STATISTICAL ANALYSIS PLAN

Study Title:	A Randomized Open-Label Phase 3 Study Of Sacituzumab Govitecan Versus Treatment Of Physician's Choice In Subjects With Metastatic Or Locally Advanced Unresectable Urothelial Cancer
Name of Test Drug:	Sacituzumab Govitecan
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CONFIDENTIAL AND PROPRIETARY INFORMATION

REVISION HISTORY

Version Number	Version Date	Summary of Revisions
1.0	30JUN2020	Initial version
2.0	16NOV2020	Update sample size, exploratory objectives, interim analysis, and stratification factors, subgroup analysis to align with concurrent protocol amendment in these sections. Clarification of AESI definitions. Clarification of sensitivity analysis definitions of PFS in Table 4. Update of SAS version number.
3.0	18DEC2020	In accordance with the protocol amendment, update stratification factors. Add endpoints and analyses for blinded independent central review (BICR) of all tumor assessments using RECIST 1.1, and addition of multiplicity adjustment due to addition of BICR.
4.0	25AUG2021	Update sponsorship per protocol amendment 4. Establish SAP timing and relation to protocol. Define study completion. Clarify events and censoring for PFS. Remove efficacy analyses in Safety Population. Clarify sample size determination. Add example stopping boundaries for interim analysis. Distinguish sources for stratification variables. Clarify handling of protocol deviations. Remove UGT1A1 outputs since optional in protocol amendment 4. Provide additional data handling rules. Minor editorial changes.
5.0	11JUL2022	Changes across the SAP based on the changes of protocol amendment 5 from protocol amendment 4: main change including sample size in Section 4.1 increased from 600 to 696 participants; Section 3.6 through Section 8: defined HRQoL and EQ-5D-5L analysis set, PK analysis set and immunogenicity analysis set. Section 4.2: Interim analysis changed from occurring ~65% (322 events) to around ~75% (~402) events Section 4.13 Physical functions from EORTC QLQ-C30 added to hierarchical testing with alpha control Section 4.13.3 sensitivity analysis of ORR and CBR changed from on efficacy analyzable to on per-protocol analysis set Section 4.13.5 Provided more details for PRO endpoints analysis Table 3 added analysis on per-protocol analysis set and removed analysis on safety analysis set for baseline disease characteristics, and editorial change for other endpoints Section 2.3.4 removed urinalysis from safety endpoints as only screening visit is collected in the study Section 4.3 p-values changed to be rounded to 4 decimal places from 3 decimal places Section 4.14.6 removed CO_2 since not collected in database and LDH as only screening visit is collected Section 4.16.3: removed age calculation as the age collected at the date of informed consent will be used and date of birthday is not collected in the database Section 4.16.7 removed data imputation for date of birth as it's not collected in database Section 4.16.1 added baseline definition for participants who did not receive study drug Added the abbreviations missed in the previous versions; Other editorial changes

Version Number	Version Date	Summary of Revisions
6.0	06 APR2023	Section 2.3.4: • Deleted analysis pertaining to EQ-5D-5L Section 3.5 • Response Evaluable Set was added for assessing efficacy. • EQ-5D-5L analysis set and Biomarker analysis set were deleted. Per-protocol set was removed. Section 4.4 • 'Strata' was added to specify strata information used for analyses. • Analyses of protocol deviations were updated to Important Protocol deviations. Section 4.14: • Clarified the alpha level for testing in the statistical hierarchy. • Subgroups were updated. • PFS censoring rules were updated for patients with no baseline and/or post baseline assessment. PFS censoring rules were also updated to clarify that participants will not be censored for the use of Unspecified Herbal and Traditional Medicine. • Updated the EORTC-QLQ-C30 analyses to specify domains to be analyzed and data to be included in analyses. Section 4.15: • AESI definitions were updated at the compound level and thus updated in this SAP • Updated the scope of AE subgroup tables to summaries for TEAEs by SOC and PT, Grade 3 or Higher TEAEs by SOC and PT, and TEAEs Leading to Study Drug Discontinuation by SOC and PT Section 4.16: • Analysis Visit windows for analysis of QoL were updated. • Handling of Non-Numeric Laboratory data was updated. • Handling of Missing or Incomplete Data was updated. Editorial changes throughout the document for clarity, organization and conciseness.

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LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS

A	alemtuzumab
ADA	anti-drug antibody
AE	adverse event
AESI	Adverse Events of Special Interest
ALT	alanine aminotransferase
AP	analysis plan
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BICR	blinded independent central review
BOR	best overall response
BUN	blood urea nitrogen
CBC	complete blood count
CBR	clinical benefit rate
CI	confidence interval
COX	cyclooxygenase
CR	complete response
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DOR	duration of objective tumor response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EORTC	European Organization for the Research and Treatment of Cancer
EQ-5D	EuroQoL (5 dimensions)
FDA	Food and Drug Administration
Gilead	Gilead Sciences/Gilead Sciences, Inc.
HA	hyaluronic acid
HRQOL	Health-Related Quality of Life
in %	intensity
ITT	Intent-to-Treat
IV	intravenously
KM	Kaplan-Meier
LAN	long-acting nitrate
LDH	lactate dehydrogenase
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
Met	metformin
MMRM	mixed model repeated measure

MRI	magnetic resonance imaging
NCI	National Cancer Institute
NE	not evaluable
ORR	objective response rate
OS	overall survival
P	Passage
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetics
PopPK	population pharmacokinetic
PR	partial response
PRO	patient-reported outcome
QOL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumors
RS	reference standard
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SMQ	Standardised MedDRA Query
SOCs	system organ class
TEAE	treatment-emergent adverse event
TPC	Treatment of Physician's Choice
Trop-2	trophoblast cell-surface antigen 2
TTR	Time to Response
UC	urothelial cancer
ULN	upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the proposed statistical analysis of the study entitled: “A Randomized Open-Label Phase 3 Study of Sacituzumab Govitecan Versus Treatment of Physician's Choice in Subjects with Metastatic or Locally Advanced Unresectable Urothelial Cancer”.

The purpose of this document is to ensure the credibility of the study outcomes by pre-specifying the objectives, endpoint definitions, statistical methods, and approaches used to evaluate the specified efficacy and safety endpoints.

This SAP is based on the study protocol amendment 5, dated 08JUN2022, and the electronic case report form (eCRF). To the extent that the analyses described in this SAP differ from those described in the protocol, the methods of the SAP will supersede those described in the protocol. The SAP will be finalized before the formal interim analysis and database finalization. Any analysis not described in this plan will be considered exploratory and will be documented in the clinical study report as a post hoc analysis or changes to the planned analysis.

To comply with regulatory electronic submission guidelines, listings of all clinical data will be submitted as electronic data sets. Specific listings will be generated as described.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Overview of Study

This is a Phase 3, randomized, global, open-label, multicenter study of IMMU-132 (Sacituzumab govitecan) in subjects/participants (hereafter in this SAP, 'participants' is used) with metastatic or locally advanced unresectable urothelial cancer (UC).

Approximately 696 participants will be randomized 1:1 to receive either sacituzumab govitecan at a dose level of 10 mg/kg on Days 1 and 8 of a 21-day cycle or Treatment of Physician's Choice (TPC). The TPC arm consists of 1 of 3 standard of care chemotherapeutic options including paclitaxel, docetaxel, and vinflunine, (in countries where vinflunine is approved and is commercially available) administered intravenously (IV) at standard of care doses of 175, 75, and 320 mg/m^2, respectively, on Day 1 of 21-day cycles, and the determined dosing schedule for these treatments should be adhered to. Participants will be stratified by their type of prior platinum therapy (cisplatin or carboplatin), Bellmunt risk factors (0-1 or 2-3), and setting in which prior type of therapy in which platinum therapy was administered (neo-adjuvant/adjuvant or locally advanced unresectable/metastatic). The most recent line of platinum therapy should be used for the stratification factor.

The study will be completed after all overall survival events (536 deaths) have been documented for the primary efficacy analysis with appropriate follow-up as designated. An interim analysis is planned ~75% of overall survival events (~402 deaths) have been documented (Refer to Section 4.2). The clinical data cutoff date will correspond to the date when the target number of primary efficacy events have been documented.

2.2. Study Objectives

2.2.1. Primary Objective

To assess overall survival (OS) with sacituzumab govitecan compared with TPC in participants with metastatic or locally advanced unresectable UC

2.2.2. Secondary Objectives

1) To assess progression-free survival (PFS) of sacituzumab govitecan compared with TPC by investigator assessment and blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

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

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

4) To assess Quality of Life (QOL) based on European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life of Cancer Patients (QLQ-C30) questionnaire with sacituzumab govitecan compared with TPC

2.2.3. Exploratory Objectives

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

2) To investigate candidate blood and tumor biomarkers of response

3) To investigate potential correlation between serum sacituzumab govitecan pharmacokinetics (PK) and the development of immunogenicity (anti-drug antibody [ADA])

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

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

2.3. Clinical Trial Endpoints

2.3.1. Efficacy Endpoints

2.3.1.1. Overall Survival (OS)

The primary efficacy endpoint is Overall Survival. OS is measured from the date of randomization to death from any cause. Participants without documentation of death are censored on the date they were last known to be alive.

2.3.1.2. Progression-free Survival (PFS)

Progression free survival (PFS) is a secondary endpoint. PFS will be based on tumor assessments evaluated by investigators and BICR using RECIST v1.1 criteria {Eisenhauer 2009}. US Food and Drug Administration (FDA) definitions and guidance as described in Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (December 2018) and Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics (April 2015) are referenced in relevant endpoint definitions.

PFS by BICR is a key secondary endpoint. PFS will be defined as the time from randomization until objective tumor progression or death due to any cause, whichever comes first.

The date of progression will be the earliest time when tumor progression is observed based on RECIST v1.1. It will be the date that shows a predefined increase (20% +) and an 5mm absolute increase in the sum of the target lesion diameters or the appearance of new lesions or the unequivocal progression of non-target lesions.

2.3.1.3. Objective Response Rate (ORR), Clinical Benefit Rate (CBR), Time to Response (TTR), Duration of Response (DOR)

ORR, CBR, TBR and DOR are secondary endpoints. Objective tumor response will be evaluated from computed tomography (CT) scans (or magnetic resonance imaging [MRI]) using RECIST v1.1 criteria according to investigator assessments and BICR. Using these criteria, the best overall response (BOR) of participants will be classified based on tumor response into the categories of complete response (CR), partial response (PR), stable disease (SD), non-CR/non-PD, progressive disease (PD), or not evaluable (NE). A BOR of CR or PR can only be claimed if the initial radiographic assessment of CR or PR is confirmed at a subsequent time point at least 4 weeks later. Two positive response scans separated by a scan of NE can still be considered a confirmation of response. The endpoint of ORR will be defined as the percentage of the best overall response as CR or PR, relative to the size of population under evaluation.

In addition to ORR, clinical benefit rate (CBR) is defined as the proportion of participants with best overall response of CR or PR or else SD with a duration of at least 6 months. For SD participants, the duration of SD is defined as the time from randomization to the first documented PD or the last adequate response assessment.

Time to onset of objective response (CR or PR; TTR) will be calculated for objective responders as the time from randomization to the first documentation of response of CR or PR, which must be confirmed subsequently.

For participants with a best overall response of CR or PR, duration of objective response (DOR) will be calculated as the time from the first documented response of CR or PR to the date of progression or death. Participants who do not progress or die after response will be censored, using the censoring rules as described in Section 4.14.4.

2.3.2. Safety Endpoints

Safety and tolerability will be evaluated based on adverse events (AEs), standard safety laboratories (such as complete blood count [CBC] with differential and platelet count, serum chemistries), physical examination, electrocardiogram (ECG), and vital signs.

Treatment-emergent adverse events (TEAEs) are defined as any AEs that begin or worsen on or after the start of study drug through 30 days after the last dose of study drug.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) system based on preferred terms (PTs) and system organ class (SOCs). AEs and selected laboratory parameters will be classified for severity using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 toxicity grades. Non-numeric components of laboratory grading algorithm (such as a criterion requiring hospitalization) will not be included in the grade calculations. Only TEAEs will be summarized.

2.3.3. Pharmacokinetic and Immunogenicity Evaluations

PK and ADA analyses using validated assays will be performed from serum samples obtained according to the study schedule of all participants receiving sacituzumab govitecan. ADA samples are required from all participants receiving sacituzumab govitecan with serum samples obtained according to the study schedule.

2.3.4. Patient-reported Outcomes (PRO)

PRO evaluation will be based on the EORTC QLQ-C30 instrument according to study schedule. Standard scoring algorithms of these patient-reported outcome instruments will be applied. Change from baseline in the physical functioning, pain, and fatigue scales of the EORTC-QLQ-C30 score are secondary endpoints of the study.

A separate PRO analyses plan will document PRO endpoints and analyses not described in this SAP.

2.3.5. Biomarkers Evaluations

Biomarker analyses will be performed on samples from all participants that consented for biomarker analysis, including Trop-2 expression. A separate biomarker analyses plan will document biomarker endpoints and analyses.

3. ANALYSIS SETS

The following analysis sets are defined and used for relevant safety, efficacy, pharmacokinetic and pharmacodynamic analyses. An overview of the analyses and their analysis sets are provided in Table 1

3.1. All Screened Participants Set

The All Screened Participants Set is defined as all participants who have signed an informed consent and participated in screening procedures at the investigative site to assess eligibility.

3.2. Intent-to-Treat (ITT) Analysis Set

The ITT Analysis Set is defined as all participants who have been randomized to the trial. This is the primary analysis set for efficacy analyses. Participants will be analyzed according to the treatment arms to which they were randomized.

3.3. Safety Analysis Set

All participants administered at least 1 dose of sacituzumab govitecan or TPC will be included in the Safety Analysis Set. For the analysis, participants are assigned to treatment arms based on the treatment they actually received. Safety endpoints will be analyzed using the safety analysis set.

3.4. Response Evaluable Analysis Set

The Response Evaluable Analysis Set is defined as participants in the ITT who received at least 1 dose of study drug and had measurable disease at baseline. The determination of measurable disease should be based on BICR assessments for evaluation of ORR by BICR and on investigator assessments for determination of ORR by investigator. The response evaluable analysis set will be used in the analysis of ORR and CBR in addition to the analyses based on the ITT set.

3.5. HRQoL Evaluable Analysis Set

HRQoL Evaluable Analysis Set is defined as participants in the ITT Analysis Set who had an evaluable assessment of the EORTC QLQ-C30 at baseline and at least 1 evaluable assessment at postbaseline visits. An evaluable assessment at a given visit is defined as at least 1 of the 15 domains/scales being non-missing at that scheduled assessment visit.

3.6. Pharmacokinetic Analysis Set

PK Analysis Set will include all participants in the ITT who received at least 1 dose of sacituzumab govitecan and have at least 1 evaluable post-dose concentration value reported by the PK laboratory.

3.7. Immunogenicity Analysis Set

Immunogenicity Analysis Set will include all participants in the Safety Analysis Set who had at least 1 dose of sacituzumab govitecan treatment and have at least 1 evaluable postbaseline ADA test result.

Table 1. An Overview of Analyses and Analysis Sets

Analysis Category	All Screened Participants	Intent-to- Treat (ITT) Analysis Set	Safety Analysis Set	Response Evaluable Set	HRQoL Evaluable Analysis Set	PK/ Immunogenicity Analysis Set
Enrollment and Eligibility	X					
Demographics		X	X			
Baseline Disease Characteristics		X				
Participant Disposition		X				
Protocol Deviation		X				
Prior Anticancer Therapy, Prior and Concomitant Medications		X				
Exposure to Study Therapies			X			
Efficacy on primary endpoint OS		X				
Efficacy on secondary endpoints (PFS, TTR, DOR)		X				
Efficacy on secondary endpoints (ORR, CBR)		X		X		
Patient Reported Outcome (PRO)					X	
Efficacy Subgroup Analyses		X				
Safety Analyses (AE, AESI, Death, Vital Sign, Clinical Lab, ECOG, Physical Exam and Pregnancy Test)			X			
Immunogenicity						X (Immunogenicity)
PK						X (PK)

4. STATISTICAL METHODS AND ANALYSES

4.1. Determination of Sample Size

The study will randomize approximately 696 participants and has a projected enrollment period of 23 months. The final OS analysis will occur after 536 deaths have occurred, which is projected to happen approximately 19 months after the last participant is enrolled and will provide 90% power to demonstrate a hazard ratio of 0.755 equating to a 2.7-month improvement in OS from 8.3 months to 11 months at a two-sided alpha of 5% with yearly discontinuation rate of 10% under exponential survival distribution assumption.

4.2. Interim analysis

An interim analysis is planned when ~75% of the total 536 OS events (~402 deaths) have been observed, which is projected to occur around month 30 of the study and provides a 70% chance that median follow-up covers median OS.

This supersedes the protocol-specified timing of the interim analysis (planned when ~65% of targeted OS events have been observed). Based on simulation conducted by Gilead subsequent to the protocol, based on reverse Kaplan-Meier (KM) method, the protocol specified timing of the interim analyses would have provided a less than 10% chance that the median OS is within median follow-up time, and is therefore not considered adequate for the timing of the interim analysis.

A Lan-DeMets spending function that approximates O'Brien/Fleming stopping boundaries will be applied to the interim OS analysis. Table 2 shows the interim and final stopping boundaries if the interim analysis includes exactly 402 (75%, Gilead planned interim analysis timing point) OS events. The interim boundary for declaring superiority will be derived based on the actual number of deaths and will apply the Lan-DeMets alpha spending function that approximates O'Brien and Fleming stopping boundaries.

Table 2. Stopping Boundaries for Efficacy Superiority Analyses at 75% of 536 Total Events for Gilead Planned Interim Analysis Time point

Planned analysis	Events (%)	Stopping Boundary	
		Two-sided significance level	Corresponding HR[a]
Interim OS Analysis	402 (75%)	0.0193	0.792
Final OS Analysis	536 (100%)	0.0442	0.841

a Under exponential distribution assumption

No futility analysis is planned in this study.

4.3. Overview of General Approaches

Continuous data will be summarized using descriptive statistics: n, mean, median, standard deviation, minimum and maximum. Categorical data will be summarized using counts and percentages. For summary statistics, the tables will be presented by treatment arm unless otherwise specified. In general, a data listing will be provided for reference on endpoints for which summary statistics or analyses are conducted.

All statistical analyses will be performed using a 2-sided hypothesis test at the overall 5% level of significance. *P*-values will be rounded to 4 decimal places.

Each category of analysis will be conducted for the respective analysis populations according to Table 1 unless otherwise specified.

Endpoints and analyses pertaining to the study's primary and secondary objectives will be conducted as described in respective sections of this SAP. Any notable analyses, adjustments to analyses, or analyses not conducted due to lack of sufficient quantity of data (such as insignificant numbers of participants in subgroups) or due to other technical constraints will be noted, if included in the clinical study report.

Other exploratory endpoints and analyses, such as those described in the Exploratory Analyses and Other Analyses sections, due to their nature, may require exploratory or post-hoc determination.

See Section 4.16 for data handling conventions.

4.4. Strata

Patients will be randomly assigned to treatment groups via the interactive voice or web response system (IXRS) using a stratified randomization schedule. Stratification will be based on the following variables: type of prior platinum therapy (cisplatin vs. carboplatin), Bellmunt risk factors (0-1 vs 2-3), and setting in which the most recent line of platinum therapy was administered (neoadjuvant/adjuvant vs. metastatic/locally advanced unresectable).

The stratification variables recorded in the clinical database will be used for the primary analyses. Additionally, stratification discrepancies will be reviewed and assessed. Efficacy endpoint[s] will be evaluated using stratification factors as covariates or stratification variables for analyses.

In the situation where there is insufficient information in a stratum (i.e., less than 20 patients), pooling of the stratum with the smallest adjacent stratum for stratified analyses will be performed if deemed appropriate.

4.5. Participant Accrual and Eligibility

Number and percentage of participants screened and randomized will be summarized and listed for the All Screened Participants Analysis Set by region, country and by site.

Screen failures will be summarized for the All Screened Participants Set by the Inclusion/Exclusion criteria that were not met.

A listing will be provided for each participant including informed consent date, randomization date, first dosing date, country and site for the All Screened Participants Set.

4.6. Enrollment

Key study dates (i.e., first patient screened, first patient randomized, last patient randomized, last patient last visit for the primary endpoint, and last patient last visit for the clinical study report) will be provided.

A summary of patient enrollment will be provided by treatment group for each country [within a region,] investigator [within a country and region,] and overall.

A summary of patient enrollment by stratification factors employed in the randomization (type of prior platinum therapy, Bellmunt risk factors, and prior type of therapy in which the most recent line of platinum therapy was administered) will be provided. If there are discrepancies in the value used for stratification assignment between the IXRS and the clinical database, the value collected in the clinical database will be used for the summary. A listing of patients with discrepancies in the value used for stratification assignment between the IXRS and the clinical database at the time of data finalization will be provided.

4.7. Demographics

Demographic characteristics at baseline will be summarized using descriptive statistics, including but not limited to age, age group (<65, 65-74, ≥75), sex, race, ethnicity, height, weight, and body mass index (BMI).

A listing of demographic information will be provided for the ITT Analysis Set.

4.8. Baseline Disease Characteristics

Summaries of baseline disease characteristics will include but not be limited to the following variables: disease histology, cancer diagnosis and time from diagnosis as required by eligibility criteria, creatinine clearance, and Eastern Cooperative Oncology Group (ECOG) performance status score. Prior treatment history including whether the participants have received prior urothelial cancer-related surgery and radiotherapy and types and numbers of therapy regimen as collected will also be summarized.

Medical history will be summarized by SOC and PT and sorted by frequency in SOC and by decreasing frequency in PT within SOC.

Baseline disease characteristics and medical history listings will be provided for the ITT Analysis Set.

4.9. Participant Disposition

The numbers and percentages of participants who are included in the ITT and Safety Analysis Sets will be summarized by treatment arm. The number and percentages of participants who discontinue from treatment and study, along with reasons for discontinuation, will also be presented by treatment arm. The length of follow-up in each treatment arm will be summarized descriptively and the survival status during follow-up will be presented.

A listing reflecting treatment group, date of randomization, date of first dose, date of last dose, date and reasons of treatment and study discontinuation, survival follow-up status and information for each participant will be provided for the ITT Analysis Set.

A listing of randomization scheme will be provided along with stratification factors after study unblinding at the final analysis.

4.10. Important Protocol Deviation

Important Protocol deviations including violations of Inclusion and Exclusion Criteria will be summarized by categories of deviation and listed for the ITT Analysis Set. The protocol deviations will be adjudicated by consensus of the medical monitors; of those deemed not to be important, deviations in prespecified categories will be excluded from tables and included only in listings.

4.11. Prior Anticancer Therapy, Prior and Concomitant Medications

Prior anticancer systemic therapies (as entered on the Prior Anti-Cancer Therapy eCRF), prior and concomitant medications (as entered on the Prior and Concomitant Medication eCRF) will be coded using the World Health Organization (WHO) Drug Dictionary. Prior medications include medication with a start and end date prior to first administration of study therapy.

Concomitant medications include medications that were taken at any time while on study treatment, including medications that were started before first administration of study therapy but ongoing at the time of first study therapy, or that were initiated on or after first administration but prior to 30 days after last administration of study therapy. If an end date is missing or the medication is ongoing during study treatment, the medication will be included as concomitant medication.

Prior anticancer systemic therapies will be summarized according to WHO Drug Anatomical Therapeutic Chemical (ATC) Classification, and listed additionally with treatment setting, best response, start and end dates, and date of disease progression from the treatment.

Prior medications and concomitant medications will be summarized according to WHO Drug ATC Classification. Concomitant medications of special interest may be also summarized.

Prior anticancer therapy, prior and concomitant medications listings will be provided for the ITT Analysis Set.

4.12. Concomitant Procedures and Radiotherapies

Concomitant procedures and radiotherapies are defined as the procedures administered on or after the study drug was received and will be listed for the ITT Analysis Set.

4.13. Exposure to Study Therapies

Treatment exposure to study therapies will be summarized for treatment duration, number of doses received, and number of treatment cycles received. Number and percentage of participants who had a dose reduction and reasons for dose reduction, number and percentage of participants with 0, 1, 2, 3 and > 3 dose reductions, time to the first dose reduction, number and percentage of participants who had dose interruptions, delays or infusion terminated prematurely will be summarized by treatment arm.

Duration of treatment (in months) will be summarized and number of participants with treatment duration longer than or equal to 3 months, 6 months, 12 months, and 18 months will be summarized.

Relative dose intensity will be calculated as described below and summarized. Cumulative dosage and relative dose intensity will be summarized by descriptive statistics, and relative dose intensity will be additionally summarized by the category of <50%, 50% to < 70%, 70% to <90%, 90% to <110%, ≥110%.

Delivered dose (in mg) for each infusion is calculated per eCRF form from ("Calculated Dose" x "Actual Volume Administered" / "Total Volume Prepared").

Delivered dosage (in mg/kg for sacituzumab govitecan or in mg/m^2 for TPC) of each infusion in a cycle is calculated by dividing the delivered dose (in mg) by body weight (in kg) for sacituzumab govitecan or by body surface area (in m^2) for TPC at the beginning of the cycle (the body weight or the body surface area according to which the prescribed dose is calculated and prepared per the protocol).

Cumulative dosage (in mg/kg for sacituzumab govitecan or in mg/m^2 for TPC) received for each participant is defined as the sum of all delivered doses (in mg/kg for sacituzumab govitecan or in mg/m^2 for TPC) of all infusions the participant received in the study. Total assigned dosage (in mg/kg for sacituzumab govitecan or in mg/m^2 for TPC) for each participant is defined as the product of the assigned dose (10 mg/kg for sacituzumab govitecan, or 175, 75, and 320 mg/m^2 respectively for paclitaxel, docetaxel, and vinflunine) and number of doses the participant was scheduled to receive during the participant's treatment period (number of infusions actually received by the participant plus the number of infusions the participant missed between the first and last infusion).

Relative dose intensity (in %) for each participant is calculated by dividing the participant's cumulative dosage received by the total assigned dosage as defined above, expressed as a percentage.

Treatment exposure will be summarized by the Safety Analysis Set and listed for the Safety Analysis Set.

4.14. Efficacy Analysis

4.14.1. Primary Analysis for OS (Primary Endpoint)

The primary analysis of OS in the ITT Analysis Set for comparison between sacituzumab govetican and the control TPC arm will be performed using a stratified log-rank test stratified by randomization stratification factors as employed in the randomization. Estimate of hazard ratio and its 95% confidence interval will be based on stratified Cox proportional-hazards model {Cox 1972} with treatment arm as the only covariate, stratified by the same stratification factors employed in the randomization. OS will be plotted over time using Kaplan-Meier (KM) curves, median OS and its associated 95% CIs are determined by the Brookmeyer and Crowley method with log-log transformation. Milestone OS rates at time points including 3 months, 6 months, 12 months, 18 months, 24 months will be derived from KM estimates.

Participants without documentation of death are censored on the date they were last known to be alive.

4.14.2. Secondary Analysis for PFS

PFS as assessed by BICR and separately, PFS assessed by investigator according to RECIST v1.1 will be analyzed by the same method as the primary OS analysis. PFS based on BICR will have Type I error control and is hence considered the key secondary endpoint. Milestone PFS rates at time points including 3 months, 6 months, 9 months, and 12 months, will be derived from the KM estimates as the minimum follow-up allows. The following censoring rules will be applied to the endpoint of PFS:

A) Participants who do not have progression and are alive will be censored at last date of evaluable radiographic assessment without documented progressive disease.

B) Participants in the follow-up period for progression who progress or die after missing 2 or more consecutive scheduled visits, per the scheduled assessment interval as defined in the protocol, will be censored at the last date of evaluable radiographic assessment without documented progressive disease.

C) Participants in the follow-up period for progression who receive alternative anticancer treatment before documented progressive disease or death will be censored at the last date of evaluable radiographic assessment without documented progressive disease prior to receiving alternative anticancer treatment. Participants will not be censored for the use of Unspecified Herbal and Traditional Medicine.

D) Participants without baseline tumor assessments or without additional follow-up data will be censored at the date of randomization. However, if such a participant dies without initiation of alternative anticancer treatment and no later than the time of the second scheduled assessment as defined in the protocol, this participant will be considered to have an event at the date of death.

A set of sensitivity analyses may be performed for each assessment of PFS, i.e., investigator and BICR, following the FDA Guidance of Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (December 2018) and Clinical Trial Endpoints for the Approval of Non- Small Cell Lung Cancer Drugs and Biologics (April 2015). The differences between the primary PFS definition and comparisons of their censoring rules are illustrated in Table 3.

4.14.2.1. Sensitivity Analysis 1

In the first sensitivity analyses of PFS, objectively documented progression or death will not be censored, regardless of the timing of the events.

4.14.2.2. Sensitivity Analysis 2

A second sensitivity analysis (Sensitivity Analysis 2, corresponding to Table D2 in Appendix D of Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics, April 2015) of PFS will be performed using a conservative approach by assigning the dates of discontinuation, change of treatment, or the second missed scheduled assessment as an event date.

Table 3. Sensitivity Analyses of PFS and Corresponding Censoring Rules

Case	Primary PFS definition	Sensitivity Analysis 1 (PFS Outcome 1)	Sensitivity Analysis 2 (PFS Outcome 2)
No baseline tumor assessments or no adequate response assessment[1] after randomization			
Died prior to second scheduled assessment without initiation of other anticancer treatment	Date of Death	Date of Death	Date of Death
Died after initiation of other anticancer treatment	Censored at Randomization	Progressed at date of death	Progressed at date of initiation of anticancer therapy
Did not die or died after missing 2 or more scheduled assessments	Censored at Randomization	Progressed at date of Death if died; or censored at date of randomization if did not die	Censored at randomization if did not die, progressed on the date of 2nd missed scheduled assessment
Continued scheduled response assessments until objective PD or death			
PD prior to missing 2 or more scheduled successive assessments	Date of PD	Date of PD	Date of PD
Death prior to missing 2 or more scheduled successive assessments	Date of Death	Date of Death	Date of Death
PD or death after missing 2 or more scheduled assessments	Censored at Date of last adequate response assessment prior to missed assessments	Date of PD or Death	Progressed at 2nd missed scheduled assessment
Treatment discontinuation for undocumented progression, toxicity or other reason	Not applicable, review other scenarios and censor as appropriate	Not applicable, review other scenarios and censor as appropriate	Progressed at the time of discontinuation

Case	Primary PFS definition	Sensitivity Analysis 1 (PFS Outcome 1)	Sensitivity Analysis 2 (PFS Outcome 2)
Initiated other anticancer treatment before PD or death	Censored at Date of last adequate response assessment without documented progression prior to starting other anti-cancer treatment	Date of documented progression or death	Progressed on the date of start of other anticancer treatment
Continued scheduled response assessments without objective PD or death			
Initiated other anticancer treatment	Censored at Date of last adequate response assessment without documented progression prior to starting other anti-cancer treatment	Censored at Date of last adequate response assessment without documented progression prior to starting other anti-cancer treatment	Progressed on the date of start of other anticancer treatment
No objective PD or death	Censored at Date of last adequate response assessment	Censored at Date of last adequate response assessment	Censored at Date of last adequate response assessment

1 Adequate response assessment is defined as a response assessment other than 'not assessed' or 'not evaluable'.

4.14.3. ORR and CBR

The ORR and CBR as assessed by investigators and separately by BICR will be summarized along with number and percentage of participants with a best overall response of CR, PR, SD, SD with a duration of 6 months or longer, PD, and NE. ORR and CBR will be analyzed and compared between the treatment arms using the Cochran-Mantel-Haenszel method stratified by the stratification factors used in the randomization. The 2-sided 95% CIs will be calculated by the Clopper-Pearson exact method.{Mantel 1966, Mantel 1959}.

Sensitivity analyses of ORR and CBR as assessed by investigators and BICR will be conducted in the Response Evaluable Analysis Set.

4.14.4. TTR and DOR

Only participants achieving CR or PR as assessed by investigators or BICR will be included in the respective calculation for TTR and DOR analyses. DOR is calculated as the time from the first documented response of CR or PR to the date of progression or death. Participants who do not progress or die after response will be censored, using the censoring rules as described in Table 4 below. DOR as assessed by investigators and BICR in each treatment arm will be estimated using the Kaplan-Meier method. The number and percentage of responders with a DOR greater than or equal to a timeline including 3 months, 6 months, 9 months and 12 months will be estimated.

TTR as assessed by investigators and BICR will be summarized by descriptive statistics, and by the number of percentage of responders whose TTR is within 3 months, 6 months and 12 months.

Table 4. Censoring Rules for the Endpoint of Duration of Response (DOR)

Case	Outcome	Date of Event/Censoring[1]
Subsequent PD or death after response		
PD prior to missing 2 scheduled successive assessments	DOR event	Date of objective PD
Death prior to missing 2 scheduled successive assessments	DOR event	Date of death
PD or death after missing 2 or more scheduled assessments or after initiating other anticancer treatment	Censor	Date of last adequate response assessment before missed ones, or Date of last adequate response assessment without documented progression before starting other anticancer treatment
Response without subsequent objective PD or death		
Initiated other anticancer treatment	Censor	Date of last adequate response assessment without documented progression prior to starting other anticancer treatment
No objective PD or death	Censor	Date of last adequate response assessment

1 Adequate response assessment was defined as a response assessment other than 'not assessed' or 'not evaluable'.

4.14.5. PRO

European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life of Cancer Patients, core questionnaire, version 3.0 (QLQ-C30), will be used to assess and compare the impact of treatment on Health-Related Quality of Life (HRQOL) between treatment arms.

Participants in the HRQoL Evaluable Analysis Set will be included in the analysis.

4.14.5.1. EORTC QLQ-C30

EORTC QLQ-C30 Scoring

The QLQ-C30 is composed of 15 domains involving both multi-item scales and single-item measures. These include 5 functional scales, 3 symptom scales, a global health status / QoL scale, and 6 single items.

Principals for scoring these scales:

1) Derive raw score by averaging the items that contribute to the scale.

2) Standardize the raw score by applying a linear transformation so that the scores range from 0 to 100. A higher score presents a higher (“better”) level of functioning, or higher (“worse”) level of symptoms.

Raw Score

Raw Score = RS = $(I_1 + I_2 + \ldots + I_n)/n$; where I_1, I_2, … I_n are items included in a scale

Linear transformation

Apply linear transformation to 0-100 to obtain the score S.

Functional scales: $S = \left(1 - \frac{(RS-1)}{range}\right) x100$

Symptom scales: $S = \left(\frac{(RS-1)}{range}\right) x100$

Global health status / QoL: $S = \left(\frac{(RS-1)}{range}\right) x100$

Range is the difference between the maximum possible value of RS and the minimum possible value. The QLQ-C30 has been designed so that all items in any scale take the same range of values. Therefore, the range of RS equals the range of the item values. Item numbers and item ranges for each scale is presented in Table 5.

For each QLQ-C30 assessment, scores for each scale will be computed only if at least half of the items contributing to the scale are not missing. Otherwise, the particular score will be set to missing. If the response is missing for single-item measures, that score will be set to missing.

Table 5. Scoring the EORTC QLQ-C30

	Scale	Number of items	Item range*	Version 3.0 Item numbers
Global health status / QoL				
Global health status/QoL	QL	2	6	29, 30
Functional scales				
Physical functioning	PF	5	3	1 to 5
Role functioning	RF	2	3	6, 7
Emotional functioning	EF	4	3	21 to 24
Cognitive functioning	CF	2	3	20, 25
Social functioning	SF	2	3	26, 27
Symptom scales / items				
Fatigue	FA	3	3	10, 12, 18
Nausea and vomiting	NV	2	3	14, 15
Pain	PA	2	3	9, 19
Dyspnoea	DY	1	3	8
Insomnia	SL	1	3	11
Appetite loss	AP	1	3	13
Constipation	CO	1	3	16
Diarrhoea	DI	1	3	17
Financial difficulties	FI	1	3	28

* Item range is the difference between the possible maximum and the minimum response to individual items
Abbreviations: EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Core 30 Questionnaire; QoL = quality of life

Absolute values and change from baseline values of EORTC QLQ-C30 functional scales, symptom scales and global health status QoL will be summarized descriptively.

4.14.5.1.1. EORTC QLQ-C30 Analysis

Descriptive statistics and summaries of EORTC QLQ-C30 global health status, pain, fatigue, and physical functioning up to and including Cycle 5 Day 1 will be presented by treatment group for the absolute values and change from baseline values. The mean change from baseline in these subscales will also be analyzed using a MMRM analysis including PRO data from all visits up to and including Cycle 5 Day 1, adjusting for baseline score, visit week (categorical), treatment arm, randomization stratification factors, and the interaction between visit week and treatment arm as fixed effect; visit week will be fitted as a repeated effect (repeated by patient).

Data after the initiation of new anti-cancer therapy will not be included. The Satterthwaite method will be used to calculate the degree of freedom. An unstructured covariance matrix will be used to estimate the variance-covariance of the within-patient repeated measures and if the model fails to converge, a first order autoregressive covariance matrix will be used. The interaction between measurement time points and treatment arm will be tested for different effects of treatment over time. If the interaction is not significant, the interaction term will be dropped from the model. From the model, the least square (LS) mean change from baseline for each treatment arm and the LS mean difference in change from baseline PRO score between treatments at Cycle 5 Day 1 with 95% CIs will be presented, with associated p-value for the difference between treatments.

Mean change from baseline at Cycle 5 Day 1 in the physical functioning scale will be sequentially tested after OS and PFS based on BICR for overall Type I error rate controlled at a 2-sided alpha of 0.05.

4.14.6. Multiplicity Adjustment:

To ensure the overall Type I error rate is strictly controlled at a 2-sided alpha of 0.05 for comparison between sacituzumab govitecan and the control TPC arm, a hierarchical testing strategy will be performed based on the primary endpoint of OS, key secondary endpoint of PFS based on BICR, and physical functioning score of the EORTC QLQ-C30. If the planned primary OS analysis is positive, then the secondary endpoint of PFS based on BICR and the mean change from baseline at Cycle 5 Day 1 in EORTC QLQ-C30 physical functioning score will be tested sequentially at the alpha level of 0.05. If the planned secondary endpoint of PFS based on BICR is positive, then the mean change from baseline at Cycle 5 Day 1 in EORTC QLQ-C30 physical functioning score will be tested. Stratified log-rank test will be used for testing OS and PFS. Mixed model repeated measure (MMRM) will be used for testing the mean change from baseline at Cycle 5 Day 1 in EORTC QLQ-C30 physical functioning score.

4.14.7. Other Analyses and Listings

For the secondary endpoint PFS as assessed by investigators and BICR in the ITT Analysis Set, summary tables will be provided for the number and frequency of events vs. participants whose PFS is censored. For events, PFS will be further summarized by the type of events, i.e., progression or death, and for censored participants, according to the reason for censoring according to the censoring rules in Table 3.

For the ITT Analysis Set, the following will be provided in the listings for tumor response as assessed by investigators and BICR: 1) a listing of all tumor assessments including tumor assessment results (target, non-target and new lesions), 2) a listing of tumor response at each assessment time point and best overall response for the participant, 3) a listing for all responders (CR and PR) with their best overall response, time to response, and duration of response, 4) a listing of the magnitude of tumor burden reduction in target lesions.

Plots of target-lesion tumor burden (spider plots) and plots of maximum tumor burden reduction (waterfall plot) as assessed by investigators and BICR will be provided for the ITT Analysis Set. However, only participants who have a sum of diameters for target lesions at baseline and at least 1 postbaseline tumor assessment can be rendered on the plots.

For the ITT Analysis Set, a listing will be provided for subsequent anticancer therapies including drug name, start and stop date (and study day relative to the date of randomization), progression date if radiographically progressed, end-of-treatment date and reason (including clinical or radiographical progression if progressive disease is listed as reason), and death date if known, to the extent such information is collected on the eCRFs.

For the ITT Analysis Set, a listing of investigator-assessed PFS and OS will be provided including PFS time and OS time, radiographical progression date if the participant had a radiographical progression, death date if known, censoring information for PFS and OS, and reasons for censoring of PFS and OS, respectively.

Furthermore, additional analyses (included, but not limited to subgroup analyses) may be performed, as needed for the purpose of local regulatory interactions.

4.14.8. Subgroup Analyses

Subgroup analyses including but not limited to the following demographic, disease characteristics and prognostic factors at baseline will be applied to the ITT Analysis Set, for the endpoints of OS, PFS as assessed by investigators and BICR, and ORR as assessed by investigators and BICR. Forest plots of treatment effect for these endpoints in the subgroups will be generated.

- Age group (<65, 65-74, ≥75)
- Gender (Male, Female)
- Race (White, Asian, Other)
- Number of prior anticancer regimen (1, 2, 3, 3+)
- Number of prior anticancer regimen[Type 2] (1-2, >2)
- Bellmunt Risk Factors (0-1, 2-3) per eCRF
- Geographic Region (Europe, North America, Rest of World)

- Site of Primary Tumor (Upper vs. Lower Urinary Tract)*
- Liver Metastases (yes, no) per eCRF
- Type of prior platinum therapies (Cisplatin or Carboplatin) per eCRF
- Prior type of therapy in which the most recent line of platinum therapy was administered (neo-adjuvant/adjuvant or locally advance unresectable/metastatic) per eCRF

* Patients with site of primary tumor=Metastasis per eCRF data collection are grouped in the lower urinary tract subgroup.

4.14.9. Exploratory Analyses

Exploratory analyses will be conducted as needed to support the assessment of efficacy and safety of study therapies and their comparisons. Analyses that facilitate interpretation of study results may be included in the clinical study report and the methods used in the analysis will be documented.

Another exploratory analysis that may be conducted is to compare the milestone OS rates at select time points (12 months, 18 months, and 24 months, depending on data maturity) between the sacituzumab govitecan and TPC arms, using methods described in Klein {Klein 2007}.

4.14.9.1. Efficacy in relation to tumor biomarkers

Biomarker analyses will be exploratory in nature. Efficacy endpoints (OS, PFS, ORR, DOR, CBR) will be analyzed according to Trop-2 expression to identify any potential correlation with clinical outcome-related endpoints. Biomarker results will also be summarized by descriptive statistics. Biomarker analyses will be described in a separate analysis plan.

Additional sensitivity analyses, exploratory, or ad hoc analyses to facilitate interpretation of study results may be conducted if warranted.

4.15. Safety Analyses

Safety analyses will be conducted in the Safety Analysis Set.

4.15.1. Adverse Events

The frequency and severity of AEs, classified by MedDRA, will be summarized by treatment group using MedDRA PT and SOC. An AE that occurs more than once for a participant will be counted only once in the summaries, i.e., where a participant has the same AE reported multiple times, the participant will only be counted once at the PT level in AE summary tables. Where a participant has multiple AEs within the same SOC, the participant will only be counted once at the SOC level in AE summary tables. When reporting adverse events by NCI-CTCAE v5.0 grade, summary tables will be provided using the worst NCI-CTCAE grade.

The following AE summary tables and listings will be provided. Refer to Section 2.3.2 for the definition of TEAE.

- Overall Summary of TEAEs
- Summary of TEAEs by SOC and PT
- Summary of NCI-CTCAE Grade 3 or Higher TEAEs by SOC and PT
- Summary of Treatment-related TEAEs by SOC and PT
- Summary of NCI-CTCAE Grade 3 or Higher Treatment-related TEAEs by SOC and PT
- Summary of TEAEs by Worst CTCAE Grade, SOC and PT
- Summary of Treatment-related TEAEs by Worst CTCAE Grade, SOC and PT
- Summary of Treatment-emergent Serious Adverse Events (SAEs) by SOC and PT
- Summary of Treatment-related Treatment-Emergent SAEs by SOC and PT
- Summary of TEAEs Leading to Dose Reduction by SOC and PT
- Summary of Treatment- related TEAEs Leading to Dose Reduction by SOC and PT
- Summary of TEAEs Leading to Study Drug Interruption by SOC and PT
- Summary of Treatment-related TEAEs Leading to Study Drug Interruption by SOC and PT
- Summary of TEAEs Leading to Study Drug Discontinuation by SOC and PT
- Summary of Treatment-related TEAEs Leading to Study Drug Discontinuation by SOC and PT
- Summary of TEAEs Reported by ≥10% (or 5%) Participants in Any Treatment Arm by Preferred Term
- Summary of NCI-CTCAE Grade 3 or Higher TEAEs Reported by ≥5% of Participants in Any Treatment Arm by Preferred Term
- Summary of Treatment-Emergent SAEs Reported by ≥2% Participants in Any Treatment Arm by Preferred Term
- Summary of TEAEs Leading to Death by SOC and PT

The following AE listings will be provided:

- Listing of All AEs.
- Listing of Serious TEAEs
- Listing of Grade 3 or Higher TEAEs
- Listing of TEAEs Leading to Death
- Listing of TEAEs Leading to Dose Reduction
- Listing of TEAEs Leading to Study Drug Interruption
- Listing of TEAEs Leading to Study Drug Discontinuation

TEAEs by SOC and PT, Grade 3 or Higher TEAEs by SOC and PT, and TEAEs Leading to Study Drug Discontinuation by SOC and PT for the following subgroups will be provided:

- Age group (<65 , 65-74, vs ≥75)
- Race (White, Asian, Other)

4.15.2. Adverse Events of Special Interest (AESI)

In addition to analyses of AEs, adverse events of special interest (AESI) will be assessed. Definitions of AESI, as currently defined, are provided in Table 6, including but not limited to those listed. AESI will be summarized by category. Frequency tables will be generated, showing overall summary of AESI, summary of AESI by SOC and PT, serious AESI by SOC and PT, AESI leading to treatment discontinuation by SOC and PT, AESI leading to treatment interruption by SOC and PT, Grade 3 or higher AESI by SOC and PT, treatment-related AESI (by a worst CTCAE grade of 3, 4, or 5, ≥3 and any grade) by SOC and PT. Corresponding listings will also be produced.

Table 6. Definitions of Adverse Events of Special Interest

AESI	Definition
Serious infections secondary to neutropenia	SOC: Infection and Infestations** (**Serious infections occurring after any grade Neutropenia AE)**
Severe diarrhea	PT Diarrhea (**Grade ≥3**)
Hypersensitivity*	Hypersensitivity SMQ (broad and narrow) and Anaphylactic Reactions SMQ (broad and narrow)
Neutropenia+	Preferred terms: neutropenia, neutrophil count decreased, febrile neutropenia

All definitions based on MedDRA vs 25.0 or higher, SMQ=Standard MedDRA Query
+ Grouped AE terms
* For the category of Hypersensitivity, only events whose onset dates are on the day of or 1 day after an infusion are included.
** SOC of Infections and infestations occurred within 11 days of neutropenia, febrile neutropenia or neutrophil count decreased

4.15.3. Death

All-cause deaths will be summarized (including presentation of causes of death), and deaths within 30 days of the last dose of study drug will be summarized. A listing of all death information will be generated.

4.15.4. Vital Sign

Both actual and change-from-baseline data on vital signs (heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature) will be summarized using descriptive statistics by treatment group for each study time point.

4.15.5. Electrocardiograms

ECG data will be listed.

4.15.6. Clinical Laboratory Evaluations

Routine safety laboratories, based on hematology and routine serum chemistry data (including but not limited to glucose, creatinine, BUN, total bilirubin, AST, ALT, alkaline phosphatase, serum albumin, total protein, Na, K, calcium, Cl, magnesium and phosphate), will be summarized using values at each visit and change from baseline using descriptive statistics for each treatment group. Laboratory test results for laboratory parameters, including but not limited to platelets, neutrophils, white blood count, lymphocytes and hemoglobin, will be graded according to NCI-CTCAE severity grades. A shift table of the worst NCI-CTCAE grade observed on-treatment will be tabulated for each lab parameter and presented in a frequency table by baseline grade. For parameters for which a CTCAE scale does not exist, the proportion of participants with abnormal values will be summarized by treatment group.

4.15.7. Physical Exam and Pregnancy Test

Physical exam results are listed according to body system and presented for any abnormal findings from the physical examination.

Pregnancy test results will be listed.

4.15.8. Immunogenicity

Summary of ADA prevalence, incidence (treatment-emergent and treatment-boosted), transience, and persistence will be calculated. Titer summaries at each time point per participant may also be produced for ADA-positive participants. If the ADA is further characterized as neutralizing or otherwise, the overall rate of neutralizing antibody occurrence will also be reported. Exploratory evaluations may be conducted to determine the relationship between immunogenicity assay positivity and one or more safety, PK, or efficacy parameters. These analyses and any others may be reported in a separate PK/ADA report.

4.15.9. Pharmacokinetics Analyses

Descriptive summary of PK concentration (SG, free SN-38 and total antibody - hRS7 IgG) and PK parameters will be summarized by visits. A listing of PK concentrations will also be provided. Subjects in the PK population will be included for analyses.

Pharmacokinetics analyses including population pharmacokinetics (PopPK), exposure-efficacy and exposure-safety analyses will be described in separate analyses plans.

Data from this study may be combined with data from other studies for PopPK and exposure response analyses. If applicable, results from such analyses may be summarized in a separate report, rather than in a CSR.

4.15.10. Biomarker Analyses

Exploratory biomarker analyses will be described in a separate biomarker analysis plan.

4.16. Data Handling Rules

Data and programming specification and rules, including but not limited to the following, are described below.

4.16.1. Definition of Baseline

Baseline is defined as the last assessment taken prior to or on the date of the first dose of study drug for this study, unless otherwise specified. The protocol allows up to 3 days between randomization and first dose, i.e., Cycle 1, Day 1. For participants who did not receive study drug, the baseline is the last assessment taken prior to or on the date of the randomization.

4.16.2. Analysis Visits

Study day will be calculated from the reference date and derived as follows:

- For study days on or after Reference Date: Assessment Date – Reference Date + 1
- For days prior to Reference Date: Assessment Date – Reference Date

The reference date is first dosing date of study drug if available, or the randomization date if a participant is never treated. Therefore, study day 1 is the day of first dose of study drug administration if available; otherwise, it is the randomization date.

Participant visits might not occur on protocol-specified days. Therefore, for the purpose of analysis, observations will be assigned to analysis windows for QoL data. Unless otherwise specified, collection windows for study time points and visits are permitted either 1 day before or within 2 days after scheduled visits and ±5 business days for response assessments. The study day can be mapped to the expected treatment cycle by this formula: (study day/21) + 1 rounded to the nearest whole number.

The analysis windows are provided in Table 7.

Table 7. Analysis Visit Windows for QoL Data

Phase	Arm(s)	Visit	Target day	Lower limit	Upper limit
Baseline	Both	Baseline	1	-28	1
Treatment	Both	Cycle 2 Day 1	22	2	36
		Cycle 3 Day 1	43	37	57
		Cycle 4 Day 1	64	58	78
		Cycle 5 Day 1	85	79	99
		Cycle X Day 1 (subsequent cycles beyond Cycle 5)	21*X-20	Target -6	Target + 14

4.16.3. Handling of Multiple Assessments Within Post-Baseline Visits

Any data relating to unscheduled visits will not be assigned to a particular visit or time point. However, the following exceptions will be made:

- An unscheduled visit prior to the randomization may be included in the calculation of the baseline value, if applicable.
- Unscheduled visits after the first dosing of study drug will be included in determining the maximum postbaseline toxicity grade.
- Unscheduled visits after randomization will be included in determining the efficacy endpoints such as best response.

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value, whereas a time-to-event analysis would not require 1 value per analysis window.

If multiple valid, non-missing measurements exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- For baseline, the last non-missing value on or prior to the randomization date or first dosing date of study drug, as appropriate for the parameter, will be selected, unless specified differently. If there are multiple records with the same time or no time recorded on the same day, the baseline value will be the average of the measurements for continuous data, or the measurement with the lowest severity (e.g., normal will be selected over abnormal for safety electrocardiogram [ECG] findings) for categorical data.
- For postbaseline values:
  - The record closest to the target day for that visit will be selected.
  - If there are 2 records that are equidistant from the target day, the later record will be selected.
  - If there is more than 1 record on the selected day, the average will be taken for continuous data and the worse severity will be taken for categorical data, unless otherwise specified.

For ECOG and other patient reported outcomes data, if more than one assessment is done within a visit, then the worst of the assessments will be used. If multiple collections within a visit have the same value, the first occurrence within the visit will be used.

4.16.4. Conversions from Days to Years, Months or Weeks

- Years = Number of days / 365.25 (use of SAS function)
- Months = Number of days / 30.4375 (i.e., 365.25/12)
- Weeks = Number of days / 7

Values based on the above computations will be rounded to tenths.

4.16.5. Computation of Duration

Duration for time variables based on two dates, e.g., Start Date and End Date, will be calculated as (End Date – Start Date + 1) (in days) unless otherwise specified.

4.16.6. Missing normal ranges for laboratory parameters

When either the lower limit of normal, the upper limit of normal or both are missing or are not machine readable, a standardized reference range will be used.

4.16.7. Non-Numeric Laboratory Results and Calculation of Normal Ranges

If a laboratory value is reported using non-numeric qualifier (e.g., less than [<] a certain value , or greater than [>] a certain value), the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier. Any other manipulation to laboratory data not documented here will be specified in the ADaM specification. These values will be reflected in listings of the data. When there are potential conflicts between local lab normal ranges and ranges used in CTC grading, CTC normal ranges will be used.

4.16.8. Imputation of Missing or Incomplete Dates

Missing Data Imputation for Adverse Event/Concomitant Medication Start Dates

1) Missing day only

   - If the month and year of the AE/concomitant medication are the same as the month and year of the first dose date, the first dose date day will be used.
   - If the month and year are before the month and year of the first dose date, the first day of the month will be assigned to the missing day.
   - If the month and year are after the month and year of the first dose date, the first day of the month will be assigned to the missing day.

2) Missing day and month

- If the year is the same as the year of the first dose date, the first dose date day and month will be used.
- If the year is prior to the year of the first dose date, December 31 will be assigned to the missing fields.
- If the year is after the year of the first dose date, January 1 will be assigned to the missing fields.

3) Missing day, month, and year

- The first dose date will be used.

The imputed start date should be prior or equal to the end date of the AE or medication.

4.16.8.1. Missing Data Imputation for Adverse Event/Concomitant Medication Stop Date

1) Missing day only

- The month and year are the same as the month and year of the first dose date: use the last date of the month.
- The month and year are before the month and year of the first dose date: use the last date of the month.
- The month and year are after the month and year of the first dose date: use the last date of the month.

2) Missing day and month

- The year is the same as the year of the first dose date: use December 31.
- The year is before the year of the first dose date: use December 31.
- The year is after the year of the first dose date: use December 31.

3) Missing year

Uncertain: unable to impute.

4) Missing month

- The year is the same as the year of the first dose date: use December.
- The year is before the year of the first dose date: use December.
- The year is after the year of the first dose date: use December.

5) Missing month and year

Uncertain: unable to impute

6) Missing day and year

   Uncertain: unable to impute

7) Missing day, month, year

   This event is ongoing.

If the death date is available and the imputed end date is after the death date, the death date will be used.

If the imputed end date is prior to the start date of the AE or medication, then make end date equals to start date.

4.16.8.2. Missing Data Imputation for Disease Diagnosis Date

1) Missing day only

   - The first day of the month will be assigned to the missing day

2) Missing day and month

   - January 1 will be assigned to the missing fields

3) Missing year

   Uncertain: unable to impute

4.16.8.3. Missing Data Imputation for Date of Death

Every attempt will be made to ensure that complete death dates are recorded. In those rare instances where complete death dates are not recorded, the following algorithm will be used:

1) Missing day only

   The first day of the month or day of last known alive date will be assigned to the missing day, whichever is later

2) Missing day and month

   January 1 of that year or the last known alive date will be assigned to the missing fields, whichever is later

3) Missing year

   Uncertain: unable to impute

4.17. Statistical Software used in data analysis

All statistical analyses will be performed using SAS® {SAS Institute Inc 2016} Version 9.4 or later

5. REFERENCES

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