepatic function and moderate hepatic impairment). Individual data will be listed. The impact of immunogenicity, if detected, will be explored in relation to PK and safety/tolerability of sacituzumab govitecan.

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

13.1. Study Monitoring

Monitoring procedures developed by Immunomedics or its designee will be followed, in order to comply with ICH GCP, United States (US) Food and Drug Administration (FDA), and applicable guidelines. Review of the subject's eCRFs, electronic medical/health records, or paper source documentation for completeness and accuracy will be required, and 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 center 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 center personnel within a timely manner when clarification of eCRF data is 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 IRB/IEC, and/or Immunomedics' Clinical Quality Assurance group or designee may request access to all source documents, subject's 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.

13.2. Audits and Inspections

Authorized representatives of the sponsor, a regulatory authority, an IEC, or an IRB may visit the study center to perform audits or inspections, including source data verification. The purpose of a sponsor's audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. The investigator should contact the sponsor immediately if contacted by a regulatory agency about an inspection.

13.3. 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.

14. 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 center 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 and in a reasonable manner. The investigator/institution must guarantee direct access to source documents by Immunomedics 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 and in a reasonable manner.

15. ETHICS

15.1. 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 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.

15.2. Ethical Conduct of the Study

This study is planned to be conducted in the US. 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 Regulations (CFR) Part 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 study centers where IRB/IEC approval has been obtained.

The investigator is responsible for providing his or her 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 study center.

All correspondence with the IRB/IEC should be retained in the investigator file. Copies of IRB/IEC approvals should be forwarded to Immunomedics or its 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 Immunomedics or its designee in writing within 5 working days after the implementation.

15.3. 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 subjects 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 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 Immunomedics 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.

15.4. 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 the 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.

15.5. Protocol Compliance

The investigator will conduct the study in compliance with the protocol provided by Immunomedics 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 and 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.

15.6. 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 Part 160 and 45 CFR Part 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, Immunomedics or its designee will not collect any protected health information and will only collect deidentified 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 Immunomedics or designee in connection with the development of the study drug. The study investigator is obliged to provide Immunomedics 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, Immunomedics or its designee, and the IRB/IEC for each study center.

15.7. Financial Disclosure

In accordance with 21 CFR Part 54, the 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, Immunomedics requests that every investigator and subinvestigator 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 Immunomedics. To assist Immunomedics 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.

15.8. Sponsor Discontinuation Criteria

Immunomedics 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. In the unlikely event of premature termination or discontinuation of the study and in the event that the investigator believes a subject is continuing to receive clinical benefit, the sponsor will discuss options with the investigator in order to ensure continuing supply of sacituzumab govitecan. As directed by the sponsor's designee, all study materials will be collected and all CRFs will be completed to the greatest extent possible.

16. DATA HANDLING AND RECORDKEEPING

16.1. Inspection of Records

Immunomedics or its designee will be allowed to conduct study center visits to the investigation facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

16.2. Retention of Records

Records and documents pertaining to the conduct of this study, including eCRFs, source documents, consent forms, clinical laboratory test results, and medication inventory records, must be retained by the investigator for at least 15 years. No study records shall be destroyed without prior authorization from Immunomedics. For studies conducted outside the US under a US Investigational New Drug (IND), the investigator must also comply with the US FDA IND regulations, ICH guidelines, and the regulations of the relevant national and local health authorities. Current US federal law requires an investigator to maintain such records for a period of 2 years following approval of a Biologic License Application or, if the Biologic License Application is not approved, until 2 years following notification by Immunomedics that the clinical investigations have been discontinued.

16.3. Electronic Case Report Forms

An eCRF is required and must be completed for each enrolled subject. The completed original eCRFs are the sole property of Immunomedics and should not be made available in any form to third parties, except for authorized representatives of appropriate regulatory authorities, without written permission from Immunomedics.

It is the investigator's responsibility to ensure completion of and to review and approve all eCRFs. eCRFs must be signed by the investigator or by an authorized staff member. These signatures serve to attest that the information contained on the eCRFs is true. At all times, the investigator has the final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the eCRFs. Subject source documents are the physician's subject records maintained at the study center. In most cases, the source documents will be the hospital's or the physician's chart. In cases where the source documents are the hospital's or the physician's chart, the information collected on the eCRFs must match those charts.

Queries will be issued in the eCRF system by the sponsor or its designee in cases where clarification of eCRF data entered by the study center is required. The appropriate study center personnel will address all queries per study center agreement with the sponsor during the course of the study and afterward to ensure data accuracy and completeness.

17. PUBLICATION POLICY

The conditions regulating dissemination of the information derived from this clinical study are described in the Clinical Study Agreement.

18. LIST OF REFERENCES

CAMPTOSAR, Pharmacia and Upjohn Co. CAMPTOSAR® (irinotecan) injection, for intravenous use. U.S. Prescribing Information. NY, NY. Revised January. 2020:

Cardillo TM, Govindan SV, Sharkey RM, Trisal P, Arrojo R, Liu D, et al. Sacituzumab Govitecan (IMMU-132), an Anti-Trop-2/SN-38 Antibody-Drug Conjugate: Characterization and Efficacy in Pancreatic, Gastric, and Other Cancers. Bioconjug Chem 2015;26 (5):919-31.

Cardillo TM, Govindan SV, Sharkey RM, Trisal P, Goldenberg DM. Humanized anti-Trop-2 IgG-SN-38 conjugate for effective treatment of diverse epithelial cancers: preclinical studies in human cancer xenograft models and monkeys. Clin Cancer Res 2011;17 (10):3157-69.

Cardillo TM, Sharkey RM, Rossi DL, Arrojo R, Mostafa AA, Goldenberg DM. Synthetic Lethality Exploitation by an Anti-Trop-2-SN-38 Antibody-Drug Conjugate, IMMU-132, Plus PARP Inhibitors in BRCA1/2-wild-type Triple-Negative Breast Cancer. Clin Cancer Res 2017;23 (13):3405-15.

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

Goldenberg DM, Cardillo TM, Govindan SV, Rossi EA, Sharkey RM. Trop-2 is a novel target for solid cancer therapy with sacituzumab govitecan (IMMU-132), an antibody-drug conjugate (ADC). Oncotarget 2015;6 (26):22496-512.

19. APPENDICES

Appendix 1. Investigator Signature Page

IMMUNOMEDICS, INC.
300 The American Road
Morris Plains, NJ 07950

STUDY ACKNOWLEDGMENT

A Phase 1, Open-Label, Dose-Escalation Study to Determine an Appropriate Starting Dose of Sacituzumab Govitecan in Subjects With Advanced or Metastatic Solid Tumor and Moderate Liver Impairment

Amendment 3, 16 June 2021

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

MAYANK RAO, MD MBA MS

Name (Printed)
Mayank Rao, Medical Monitor

Signature

16 JUN 2021

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 Immunomedics, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Performance Status Criteria

ECOG Performance Status Scale

Grade	Descriptions
0	Normal activity Fully active, able to carry on all predisease 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

ECOG = Eastern Cooperative Oncology Group

Appendix 3. Cockgroft-Gault Formula

$C_{Cr} = \{((140 - age) \times weight)/(72 \times S_{Cr})\} \times 0.85$ (if female) {Cockcroft 1976}

Abbreviation	Unit
C_{Cr} (creatinine clearance)	mL/minute
Age	Years
Weight	kg
S_{Cr} (serum creatinine)	mg/dL

Appendix 4. Pandemic Risk Assessment and Mitigation Plan

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

These risks can be summarized as follows:

1) Study drug supplies to sites:

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

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

2) Subject safety monitoring and follow-up:

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

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

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

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

   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 laboratory analyses.

      Mitigation plan: Local laboratories or other vendors may be utilized as appropriate to monitor subject safety until the subject can return to the site for their regular follow-up visit 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 local IRB and national laws and regulations. Remote consent will be allowed if has been approved by the local IRB. The consent process will be documented and confirmed by normal consent procedure at the earliest opportunity.

3) Protocol and monitoring compliance:

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

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

b) Monitors may be unable to carry out source data review or source data verification (SDV), or study drug accountability or assess protocol and Good Clinical Practice compliance. This may lead to delays in SDV, 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. The study monitor is to reference the Study Monitoring Plan for guidance on how to conduct a remote monitoring visit. The study staff is to save and document 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 (ie, modification of the statistical analysis plan) 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.

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

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

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

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a female-born patient is considered of childbearing potential following the initiation of puberty (Tanner Stage 2) until becoming postmenopausal unless the patient 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 follicle-stimulating hormone level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy. Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female patient of any age.

b. Definition of Male Fertility

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

2) Contraception Requirements for Female Patients

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 cytochrome P450 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.

b. Contraception Requirements for Female Patients of Childbearing Potential

The inclusion of female patients of childbearing potential requires the use of highly effective contraceptive measures that have a failure rate of less than 1% per year. Patients must have a negative serum pregnancy test at screening and a negative urine pregnancy test prior to study treatment administration on Cycle 1 Day 1. The Cycle 1 Day 1 urine pregnancy test does not need to be conducted if the screening pregnancy test was performed within 3 days before study treatment administration. Duration of required contraception for female patients in this clinical study should start from the screening visit until 6 months after the last dose of study drug.

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

Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the patient'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 patients 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)
  - Oral contraceptives (either combined or progesterone only)
  - Injectable progesterone
  - Subdermal contraceptive implant
  - Transdermal contraceptive patch
  - Contraceptive vaginal ring
- Barrier methods (each method must be used with a hormonal method)
  - Male condom (with or without spermicide)
  - Female condom (with or without spermicide)
  - Diaphragm with spermicide
  - Cervical cap with spermicide
  - Sponge with spermicide

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

3) Contraception Requirements for Male Patients

Male patients with female partners of childbearing potential must use condoms during treatment and until 3 months after last dose of study drug. If the female partner of childbearing potential is not pregnant, additional contraception recommendations should also be considered.

Male patients must also refrain from sperm donation, and/or cryopreservation of germ cells during treatment and until the end of contraception requirement. If needed, male patients should be advised to seek advice 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), 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 patients 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 protocol-required posttreatment follow-up period or 6 months after the last dose of study drug, whichever is longer. Sacituzumab govitecan must be discontinued immediately upon discussion with the medical monitor.

Male patients whose partner has become pregnant or suspects she is pregnant from start of study and throughout the study, including the protocol-required posttreatment follow-up period or 3 months after the last the dose of study drug, whichever is longer, must also report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 11.2.4.

Annex 8. Summary of Changes to the Risk Management Plan over Time

Version	Approval date Procedure	Change
4.0	16-May-2024 EMEA/H/C/005182/II/0031	**Safety Specification, Risk Minimization Measures, Summary of the Risk Management Plan** Updated to remove the important identified and potential risks except for serious infections secondary to neutropenia and the missing information of immunogenicity. **Pharmacovigilance Plan** Milestones for Study IMMU-132-15 updated **Annexes** Annex 2: Updated to reflect changes in Part III Annex 8: Updated to reflect changes noted above
3.0	26-Jul-2023 EMEA/H/C/005182/II/0020	**Safety Specification** Updated to reflect the proposed HR+/HER2- mBC indication **Risk Minimization Plan** Updated to reflect proposed SmPC update **Annexes** Annex 7 Updated references accordingly Annex 8 Updated to reflect changes noted above
2.0	02-Mar-2022 EMEA/H/C/005182/IB/0006	**Pharmacovigilance Plan** Milestones for Study IMMU-132-15 updated **Annexes** Annex 2: Updated to reflect changes in Part III