STATISTICAL ANALYSIS PLAN

Version 2.0

15-Jul-2022

A Single-arm, Open-label, Multi-center Phase 2 Study of Enfortumab Vedotin (ASG-22CE) in Chinese Participants with Locally Advanced or Metastatic Urothelial Cancer Who Previously Received Platinum-containing Chemotherapy and PD−1/PD-L1 Inhibitor Therapy (EV-203)

ISN: 7465-CL-1104

[IND: 2020LP00887]
[IND Grantor : NMPA]

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1 INTRODUCTION

This Statistical Analysis Plan (SAP) contains technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes procedures for executing the statistical analysis to fulfil the objectives of the study.

The final SAP will be approved prior to the primary database hard-lock which is defined as participants' confirmatory image scan results are available, or have discontinued from study, or had 30 days safety follow-up after progressive disease (PD), whichever comes first.

If there are any changes from the planned analyses in the final version of the SAP that impact the statistical analyses, then it will be documented in the Clinical Study Report (CSR).

1.1 Objective(s)

1.1.1 Primary Objectives

- To determine the antitumor activity of single-agent enfortumab vedotin (EV) as measured by confirmed objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 as determined by independent review committee (IRC).
- To assess thepharmacokinetics (PK) of antibody-drug conjugate (ADC), total antibody (TAb) and monomethyl auristatin E (MMAE) in Chinese participants with locally advanced or metastatic urothelial cancer.

1.1.2 Secondary Objectives

- To assess confirmed ORR per investigator assessment
- To assess duration of response (DOR)
- To assess disease control rate (DCR)
- To assess progression-free survival (PFS)
- To assess overall survival (OS)
- To assess the immunogenicity as defined by the incidence of antitherapeutic antibodies (ATA)
- To assess the safety and tolerability of enfortumab vedotin in Chinese participants with locally advanced or metastatic urothelial cancer.

1.2 Study Design

This is a single-arm, open-label, multi-center, Phase 2 study to assess the safety, efficacy and pharmacokinetics of enfortumab vedotin in Chinese participants with locally advanced (LA) or metastatic urothelial cancer (mUC) who have previously been treated with platinum-containing chemotherapy and PD-1/PD-L1 inhibitor therapy. Up to 40 participants will be enrolled including approximately 12 Chinese participants in the PK Cohort.

Details of the schedule of clinical assessments are available in the protocol.

1.3 Randomization

This is an open-label, single-arm study. No randomization takes place. Participant enrollment and dispensation of enfortumab vedotin will be performed via the interactive response

technology (IRT) system. Specific IRT procedures will be described in the respective study manual.

2 STATISTICAL HYPOTHESIS

The statistical hypothesis is that ORR will be superior to 10% historical control. No adjustment for multiplicity will be made for this study as only one primary endpoint will be tested in this single-arm study.

3 ANALYSIS SETS

In accordance with International Conference on Harmonization (ICH) recommendations in guidelines E3 and E9, the following analysis sets will be used for the analyses.

The determination of whether participants are included or excluded from the safety and efficacy analysis sets will be made prior to database hard-lock for the primary study report.

3.1 Full Analysis Set

The full analysis set (FAS) will include all participants who are enrolled and receive any amount of study drug in the study.

The FAS will be used for primary analysis of efficacy endpoints. Participant demographics and baseline disease characteristics will be summarized based on the full analysis set.

3.2 Safety Analysis Set

The safety analysis set (SAF) will include all participants who are enrolled and take any amount of study drug, and thus is equivalent to the FAS defined in this protocol. The SAF will be used for all safety and immunogenicity analyses.

3.3 Pharmacokinetics Analysis Set

The Pharmacokinetic analysis set (PKAS) will include all participants in the PK cohort who have received at least 3 of 4 doses up through Cycle 2 Day 1, and have at least 5 blood samples collected and assayed for measurement of ADC, TAb or unconjugated MMAE serum/plasma concentrations to determine at least 1 PK parameter. Time of sampling and the time of dosing on the day of sampling must be known. For non-PK Cohort, all participants who are administered study drug for which concentration data of any analyte is available will be included in PKAS. Inclusion of participants in the PKAS with missing data or major protocol deviations will be considered by the pharmacokineticist on a case-by-case basis. The PKAS will be used for PK analyses.

3.4 Efficacy Evaluable Set

The efficacy evaluable set (EES) will include all participants in the FAS who have at least one post-baseline response assesment. The EES will be used for the sensitivity analysis of the primary efficacy endpoint.

4 STATISTICAL ANALYSES

4.1 General Considerations

Continuous data will be summarized descriptively including the number of participants (n), mean, standard deviation, median, minimum and maximum. Categorical data will be summarized by frequencies and percentages. Percentages by categories will be based on the number of participants with no missing data, i.e. the percentages for the non-missing categories will add up to 100%.

Baseline will be defined as the last non-missing observation prior to first administration of study drug, unless otherwise specified.

Unless otherwise specified, CIs will be calculated at two-sided 95% level.

The two-sided 95% exact CI using the Clopper-Pearson method will be calculated for the response rates where applicable (e.g., ORR) (Clopper 1934).

For time-to-event endpoints, the median survival time will be estimated using the Kaplan-Meier method; the associated 95% CI will be calculated based on the complementary log-log transformation (Collett 1994).

Any analysis not described in this plan will be considered exploratory, and will be documented in the CSR as a post hoc analysis.

All statistical Tables, Listings and Figures (TLF) will be produced using SAS®, version 9.4 or higher on Red Hat Enterprise Linux. Sample size calculations were performed using nQuery®, version 8. Other statistical software, if used, will be described in the CSR. Specifications for table, figures, and data listing formats can be found in the TLF specifications.

4.2 Study Population

4.2.1 Participant Disposition

The following participant data will be presented:

- Number and percentage of participants with informed consent, discontinued before enrollment, and enrolled for all participants with informed consent;
- Number and percentage of participants included in each analysis set for all enrolled participants;
- Number and percentage of participants enrolled at each site for all enrolled participants;
- Number and percentage of participants discontinued treatment, by primary reason for treatment discontinuation for all enrolled participants and for SAF;
- Number and percentage of participants completed or discontinued the 30-day follow-up visit, by primary reason for 30-day follow-up discontinuation for all enrolled participants and for SAF;
- Number and percentage of participants discontinued post-treatment period, by primary reason for post-treatment discontinuation for all enrolled participants and for SAF;

- Number and percentage of participants discontinued long term follow-up period, by primary reason for long term follow-up discontinuation for all enrolled participants and for SAF;
- Number and percentage of screen failure participants, by primary reason for screen failure for screen failure participants only;

All disposition details and dates of first and last evaluations for each participant will be listed.

4.2.2 Protocol Deviations

The number and percentage of participants with the following protocol deviation criteria will be summarized for each criterion and overall, by investigative site and overall for all enrolled participants. Participants deviating from a criterion more than once will be counted once for the corresponding criterion. Any participants who have more than one major protocol deviation will be counted once in the overall summary. A data listing will be provided by site and participant. The protocol deviation criteria will be uniquely identified in the summary table and listing.

The unique identifiers will be as follows:

PD1 - Entered into the study even though they did not satisfy entry criteria,

PD2 - Developed withdrawal criteria during the study and was not withdrawn,

PD3 - Received wrong treatment or incorrect dose,

PD4 - Received excluded concomitant treatment.

4.2.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized by descriptive statistics for all enrolled participants and FAS, and will only be presented for FAS in the case that enrolled patients are the same as FAS.

Demographic variables:

- Age, Age categories (<65, ≥ 65 to <75, ≥ 75 years)
- Sex
- Ethnicity
- Race
- Baseline height
- Baseline weight, baseline weight groups (≤100, >100 kg)
- Baseline BMI, baseline BMI categories (<18.5, ≥ 18.5 to <25, ≥ 25 to <30, ≥ 30 kg/m^2

Baseline characteristics

- ECOG performance status (0, 1)

- Prior PD-L1 testing
- Bellmunt risk score (0-1, ≥2) (Bellmunt 2010)

  The score is derived based on the presence of 0, 1, 2, or 3 of the following risk factors: ECOG > 0; Hemoglobin < 10 g/dL; Presence of liver metastasis.
- Hemoglobin, hemoglobin categories (<10 g/dL, ≥10 g/dL)
- HbA1c , HbA1c categories (<5.7%, >=5.7% to <6.5%, >=6.5%)
- Albumin, Albumin categories (<LLN, ≥LLN)
- Renal function group based on estimated creatinine clearance (by Cockcroft-Gault formula)

  Normal: ≥90 mL/min
  Mild: ≥60 and <90 mL/min
  Moderate: ≥30 and <60 mL/min
  Severe: ≥15 and < 30 mL/min

  Cockcroft-Gault formula for estimating CrCl (ml/min):

$$\frac{[140 - age(years)] * body\ weight\ (kg) * (0.85\ if\ female)}{serum\ creatinine(mg/dl) * 72}$$

- Hepatic dysfunction group defined per NCI-ODWG criteria below

  Normal: Total bilirubin ≤ULN and AST ≤ULN
  Mild: (ULN<Total bilirubin ≤1.5 x ULN) or (Total bilirubin ≤ ULN and AST >ULN)
  Moderate: 1.5ULN < Total bilirubin ≤ 3 x ULN, any AST
  Severe: Total bilirubin >3 x ULN, any AST
- History of diabetes/hyperglycemia defined as any hyperglycemia Sponsor Specific Query (SSQ)/Customized Medical Query (CMQ)

Urothelial cancer disease history:

- Time (months) from diagnosis of locally advanced/metastatic disease to date of first dose (first dose date – date of initial diagnosis of locally advanced/metastatic disease +1)/30.4375
- Primary disease site of origin
- Histology type at initial diagnosis.
- Current extent of disease
- Liver metastasis
- Visceral metastasis
- Lymph node only metastasis
- CNS metastases

Medical history other than mUC and conditions existing at baseline will be coded in MedDRA Version 24.0 and summarized by System Organ Class (SOC) and Preferred Term (PT) as well as by PT alone. Baseline conditions are defined as those ongoing at the time of informed consent and before the first dose of study drug. For ongoing medical conditions,

Common Terminology Criteria for Adverse Events (CTCAE) grade will be provided in listing.

4.2.4 Prior Systemic Anti-Cancer Therapy

Prior systemic anti-cancer therapy will be summarized by descriptive statistics for FAS and EES. Number and percentage of participants by below categories will be presented (continuous variables below will also be summarized by mean, standard deviation, median, min and max):

- Number of prior lines of systemic therapy (1, 2 and ≥3 lines)
- Type of prior CPI received
- Type of prior platinum-based treatment received
- Settings of prior systemic therapy
- Best overall response to prior CPI therapy

4.2.5 Prior Procedures for Primary Cancer

Number and percentage of participants who underwent any prior surgery or procedure for the treatment of the primary cancer will be presented, and summarized by different types of the procedures for FAS.

4.2.6 Prior Radiation Therapy

Number and percentage of participants who previously received any radiation therapy for the treatment of primary cancer, area radiated, reason for radiation therapy, and reason for radiation therapy discontinuation will be summarized for FAS and EES.

4.2.7 Previous and Concomitant Medications

Previous medications will be summarized by therapeutic subgroup (ATC 2nd level) and chemical subgroup (ATC 4th level) and preferred WHO name for the SAF. As with previous medication, concomitant medications will be summarized by therapeutic subgroup (ATC 2nd level) and chemical subgroup (ATC 4th level) and preferred WHO name for the SAF. Participants taking the same medication multiple times will be counted once per medication and investigational period. A medication which can be classified into several chemical and/or therapeutic subgroups is presented in all chemical and therapeutic subgroups.

Previous medications are defined as medications that patients started prior to first administration of study medication. Concomitant medications are defined as any medications that patients took after the first dose of study medication and through 30 days from last dose of study drug. Medications that started prior to first administration of study drug and continued while study drug was given will be counted in both previous and concomitant medications.

4.2.8 Previous and Concomitant Non-Medication Therapy

Participants with previous and concomitant non-medication therapy and its reason for use will be presented in the listing.

4.2.9 New Anti-Cancer Therapy

Number and percentage of participants who received any new anti-cancer therapy , types of anti-cancer therapy and the reason for starting the new anti-cancer therapy will be summarized for SAF.

4.2.10 New Radiation Therapy

Number and percentage of participants who receive any subsequent radiation therapy will be presented, types of radiation therapy and the reason for starting the new radiation therapy will be summarized for SAF.

4.2.11 Extent of Exposure

The following information on drug exposure will be presented by treatment group for the SAF:

- Descriptive statistics for duration of exposure (months), number of cycles, number of infusions per participant, cumulative dose, planned dose intensity, dose intensityand relative dose intensity.
- Number and percent of participants with dose adjustment and reasons for dose adjustment.
- Number and percentage of participants who were treated at each cycle
- Number of cycles will be categorized per below categories. Counts and percentages of participants in each of these categories will be summarized.
    - less than or equal to 1 cycle
    - at least 2 cycle, less than 4 cycles
    - at least 4 cycles, less than 6 cycles
    - 6 cycles or more
    - Unknown
- RDI will be categorized according to the following categories. Counts and percentages of participants in each of these categories will also be summarized.
    - less than 50%
    - at least 50%, less or equal to 80%
    - greater than 80%
    - Unknown

Duration of exposure (month) = (Last date of exposure – First dose date + 1)/30.4375.

For EV, last date of exposure = (date of initial dose of the last cycle + 28– 1) or death date if death occurred within the last cycle. For participants who are continuing study treatment at data cutoff date, data cutoff date will be used as the last date of exposure.

Number of cycles is the total number of cycles with non-zero dosing.

Cumulative dose is the sum of (total dose administrated) across all days.

Total dose administrated on a dosing day (mg) = final concentration (mg/ml) * actual volume administrated (ml).

Planned dose intensity (mg/kg/cycle) is the initial dose of EV multiplied by planned number of dosing days per cycle.

For example, participant is planned to receive EV at a dose of 1.25mg/kg on days 1,8,15 of each cycle, the intended dose intensity = 1.25 mg/kg*3=3.75 mg/kg per cycle.

(Actual) Dose intensity (mg/kg/cycle) is defined as the actual dose of study drug per unit of time that a participant received over the entire treatment period, defined as below:

$$Dose\ intensity = \frac{\sum_{i=1}^{NC}\sum_{j=1}^{3}(TD_{i,j}/W_{i,j})}{Duration\ of\ exposure/28}$$

Where $TD_{i,j}$ is the actual total drug administrated at cycle i day j, $W_{i,j}$ is the body weight of the participant at cycle i day 1 , and NC is the total numberj of cycles with non-zero dosing. If the body weight is greater than 100kg, then $W_{i,j} = 100kg$. If there is no dose administrated in a planned dosing day in a cycle, $TD_{i,j} = 0mg$. Here the duration of exposure is in days.

For the purpose of computing actual, planned and relative dose intensity, neither death nor cutoff dates are used in the derivation of duration of exposure.

Relative dose intensity (%) is defined as

$$\frac{Dose\ intensity}{Planned\ dose\ intensity} \times 100$$

4.3 Primary Endpoint(s) Analysis

4.3.1 Definition of Endpoint(s)

The primary endpoint is efficacy variable:

- Confirmed ORR per RECIST V1.1 by IRC
- Selected PK parameters of ADC, TAb and unconjugated MMAE

Objective response rate (ORR) is defined as the proportion of participants with best overall response (BOR) as confirmed complete response (CR) or partial response (PR), per RECIST v1.1. Participants who do not have at least 2 (initial response and confirmation scan) post baseline response assessments will be counted as non-responders.

Best overall response (BOR) is determined once all tumor timepoint response data for the participant is available. Responses recorded after new anticancer therapy or progressive disease (PD), will be excluded from BOR derivation.

Confirmation of CR or PR should occur at the next assessment (not less than 4 weeks following the initial assessment at which CR/PR is observed).

The BOR with confirmation will be derived according to below criteria per RECIST V1.1:

- If a patient has at least two CR and the first and the last CR dates are at least 28 days apart, then the best overall response is defined as confirmed CR

- If a patient has PR and another CR/PR with at least 28 days apart, then the best overall response for this patient is confirmed PR
- For those patients who do not have confirmed CR or PR, if the patient had at least one tumor assessment record of CR/PR/SD which is at least 49 days after date of first dose, then best overall response is defined as SD
- For those patients who do not have confirmed CR, confirmed PR or SD defined as above, but they have a tumor assessment as PD, their best overall response is PD
- Otherwise, best overall response is defined as Not Evaluable (NE) or No Data (ND) for participants without any post-baseline tumor assessment data

4.3.2 Main Analytical Approach

The primary analysis of efficacy endpoints will be performed using the FAS.

The primary efficacy analysis will be performed by testing the null hypothesis of ORR being less than or equal to 10% against the alternative hypothesis that ORR is greater than 10% at overall 1-sided 2.5% level of significance. The study will be considered successful if the lower bound of the 2-sided 95% exact Clopper-Pearson CI for ORR is greater than 10%, so that the null hypothesis that the ORR is less than or equal to 10% can be rejected. The primary analysis will be done once confirmatory image scan results are available, or have discontinued from study, or had 30 days safety follow-up after PD, whichever comes first.

The confirmed ORR per IRC and its exact two-sided 95% CI will be calculated for the FAS.

In addition, the ORR per IRC will be summarized by the subgroups defined in Section 4.7.1.

Time to response per IRC will be calculated as the time from the first dose of study drug to the first documentation of objective response (CR or PR that is subsequently confirmed). Time to response per IRC will be summarized for the confirmed responders only, and will be presented together with duration of response by a swimmer plot.

4.3.3 Sensitivity Analysis

For sensitivity analysis purpose, the planned analysis for primary efficacy endpoint will be performed using EES.

ORR based on BOR regardless of the confirmation will also be calculated to evaluate the impact on ORR due to missing of confirmatory scans or PD after the initial response.

4.4 Secondary Endpoint(s) Analysis

4.4.1 Definition of Endpoint(s)

The secondary endpoints are:

- Confirmed ORR per RECIST V1.1 per investigator assessment
- DOR per RECIST V1.1 per IRC and per investigator assessment

Duration of response (DOR) is defined as the time from first documentation of objective response (CR or PR that is subsequently confirmed) to the first documentation of PD or to death due to any cause, whichever comes first. DOR will only be calculated for the participants achieving a confirmed CR or PR.

DOR will be censored as described below:

- If a participant has neither PD nor death, DOR will be censored at the date of last evaluable radiological tumor assessment.
- If a participant starts a new anticancer treatment before any PD event or death, DOR will be censored at the date of last evaluable radiological tumor assessment prior to the date of new anti-cancer treatment.

For a participant who is censored, the last evaluable radiological tumor assessment refers to the participant's last radiological tumor assessment where the response is CR PR or SD.

DOR (in days) will be calculated as: (Date of documented disease progression or death or censoring) – (Date of the first CR/PR) +1.

To apply the cutoff date to DOR is to exclude tumor assessments, death and anti-cancer therapy date after cutoff date in the analysis.

- DCR per RECIST V1.1 per IRC and per investigator assessment

  Disease control rate (DCR) is defined as the proportion of participants with BOR of confirmed CR or confirmed PR or SD, per RECIST v1.1. Definition of BOR is specified in Section 4.3.1.

- PFS per RECIST V1.1 per IRC and per investigator assessment

  Progression-free survival (PFS) is defined as the time from the date of first dose of study drug to the date of first documented radiological disease progression (PD) or death due to any cause, whichever comes first. PFS will be censored as the following:

  - If a participant has neither PD nor death, PFS will be censored at the date of last evaluable radiological tumor assessment or at the first dose date if no evaluable postbaseline radiological assessment is avaliable
  - If a participant starts a new anticancer treatment before any PD event or death, PFS will be censored at the date of last evaluable radiological tumor assessment prior to the date of new anti-cancer treatment.

  For a participant who is censored, the last evaluable radiological tumor assessment refers to the participant's last radiological tumour assessment where the response is CR PR or SD.

  PFS (in days) will be calculated as: (Date of documented disease progression or death or censoring) – (Date of first dose of study drug) +1.

  To apply the cutoff date to PFS is to exclude tumor assessments, death and anti-cancer therapy date after cutoff date in the analysis.

- OS

  Overall survival (OS) is defined as the time from the date of first dose of study drug to the date of death due to any cause. For a participant who is not known to have died by

the end of study follow-up, OS is cencored at the date of last known alive date or at the analysis cutoff date, whichever is earlier. All dates which can support a participant's survival status (i.e., lab testing date, drug administration date) will be used to derive the last known alive date. Participants with death or last known alive date after the analysis cutoff date will be censored at the cutoff date.

OS (in days) will be calculated as (Date of death or censoring) – (Date of first dose of study drug) +1.

4.4.2 Main Analytical Approach

All analysis of secondary endpoints will be presented for FAS, unless specified otherwise.

4.4.2.1 DOR per IRC

Number and percentage of participants with event and each event type (death, PD), censoring and each censoring type (no event, start new anti-cancer treatment before PD or death) will be summarized. DOR will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median DOR and its two-sided 95% CI will be calculated.

In addition, the DOR rate at 6 and 12 months will be summarized along with 95% CI. The DOR at 6 and 12 months is defined as the proportion of the responders who are still ongoing response after 6 and 12 months from their first documented response.

4.4.2.2 DCR per IRC

DCR will be summarized and the exact 2-sided 95% CI will be calculated using the Clopper-Pearson method.

4.4.2.3 PFS per IRC

Number and percentage of participants with event and each event type (death, PD), censoring and each censoring type (no event, start new anti-cancer treatment before PD or death) will be summarized. PFS per IRC will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median PFS and its two-sided 95% CI will be calculated. In addition, the 6- and 12-month PFS rates will be summarized along with the corresponding 95% CI.

4.4.2.4 Confirmed ORR per Investigator Assessment

The exact 2-sided 95% CI will be calculated for the confirmed ORR per investigator.

Time to response per investigator will be analyzed in the same way as the time to response per IRC.

4.4.2.5 Concordance between Investigator and IRC Assessment

A summary of the concordance between investigator and IRC assessment will be provided. The percent agreement will be calculated as the proportion of participants whose best overall response per IRC match the best overall response per investigator. Percent agreement = (Number of matched responders + Number of matched non-responders) / Total number of participants assessed.

4.4.2.6 DOR per Investigator Assessment

DOR per investigator will be analyzed in the same way as the DOR per IRC.

4.4.2.7 DCR per Investigator Assessment

DCR per investigator will be analyzed in the same way as the DCR per IRC.

4.4.2.8 PFS per Investigator Assessment

PFS per investigator will be analyzed in the same way as the PFS per IRC.

4.4.2.9 Overall Survival

Number of participants with event and censoring will be summarized. OS will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median OS and its two-sided 95% CI will be calculated. The OS rates at 6 and 12 months will be summarized along with the corresponding 95% CI.

4.4.2.10 Tumor Shrinkage per IRC

The maximum percent reduction from baseline in the sum of diameters (longest diameter for non-nodal lesions and short axis for nodal lesions) in target lesion(s) per IRC will be calculated for each participant with both baseline and at least 1 post-baseline measurements and presented graphically with a waterfall plot. The percent change from baseline for each participant at each assessment will be presented with a spider plot.

4.4.2.11 Tumor Shrinkage per Investigator Assessment

Tumor shrinkage per intevestigator will be analyzed in the same way as the tumor shrinkage per IRC.

4.4.3 Sensitivity Analysis

The following sensitivity analysis will be performed for the DOR per IRC:

1. A sensitivity analysis to censor participants who progressed or died after an extended loss to follow up (i.e., ≥2 consecutive missed response assessments) at the date of the last adequate response assessment prior to the missed visits.

The following sensitivity analysis will be performed for the PFS per IRC:

1. A sensitivity analysis to censor participants who progressed or died after an extended loss to follow up (i.e., ≥2 consecutive missed response assessments) at the date of the last adequate response assessment prior to the missed visits.

4.5 Analysis of Safety

Safety endpoints are secondary endpoints in this study. The SAF will be used for the safety analysis.

Safety endpoints include AEs, laboratory tests, vital signs, ECGs and ECOG performance status. Safety will be assessed by evaluation of the following variables:

- Treatment-emergent adverse events (TEAEs; frequency, severity, seriousness, and relationship to study drug).
  - TEAE is defined as an adverse event observed after starting administration of the study drug and within 30 days after taking the last dose of study drug. If the adverse event occurs on the first dosing date and the onset check box is marked "Onset after first dose of study drug" or the onset check box is left blank, then the adverse event will be considered treatment emergent. If the adverse event occurs on the first dosing date and the onset check box is marked "Onset before first dose of study drug", then the adverse event will not be considered treatment emergent. If a participant experiences an event both during the pre investigational period and during the investigational period, the event will be considered as TEAE only if it has worsened in severity (i.e., it is reported with a new start date). If a complete onset date is unknown, and the onset check box is marked "Onset after first study drug taken", then the adverse events will be considered treatment emergent. If the onset check box is marked "Onset before study drug taken", then the adverse event will not be considered treatment emergent. If onset check box is left blank, imputed onset date as specified in Section 4.11.2 will be used to determine whether an adverse event is treatment emergent.
  - A drug-related TEAE is defined as any TEAE with relationship "yes" to study treatment as assessed by the investigator or with missing assessment of the causal relationship.
- Serious adverse events (SAEs) include adverse events that are flagged as serious by the investigator on eCRF or the SAE flag by the investigator on CRF is missing, or upgraded by the Sponsor based on review of the Sponsor's list of Important Medical Events.
- Adverse events of special interest
  - Peripheral neuropathy, corneal disorders and blurred vision, dry eye, hyperglycemia, skin reactions, and infusion related reactions (IRR) are considered adverse events of special interest (AESI) for enfortumab vedotin. These are medical concepts of composite terms based on the search criteria (standard MedDRA query [SMQ] or sponsor specified query [SSQ]). Other AEs may be added to AESI as necessary. The search criteria for AESI will be maintained in a separate document and finalized prior to final database lock.
  - For selected AESI, time to onset of AESI will be calculated.

    Time to onset of a specific AESI will be calculated as time from the first dose of study drug to the start of first treatment-emergent event that meets the respective search criteria.

    Time to onset is defined at the participant level.
- Clinical laboratory variables
  Below is a table of the laboratory tests that will be performed during the conduct of the study. Refer to the Schedule of Assessments in the protocol for study visit collection dates.

Laboratory Assessments

Panel/Assessments	Parameters to be Analyzed
Hematology	Hematocrit Hemoglobin Platelets Red blood cell count White blood cell count White blood cell count differential
Biochemistry	Albumin Alanine aminotransferase Alkaline phosphatase Aspartate aminotransferase Bicarbonate Blood urea Blood urea nitrogen Calcium Chloride Creatinine Hemoglobin A1c (HbA1c, screening and EOT only) High density lipoprotein (HDL) (Screening only) Glucose[a] Lactate dehydrogenase Low-density lipoprotein (LDL) (Screening only) Magnesium Phosphate Potassium Serum HCG for female participants Sodium Total and direct bilirubin Total cholesterol (Screening only) Total protein Triglyceride (Screening only)
Urinalysis	Specific gravity pH Blood Protein Glucose Bilirubin Microscopic (epithelial cells, bacteria, casts, crystals, WBC and RBC)
Serology	Hepatitis B and C at screening

EOT: end of treatment; HbA1c: hemoglobin A1c; HCG: human chorionic gonadotropin

a. Glucose at screening and on Cycle 1 Day 8 are required to be tested in fasting status in order to ensure accurate interpretation of glucose values. Fasting is not necessary for biochemistry laboratory tests performed at all other visits.

- Vital signs (systolic and diastolic blood pressures (mmHg), radial pulse rate (beats/minute) and body temperature (C)) and weight
- 12-lead electrocardiogram (ECG)
- ECOG performance scores

4.5.1 Adverse Events

All adverse event (AE) recorded on treatment including within 30 days from the last study treatment will be summarized.

The coding dictionary for this study will be MedDRA. It will be used to summarize AEs by SOC and PT. AEs will be graded using National Cancer Institute's Common Terminology Criteria for AEs (NCI-CTCAE, Version 4.03).

An overview table will include the following details by treatment group and overall:

- Number and percentage of participants with TEAEs,
- Number and percentage of participants with causally drug-related TEAEs,
- Number and percentage of participants with serious TEAEs and Astellas upgraded serious TEAE,
- Number and percentage of participants with serious drug-related TEAEs and Astellas upgraded serious drug-related TEAE,
- Number and percentage of participants with TEAEs leading to permanent discontinuation of study drug,
- Number and percentage of participants with drug-related TEAEs leading to permanent discontinuation of study drug,
- Number and percentage of participants with grade 3 or higher TEAE
- Number and percentage of participants with grade 3 or higher drug-related TEAE
- Number and percentage of participants with TEAEs leading to dose reduction,
- Number and percentage of participants with drug-related TEAEs leading to dose reduction,
- Number and percentage of participants with TEAEs leading to drug interruption,
- Number and percentage of participants with drug-related TEAEs leading to drug interruption,
- Number and percentage of participants with TEAEs leading to death,
- Number and percentage of participants with drug-related TEAEs leading to death
- Number and percentage of participants with TEAEs leading to death excluding disease progression,
- Number and percentage of participants with drug-related TEAEs leading to death excluding disease progression, and
- Number of deaths

The above overview table will be repeated to report the number of events (all TEAEs which may include multiple events of the same preferred term with the same or different CTCAE grades) and the number of events adjusted by patient year (defined as the total duration of exposure in years).

The number and percentage of participants with TEAEs, as classified by SOC and PT will be summarized by treatment group and overall. Summaries will be provided for:

- TEAEs
- Drug-related TEAEs,

- serious TEAEs and Astellas upgraded serious TEAE,
- drug-related serious TEAEs and drug-related Astellas upgraded serious TEAE,
- TEAEs leading to permanent discontinuation of study drug,
- Drug-related TEAEs leading to permanent discontinuation of study drug,
- TEAEs leading to dose reduction,
- Drug-related TEAEs leading to dose reduction,
- TEAEs leading to drug interruption,
- Drug-related TEAEs leading to drug interruption,
- TEAEs leading to death
- Drug-related TEAEs leading to death
- TEAEs leading to death excluding disease progression
- Drug-related TEAEs leading to death excluding disease progression
- grade 3 or higher TEAEs
- grade 3 or higher drug-related TEAEs
- TEAEs excluding serious adverse events that equal to or exceed a threshold of 5% in any dose level

AE summary tables will include participant counts as opposed to AE counts. If a participant experiences more than one episode of a particular AE, that participant will be counted only once for that event. If a participant has more than one AE that code to the same preferred term, the participant will be counted only once for that preferred term. Similarly, if a participant has more than one AE within a body system, the participant will be counted only once in that body system.

TEAEs and the number and percentage of participants with TEAEs, as classified by SOC and PT will also be summarized by NCI-CTCAE severity grade and by relationship to study drug. If an adverse event changes in severity grade or relationship, then the participant will be counted only once with the worst severity grade and highest degree of relationship. The adverse event however will be presented in each category they were classified to. If a participant has an event more than once with missing severity grade and with non-missing severity grade, then the participant will be counted as the highest non-missing grade. If a participant has an event more than once with missing relationship and with non-missing relationship, then the participant will be counted as relationship=Yes. Drug-related TEAEs will be presented in a similar way by severity only.

The number and percentage of sujects with treatment-emergent adverse events of interest (AESI) as classified by SSQ/CMQ or SMQ and PT will be summarized. For selected AESI, time to onset will be summarized at the participant level. All AEs, deaths, SAEs and withdraws due to adverse events will be displayed in listings.

4.5.1.1 Ophthalmology Examination

The following ophthalmologic variables will be summarized by descriptive statistics and will be presented at each visit where ophthalmologic assessment is performed, by eye, and overall:

- Visual acuity: method of assessment, visual acuity score (VAS) and result (normal, abnormal-not clinically significant, abnormal-clinically significant)
- Slit lamp biomicroscopy: location of biomicroscopy, biomicroscopy interpretation (normal,abnormal-not clinically significant, abnormal-clinically significant)
- Tonometry: intraocular pressure result
- Dilated fundus examination: interpretation (normal, abnormal-not clinically significant, abnormal-clinically significant)

4.5.2 Additional Safety Assessments

4.5.2.1 Clinical Laboratory Evaluation

The baseline value will be the last nonmissing value taken on or prior to first dose of study drug.

All laboratory results (hematology, biochemistry and urinalysis analysis) by local laboratories up to the end of treatment visit will be presented in standardized units. Both observed value and changes from baseline will be summarized using mean, standard deviation, minimum, maximum, and median for each scheduled visit. Plots of median, 25th percentile, and 75th percentile lab values at each scheduled assessment time will be provided for each laboratory parameter.

Frequency tabulations of qualitative clinical laboratory variables will be presented.

Laboratory results will be graded using NCI-CTCAE(Version 4.03), where possible. Parameters that have criteria available for both low and high values, i.e., hypo- and hyper-, will be summarized for both criteria. The same participant can be counted for both values if the participant has different laboratory values meeting each criterion. NCI-CTCAE grade of laboratory evaluations will be summarized by number and percentage of participants for each visit. Shift from baseline to maximum post-baseline NCI CTCAE grade will be summarized for each lab test. Laboratory abnormalities reported in ≥ 10% (All Grade) or ≥ 5% (Grade 3-4) of all subjects in SAF will be presented.

Laboratory results and NCI CTCAE grades for hematology and serum chemistry will be presented in data listings. Normal ranges will be documented and out-of-range values will be flagged. A separate listing of laboratory results with CTCAE grade 3 or higher will be presented.

4.5.2.2 Liver Safety Assessment

The liver safety assessment will be summarized based on the measurements of alkaline phosphatase (ALP), alanine transaminase (ALT), total bilirubin, aspartate transaminase (AST), and their combination as defined below. The participant's highest value during the investigational period will be used. The number and percentage of participants meeting the criteria post-baseline will be summarized.

- ALT: > 3×ULN, > 5×ULN, > 10×ULN, > 20×ULN
- AST: > 3×ULN, > 5×ULN, > 10×ULN, > 20×ULN

- ALT or AST: > 3×ULN, > 5×ULN, > 10×ULN, > 20×ULN
- ALP: > 1.5×ULN
- Total bilirubin: > 2×ULN
- (ALT or AST > 3×ULN) and Total bilirubin > 2×ULN*
- (ALT or AST > 3×ULN) and Total bilirubin > 2×ULN and ALP < 2×ULN*

*Combination of values measured on the same day or within 1 day apart.

The denominator for each criterion will be the number of participants who have at least one value postbaseline.

In addition, participants with the post-baseline liver function test results that are consistent with the Hy's law criteria will be listed.

4.5.2.3 Vital Signs

The baseline visit is the last nonmissing value taken prior to initial study drug administration. Vital signs (systolic blood pressure, diastolic blood pressure, pulse rate and body temperature) and weight will be summarized using mean, standard deviation, minimum, maximum and median by visit. Additionally, a within-participant change will be calculated per visit as the post-baseline measurement minus the baseline measurement and summarized by visit.

Vital signs data will be listed.

4.5.2.4 Electrocardiograms

ECG variables will be summarized using mean, standard deviation, minimum, maximum, and median for each scheduled visit. The number and percentage of participants with normal and abnormal results for the overall interpretation will be tabulated.

4.5.2.5 ECOG Performance Status

Summary statistics (number and percent of participants) for each category of the ECOG performance status at each assessment will be provided. ECOG performance status range from 0 (fully active) to 5 (dead). Negative change scores indicate an improvement and positive scores indicate a decline in performance. ECOG will also be summarized using shift table from baseline to the best and worst post-baseline score.

4.6 Analysis of Pharmacokinetics

Pharmacokinetic parameters are primary endpoints in this study. The Pharmacokinetic analysis set (PKAS) will be used for all summaries and analyses of the pharmacokinetic data.

Descriptive statistics will include n, mean, standard deviation, minimum, median, maximum, coefficient of variation (CV), geometric mean and geometric CV. For the pharmacokinetic parameter t_{max}, only n, median, minimum and maximum will be calculated.

4.6.1 Pharmacokinetic Concentrations

Descriptive statistics will be used to summarize plasma or serum concentrations of ADC, TAb and unconjugated MMAE by Cycle, Day and Time Point for the PK and Non-PK Cohorts separately. Standard graphics including mean (standard deviation) plasma or serum -concentration time profiles (linear and semi-logarithmic scales) and overlay (spaghetti) plots will be produced for each analyte for PK cohort. Standard deviation will not be displayed for the semilogarithmic scale plots.

4.6.2 Estimation of Pharmacokinetic Parameter

Noncompartmental analysis will be used for the calculation of plasma and serum pharmacokinetic parameters using Phoenix WinNonlin software version 6.3 or higher (Certara LP, 100 Overlook Center, Suite 101, Princeton, NJ 08540, US).

Participants in the PK cohort will have the following pharmacokinetic parameter estimates calculated if data permit for each of the 3 analytes (ADC, TAb and unconjugated MMAE),:

- C_{max} after first dose and third dose in Cycle 1
- T_{max} after first dose and third dose in Cycle 1
- $AUC_{0\text{-}7d}$ after first dose and third dose in Cycle 1
- $R_{ac}(C_{max})$ after third dose in Cycle 1
- $R_{ac}(AUC_{0\text{-}7d})$ after third dose in Cycle 1
- $t_{1/2}$ after third dose in Cycle 1 as appropriate
- CL and V_{ss} after third dose in Cycle 1 as appropriate

Descriptive statistics will be used to summarize plasma or serum pharmacokinetic parameters of ADC, TAb and unconjugated MMAE separately, by day after the first and third dose in Cycle 1 as appropriate for participants in the PK cohort. Participants who change dosage from 1.25 mg/kg will be excluded from the summary statistics.

4.7 Subgroups of Interest

4.7.1 Subgroup Analysis for Primary Efficacy Endpoint

As exploratory analyses, subgroup analyses will be conducted for the primary efficacy endpoint. Subgroup analyses to be conducted are:

- Age (<65, ≥65 years old)
- Age (<75, ≥75 years old)
- Sex (female, male)
- ECOG performance score at baseline (0, 1)
- Bellmunt risk score (0-1, ≥2)
- Primary tumor sites (upper tract and bladder/other)

- Liver metastasis (yes, no)
- Number of prior systemic therapy in locally advanced or metastatic setting (1-2, ≥3)
- Best response to prior CPI (responder, non-responder)

A subgroup analysis may not be performed if the number of participants in the subgroup is not sufficiently large (e.g., <5).

The confirmed ORR per investigator by the same subgroups will be presented graphically.

4.8 Other Analysis

4.8.1 Analysis of Immunogenicity

The incidence of ATA formation to the enfortumab vedotin will be evaluated.
The number and percentage of participants with positive post-baseline ATA will be presented by baseline ATA status. In addition, individual participant ATA results including titer levels (if available) will be displayed at each visit in a listing.

4.8.2 Other Analyses Due to COVID-19

Assessments that are affected by COVID-19 will be listed.

4.9 Interim Analysis (and Early Discontinuation of the Clinical Study)

No formal interim analysis is planned.

4.10 Sample Size Determination

Up to 40 participants will be enrolled to study of which approximately 12 participants will be enrolled to the PK cohort. Additional participants may be enrolled in the PK cohort to compensate for participants who become unevaluable for the PK relevant primary endpoint.

The study was designed to estimate the confirmed ORR in participants receiving enfortumab vedotin and to detect an improvement in the ORR compared with a historical 10% response rate which was previously applied in the study EV-201(Cohort 1). The Study EV-201 (Cohort 1) was the pivotal study led to the US registration approval for the same patient population, of which the primary efficacy outcome was 44% ORR with 95% confidence interval (CI) of (35.1%, 53.2%).

The study sample size was determined to detect the ORR improvement of 25% from 10% with sufficient statistical power. The power for various sample size were listed in following table:

Sample Size	Approximate Power Based on Exact Method to Detect a 25% Increase in ORR from 10%
N=30	87%
N=35	95%
N=40	97%
N=50	99%

Therefore, 35 – 40 sample size will be appropriate to have sufficient statistical power to detect the 25% improvement of ORR from 10%.

Up to 40 participants will be enrolled in this study to ensure collection of sufficient efficacy and safety data. Using the estimate of up to 40 participants, the study will have over 97% power to detect a 25% increase in ORR from 10% to 35%, at one-sided significant level of 0.025, based on exact methods.

4.11 Additional Conventions

4.11.1 Analysis Windows

CRF visit will be used for analysis. For safety analysis, in the case of multiple observations at a specific visit, the observation which is the latest will be used. If more than one observation is made on the same day, an average value if continuous or the worst value if categorical will be included in the analysis.

4.11.2 Imputation Rules for Incomplete Dates

In the imputation of missing or partial dates, if the imputed date is after min (death date, cutoff date), min (death date, cutoff date) will be used as imputed date.

Missing or partial start and stop dates of adverse events and prior and concomitant medication will be imputed using the following algorithm:

- Imputation rules for partial or missing stop dates:
    - If the month and year are present, then impute as the last day of that month.
    - If only the year is present, impute as December 31 of that year.
    - If the stop date is entirely missing, assume the event or medication is ongoing.
- Imputation rules for partial or missing start dates:

Start Date		Stop Date						
		Complete: *yyyymmdd*		**Partial: *yyyymm***		**Partial: *yyyy***		**missing**
		< 1st administration	**≥ 1st administration**	**< 1st administration *yyyymm***	**≥ 1st administration *yyyymm***	**< 1st administration *yyyy***	**≥ 1st administration *yyyy***	
Partial: *yyyymm*	= 1st administration *yyyymm*	2	1	n/a	1	n/a	1	1
	≠ 1st administration *yyyymm*		2	2	2	2	2	2
Partial: *yyyy*	= 1st administration *yyyy*	3	1	3	1	n/a	1	1
	≠ 1st administration *yyyy*		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1 = Impute as the date of first administration; 2 = Impute as the first of the month; 3 = Impute as January 1 of the year;
4 = Impute as January 1 of the stop year

The imputed dates will be used to determine whether an AE is/is not treatment emergent. Listings of AEs and concomitant medications will present the actual partial dates; imputed dates will not be shown.

In the case of partial starting date of subsequent anti-cancer therapy, the date will be imputed to the first day of the month but not earlier than the last dosing date of the study drug. A month and year must be present or the date will remain missing.

Partial missing date of prior therapy: for start date, the date will be imputed to the first day of the month; for the end date, the date will be imputed to the last day of the month or 14 days before the first dose of study drug, whichever is earlier. A month and year must be present or the date will remain missing.

For continuous variables (e.g., clinical laboratory measurement, vital signs), participants with missing baseline variable will be excluded from the analysis of change from baseline.

Participants who do not satisfy the criteria to be counted as responders or have insufficient data to determine or confirm a response per the RECIST guidelines (Version 1.1) will be considered as non-responders in the final analysis of response rates. No imputation of data will be done to determine individual participant response.

For all analyses other than PK analysis, all values will be included in the analyses. For analysis of PK data, only samples for which the time of sampling relative to the dose administration and the exact dose is known will be included.

4.11.3 Outliers

All values will be included in the analysis.

5 REVISION AND RATIONALE

Version	Date	Changes	Comment/rationale for change
1.0	20-JUL-2021	NA	Original Version
2.0	14-Mar-2022	Section 4.2.11 Extent of Exposure Clarified the definition of duration of exposure, when it was analyzed as a single paramenter and when it was used in calculating dose intensity, respectively.	When calculating duration as a single parameter,apply datacut if there is one, however when calculating dose intensity, do not apply datacut, use the "initial dose of last cycle +28-1" rule. The reason is that if the cutoff date is applied, the calculated relative dose intensity almost always exceed 1 under perfect compliance, which may cause confusion.
	14-Mar-2022	Section 4.5.1 Adverse Events 1. Updated AESI terms per EV AESI list version 8 2. Removed the analysis of time to improvement and resolution of AESI	1. AESI list was updated from v7 to v8 2. Analysis of time to improvement and resolution are removed because per current CRF design it is difficult to identify records from the same event to allow performing this type of analysis.
	14-Mar-2022	Section 4.8.1 Analysis of Immunogenicity Revised the definition and analysis of ATA	Clarify the definition and analysis of ATA.
	14-Mar-2022	Section 4.7.1 Subgroup Analyses Removed subgroup analysis for safety endpoints.	Reomved considering such analyses would be not that informative based on current relative small sample size and single-arm design.
	10-Jun-2022	Changed all "subject" to "participant"	Per newly updated company level standard term
	10-Jun-2022	Section 4.3.2 Main Analytical Approach. For the analysis of time to response, add a swimmer plot	Use swimmer plot to visualize all participants' time to response and duration of response.
	10-Jun-2022	Section 4.4.1 Definition of secondary endpoint. Regarding the definition of censoring rule of DOR, remove the sentence of censoring at the date of first CR/PR if no subsequent post-baseline radiological assessment is available	This sentence is not applicable to DOR since only confirmed responders are included in the analysis.
	10-Jun-2022	Section 4.4.2.5. Add concordance analysis between ORR per IRC and per investigator assessment	Add concordance analysis to show discrepancy between ORR per IRC and per investigator assessment.
	10-Jun-2022	Section 4.4.2.10 Tumor shrinkage per IRC, add a spider plot.	Use spider plot to show visualize tumor size change over time with one curve per each participant.
	10-Jun-2022	Section 4.4.2.11 Add tumor shrinkage summary per investigator assessment	There is a set of analysis per IRC, add the same analysis for investigator

Version	Date	Changes	Comment/rationale for change
			since all efficacy endpoints are done both ways.
	10-Jun-2022	Section 4.7.1 Subgroup analysis, 1. Remove the subgroup analysis for time to response. 2. Remove the subgroup analysis for ORR by four PD-L1 subgroups and by weight.	1.Sample size is relatively small for time to response subgroup analysis. 2. For PD-L1 subgroups, sample size is too small for each subgroup to do subgroup analysis. Similar for by weight subgroup analysis, one category will have zero participants so we remove this subgroup analysis.
	12-Jul-2022	In PKAS definition, the requirement for having samples for all three analytes (ADC, Tab and unconjugated MMAE) has been modified to having samples from at least one of the three analytes.	Having enough samples from at least one analyte is sufficient for a subject to be included in PKAS.
	15-Jul-2022	Remove the summary of dose interruption and dose reduction	Dose reduction is caused by AE which had already analyzed and displayed on table 'Treatment-Emergent Adverse Events and Death, Event Numbers', this is a duplicated information. Per our discussion, there is no appropriate method to do the analyses for 'Dose interruption' based on the data on study drug administration page, while 'TEAE leading to dose interruption' in safety analyses and listing which provide the detailed information could help to present this data in different aspects.

6 SUPPORTING DOCUMENTATION

6.1 Appendix 1 List of Abbreviations

Abbreviations	Description of abbreviations
1L	first-line
2L	second-line
ADC	antibody-drug conjugate
ADL	activities of daily living
AE	adverse event
AEOI	AE of interest
AKI	acute kidney injury
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATA	antitherapeutic antibodies
AUC	area under the concentration-time curve
AUC_{4d}	area under the concentration-time curve from time 0 to 4 days
AUC_{7d}	area under the concentration-time curve from time 0 to 7 days
BMI	body mass index
BUN	blood urea nitrogen
CHO	Chinese hamster ovary
CI	confidence interval
C_{max}	maximum concentration
CNS	central nervous system
CrCl	creatinine clearance
CR	complete response
CRF	case report form
CRM	continual reassessment method
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
CTCAE	common terminology criteria for adverse events
C_{trough}	trough concentration
CV	coefficient of variation
DCR	disease control rate
DILI	drug-induced liver injury
DOR	duration of response
ECG	Electrocardiogram
EES	efficacy evaluable set
eCOA	electronic clinical outcome assessment
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	end of treatment
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate

Abbreviations	Description of abbreviations
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practices
HbA1c	hemoglobin A1c
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein cholesterol
HRT	hormone replacement therapy
ICD	immunogenic cell death
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	international normalized ratio
IRC	independent review committee
IRR	infusion related reaction
IP	investigational product
IRB	Institutional Review Board
IRT	interactive response technology
ISN	international study number
LA	locally advanced
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
IV	intravenous
MMAE	monomethyl auristatin E
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mUC	metastatic urothelial cancer
NCI-CTCAE	National Cancer Institute-common terminology criteria for adverse event
NMPA	National Medical Products Administration
NOAEL	no observed adverse effect level
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
P-gp	P-glycoprotein
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death protein-1
PD-L1	programmed death ligand-1
PFS	progression-free survival
PK	Pharmacokinetic(s)
PKAS	pharmacokinetic analysis set
PR	partial response
QA	quality assurance
QC	quality control
QTL	quality tolerance limit
$R_{ac}(AUC)$	accumulation ratio calculated using AUC
$R_{ac}(C_{max})$	accumulation ratio calculated using C_{max}
RBC	red blood cell

Abbreviations	Description of abbreviations
RECIST	Response Evaluation Criteria in Solid Tumor (new guidelines to evaluate the response to treatment in solid tumors)
RP2D	Recommended Phase 2 Dose
(S)AE	serious adverse event or adverse event
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SD	stable disease
SOP	standard operating procedure
$t_{½}$	terminal elimination half-life
TAb	total antibody
TEAE	treatment-emergent adverse event
TBL	total bilirubin
t_{max}	time of maximum concentration
ULN	upper limit of normal
UC	urothelial cancer
US	United States
VA	visual acuity
V_{ss}	volume of distribution at steady state
WOCBP	woman of childbearing potential

6.2 Appendix 2 List of Key Terms

Terms	Definition of terms
Baseline	Assessments of participants as they enter a study before they receive any treatment.
Endpoint	Variable that pertains to the efficacy or safety evaluations of a study. Note: Not all endpoints are themselves assessments since certain endpoints might apply to populations or emerge from analysis of results. That is, endpoints might be facts about assessments (e.g., prolongation of survival).
Enroll	To register or enter a participant into a study. Note: Once a participant has received the study drug or placebo, the protocol applies to the participant.
Investigational Product	The drug, device, therapy or process under investigation in a study that is believed to have an effect on outcomes of interest in a study (e.g., health-related quality of life, efficacy, safety and pharmacoeconomics).
Post investigational period	Period of time after the last assessment of the protocol. Follow-up observations for sustained adverse events and/or survival are done in this period.
Screening	A process of active consideration of potential participants for enrollment in a study.
Screen failure	Potential participant who signed the ICF, but did not meet one or more criteria required for participation in the study and was not enrolled.
Screening period	Period of time before entering the investigational period, usually from the time when a participant signs the consent form until just before the test product or comparative drug (sometimes without randomization) is given to a participant.
Study period	Period of time from the first study site initiation date to the last study site completing the study.
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

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8 SIGNATURE

(E-signatures are attached at the end of document)

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