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

ISN/Protocol 7465-CL-1104

Amendment 2 [Substantial]

29 Mar 2022

Sponsor:

Astellas Pharma China, Inc.

No 3 Jia 6 Road 10
Shenyang Economic and Technological Development Zone,
Shenyang 110027 China

Protocol History:
Version 1.0 [31 Jul 2020]
Version 2.0 [12 Feb 2021]

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SIGNATURES

1. SPONSOR'S SIGNATURES

Required signatures (e.g., protocol authors and contributors, etc.) are located in [Section 12 Sponsor's Signatures].

2. INVESTIGATOR'S SIGNATURE

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

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I have read all pages of this protocol for which Astellas is the sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and applicable local regulations. I will also ensure that subinvestigator(s) and other relevant members of my personnel have access to copies of this protocol and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents.

Principal Investigator:

Signature: .....

Date (DD-MMM-YYYY)

Printed Name: .....

<Insert name and qualification of the investigator>

Address of trial site: .....

.....

CONTACT DETAILS OF SPONSOR'S KEY PERSONNEL

24-hour Contact for Serious Adverse Events See [Section 10.3.6 Reporting Procedures for Serious Adverse Events]	PPD , Development Medical Department - Oncology Astellas Pharma China, Inc. PPD **Please fax or email the serious adverse events/special situations worksheet to:** **Astellas Pharma Global Development Inc.** **Pharmacovigilance** International fax number: +44-800-471-5263 Alternate fax number: +1-888-396-3750 Email: safety-us@astellas.com* *Please use email in general.
Medical Monitor/Medical Expert:	PPD , Development Medical Department - Oncology Astellas Pharma China, Inc. PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment 1 [Substantial]	12 Feb 2021
Original Protocol	31 Jul 2020

Amendment 2 [Substantial] 29 Mar 2022

This amendment is considered to be [substantial] based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and EU Clinical Trial Regulation.

Overall Rationale for the Amendment:

To align the protocol with updated skin toxicity management guidance in the CHMP-approved EU Summary of Product Characteristics of EV

Summary of Changes

Substantial Changes

Section Number	Description of Change	Brief Rationale
6.5 (Table 8), 6.5.1	Additional information added for the recommended dose modifications for EV associated nonhematologic toxicities	Guidance is added to clarify dose modifications recommendations for rashes and skin reactions.

Nonsubstantial Changes

Section Number	Description of Change	Brief Rationale
Contact Details of Sponsor's Key Personnel	PPD is the current 24-hour contact for SAEs and the medical monitor/medical expert	To provide updated staffing information
5.2	Update exclusion criterion #9	To clarify expected treatment of participants at baseline with positive hepatitis B surface antigens and/or anti-hepatitis B core antibodies
10.3.4	Correct NCI-CTCAE version to Version 4.03	To correct an error
Throughout	Minor administrative-type changes, e.g., typos, format, numbering, consistency throughout the protocol.	To provide clarifications to the protocol and to ensure complete understanding of study procedures.

1 PROTOCOL SUMMARY

1.1 Synopsis

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

Planned Study Period/Duration:
From approximately 2Q2021 to 4Q2023

Planned Total Number of Study Sites and Location(s):
Approximately 5 study sites in China.
One to 2 study centers will be designated as a "pharmacokinetic (PK) cohort site". PK samples after single and repeated doses will be collected from approximately 12 participants enrolled at the PK cohort site(s).

Study Objectives, Endpoints and Estimands:

Objectives	Endpoints
Primary	
• 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)	• Confirmed ORR per RECIST V1.1 by IRC
• To assess the PK of antibody-drug conjugate (ADC), total antibody (TAb) and monomethyl auristatin E (MMAE) in Chinese participants with locally advanced or metastatic urothelial cancer.	• PK variables Selected PK parameters of ADC, TAb and MMAE are as follows: • Maximum observed concentrations (C_{max}) • Trough concentration (C_{trough}) • Time to maximum concentration (T_{max}) • Area under concentration-time curve from 0 to day 7 (AUC_{0-7d}) • Area under concentration-time curve from 0 to day 28 (AUC_{0-28d}) • Accumulation ratio of C_{max} ($R_{ac}[C_{max}]$) • Accumulation ratio of AUC_{0-7d} ($R_{ac}[AUC_{0-7d}]$) • Terminal or apparent terminal half-life ($t_{1/2}$) as appropriate • Systemic clearance (CL) and volume of distribution at steady state (V_{ss}) as appropriate

Table continued on next page

Secondary	
• To assess confirmed ORR per investigator assessment	• Confirmed ORR per RECIST V1.1 per investigator assessment
• To assess duration of response (DOR)	• DOR per RECIST V1.1 per IRC and per investigator assessment
• To assess disease control rate (DCR)	• DCR per RECIST V1.1 per IRC and per investigator assessment
• To assess progression-free survival (PFS)	• PFS per RECIST V1.1 per IRC and per investigator assessment
• To assess overall survival (OS)	• OS
• To assess the immunogenicity as defined by the incidence of antitherapeutic antibodies (ATA)	• Incidence of ATA to ADC

• To assess the safety and tolerability of enfortumab vedotin in Chinese participants with locally advanced or metastatic urothelial cancer.	• Safety variables:
	  • Adverse events (AEs)
	  • Laboratory tests
	  • Vital sign measurements
	  • 12-lead electrocardiogram (ECG)
	  • Eastern Cooperative Oncology Group (ECOG) performance status

ADC: antibody-drug conjugate; AE: adverse event; ATA: antitherapeutic antibodies; 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; CL: clearance; C_{max}: maximum concentration; C_{trough}: trough concentration; DCR: disease control rate; DOR: duration of response; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EV: enfortumab vedotin; IRC: independent review committee; MMAE: monomethyl auristatin E; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PK: pharmacokinetic; R_{ac}(AUC): accumulation ratio calculated using AUC; $R_{ac}(C_{max})$: accumulation ratio calculated using C_{max}; $t_{1/2}$: terminal half-life; TAb: total antibody; t_{max}: time of maximum concentration; V_{ss}: volume of distribution at steady state.

Estimands

Not Applicable.

Study Population:

The population to be studied includes Chinese participants with locally advanced (LA) or metastatic urothelial cancer (mUC) who previously received therapy with platinum-containing chemotherapy and programmed cell death protein-1 (PD-1)/ programmed death ligand-1 (PD-L1) inhibitor therapy, with baseline measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. Participants who received PD-1/PD-L1 inhibitor therapy in the neoadjuvant/adjuvant setting and had recurrent or progressive disease (PD) either during therapy or within 3 months of therapy completion are eligible.

Participants who received prior treatment with platinum-containing chemotherapy defined as those who received platinum in the neoadjuvant/adjuvant setting and had recurrent or progressive disease within 12 months of completion or received treatment with platinum in the LA (defined as unresectable with curative intent) or metastatic setting.

Number of Participants:

Up to 40 Chinese participants will be enrolled in this study, of which approximately 12 participants from 1 to 2 PK cohort site(s) will participate in intense PK sample collection.

Study Design Overview:

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 LA or 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 PK participants in the PK Cohort.

All participants will receive enfortumab vedotin at 1.25 mg/kg dose level administered as an intravenous (IV) infusion on Days 1, 8 and 15 of every 4-week (28 days) cycle. Participants will continue on study treatment until one or more of the following discontinuation criteria are met:

- Participant requests to stop treatment.
- Investigator decides it is in the participant's best interest to discontinue.
- Participant develops documented radiological disease progression per RECIST V1.1 by investigator assessment.
- Participant starts a new anticancer therapy.
- Participant develops unacceptable toxicity.
- Female participant becomes pregnant.
- Participant is noncompliant with the protocol based on the investigator or medical monitor assessment.
- Participant did not receive study drug continuously for >2 cycles (i.e., > 6 consecutive doses not received). Medical Monitor consultation is required after the participant was unable to receive one full cycle of study drug administration (i.e., 3 consecutive doses). Dose delays for patients who are responding to treatment may be extended beyond 8 weeks in consultation with Medical Monitor, if the patient's toxicity does not otherwise require permanent discontinuation.

The participants who discontinue study treatment for reasons other than objective disease progression per RECIST V 1.1 will be followed every 8 weeks (± 1 week) for response assessments. After 1 year from the start of treatment, the frequency of response assessments will be reduced to every 12 weeks (± 1 week). The tumor assessments will continue until the participant has radiological disease progression per RECIST V1.1 as determined by the investigator assessment, initiates a new anticancer therapy, dies, withdraws study consent, lost to follow-up or the study closes, whichever comes first. All participants are to be followed for survival status and subsequent anticancer therapy until death, lost to follow-up, withdrawal of consent from study, or study closure, whichever occurs first. The study will be closed approximately 2 years after the last participant enrollment or no participants remain in long-term follow-up, whichever occurs first. A provision of drug supply to the participants who are still benefiting from treatment will be prepared prior to study closure. Additionally, the sponsor may terminate the study at any time.

One to 2 study centers will be designated as a "PK cohort site". Approximately 12 participants enrolled at the PK cohort site(s) will have intense PK samples collected after single and repeated doses. The other participants enrolled at non-PK cohort sites will have sparse PK samples collected. Additional participants may be enrolled in PK cohort to compensate for participants who become unevaluable for the PK relevant primary endpoint (PK evaluable).

Blood samples for pharmacokinetics and antitherapeutic antibodies (ATA) will be collected at protocol-specified time points. Validated assays will be used to measure the concentrations of antibody-drug conjugate (ADC), total antibody and monomethyl auristatin E (MMAE) in serum or plasma and to assess ATA.

An ongoing review of participant safety and serious adverse events (SAEs) will also be conducted by the sponsor's Drug Safety Department.

After treatment discontinuation, participant will have an end of treatment (EOT) visit for a 30-day Safety Follow-up.

Safety data will be monitored closely throughout the study per the Sponsor relevant study monitoring plan.

Treatment Groups and Duration:

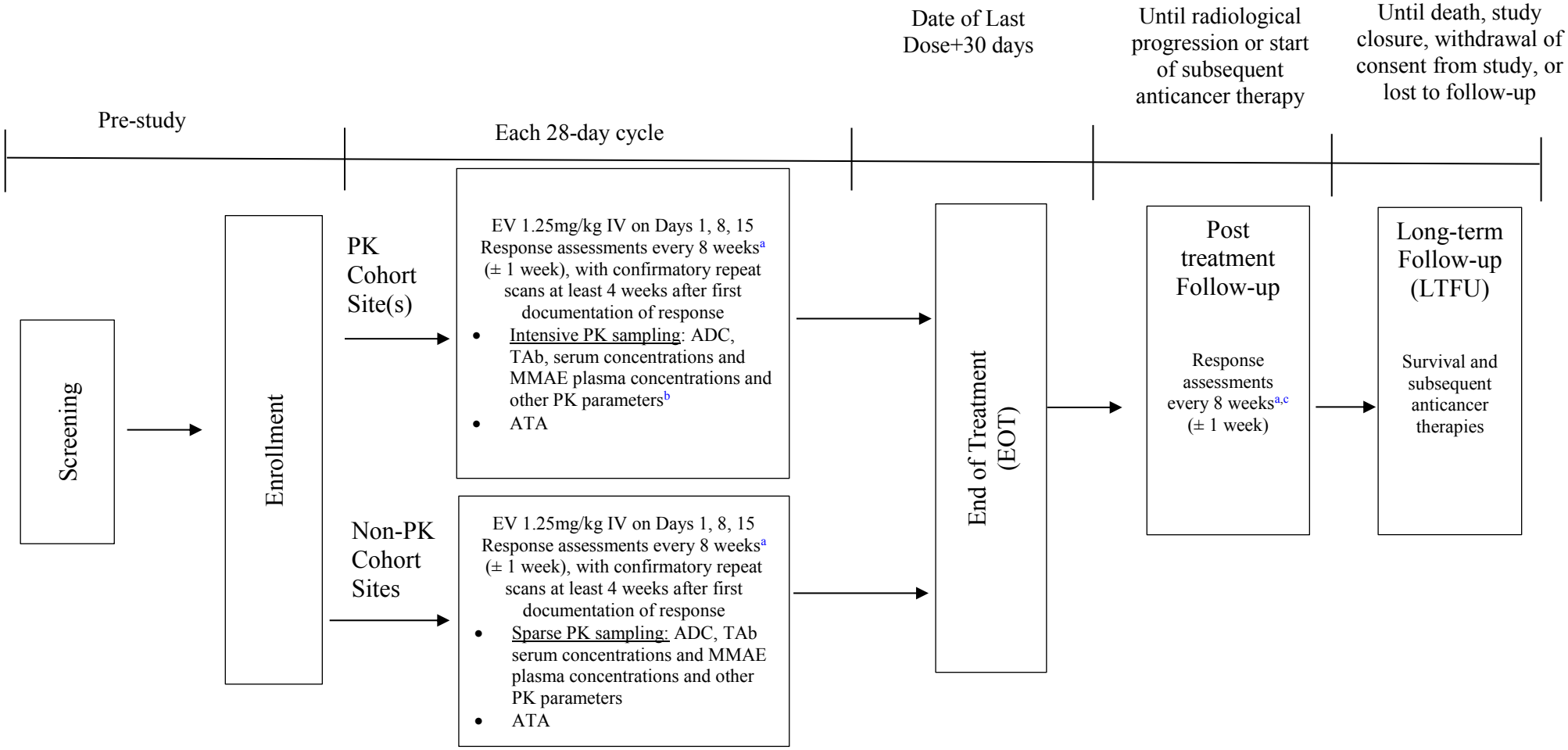
Arm/IP Name	Enfortumab vedotin
Use	test product
Dose	1.25 mg/kg
Frequency	Days 1, 8 and 15 of every 4-week (28 days) cycle
Route	IV infusion
Duration	8 months

IP: investigational product; IV: intravenous infusion

The anticipated treatment duration of the study for each participant, from first dose to disease progression per relevant publication in the same target population and treatment setting, is approximately 8 months.

1.2 Study Schema

Figure 1 Study Schema



Footnotes appear on next page

ADC: antibody-drug conjugate; EOT: End of Treatment; EV: Enfortumab vedotin; FU: follow-up; MMAE: monomethyl auristatin E; PK: pharmacokinetic; TAb: total antibody;

a. Participants will have disease response assessments every 8 weeks (± 1 week) for the first year on study treatment. After 1 year from the start of treatment, the frequency of response assessments will be reduced to every 12 weeks (± 1 week). The schedule of response assessments should not be adjusted after the confirmatory scan.
b. One to 2 study sites will be designated as the PK cohort site(s). Approximately 12 participants will be enrolled in PK cohort. Additional participants may be enrolled in PK cohort to compensate for participants who become unevaluable for the PK relevant primary endpoint (PK evaluable).
c. Only participants that have not met radiographic disease progression in the Treatment Period will go into Post-Treatment Period, while participants that have met radiographic disease progression within the Treatment Period will go into the Long-Term Follow-Up directly.

1.3 Schedule of Assessments

Table 1 Schedule of Assessments

		Screening/ Baseline		Enrollment	Every 28-day Cycle				EOT[b] (30-day Safety Follow-up)	Post-Treatment Follow-up	Long-term Follow-up
	Day	**Day -28 to -1**	**Day -7 to -1**	**Within 7 Days of 1st dose**	**Day 1**	**Day 8**	**Day 15**	**Every 8 weeks**	**Date of Last Dose +30 days**	**Every 8 weeks**	**Every 12 weeks**
	Visit window				**± 3 days[a]**	**± 3 days**	**± 3 days**	**± 7 days**	**+7 days**	**± 7 days**	**± 7 days**
Screening/baseline assessments	Inclusion/exclusion	X		Submit confirmation of eligibility prior to treatment							
	Medical history/Disease history/demographics	X									
	Informed consent	X									
	Brain scan[c]	X						X		X	
	Bone scan[c]	X						X		X	
	Hepatitis B and C screening	X									
	Urinalysis with microscopic analysis	X									
	HbA1c[d]		X						X		
Safety assessments	Pregnancy test[e]		X		X				X	X	X
	Full physical examination (including weight)		X		X[f]				X		
	Height		X								
	Vital signs		X		X	X	X		X		
	Hematology[h,i]		X		X[f]	X[g]	X[g]		X		
	Biochemistry[h,i]		X		X[f]	X	X		X		
	CrCl		X								
	ECOG performance status		X		X				X		
	12-lead ECG[j]		X						X		
	Ophthalmological assessment[k]	X							X		
	Prior and Concomitant medications[l]	Every Visit									
	AEs assessment[m]										

Table continued on next page

		Screening/ Baseline		Enrollment	Every 28-day Cycle				EOT[b] (30-day Safety Follow-up)	Post-Treatment Follow-up	Long-term Follow-up
	Day	**Day -28 to -1**	**Day -7 to -1**	**Within 7 Days of 1st dose**	**Day 1**	**Day 8**	**Day 15**	**Every 8 weeks**	**Date of Last Dose +30 days**	**Every 8 weeks**	**Every 12 weeks**
	Visit window				**± 3 days[a]**	**± 3 days**	**± 3 days**	**± 7 days**	**+7 days**	**± 7 days**	**± 7 days**
Treatment	Study drug administration[n]				X	X	X				
PK/ATA	Blood sample collection	See PK and ATA Tables (Table 2, Table 3 and Table 4) for sample collection details.									
Response assessment	CT scan with contrast of chest, abdomen, pelvis and any other region of known or suspected disease[o]	X						X[p,q]		X[p,r]	
OS	Survival status								X	X	X[s]

AE: adverse event; ATA: antitherapeutic antibodies; BCVA: best corrected visual acuity; CrCl: creatinine clearance; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOM: extra ocular movement; EOT: End of Treatment; HbA1c: hemoglobin A1c; HDL: high-density lipoprotein; IOP: inter ocular pressure; LDL: low-density lipoprotein; OS: overall survival; PK: pharmacokinetic; RECIST: Response Evaluation Criteria in Solid Tumors; VA: visual acuity.

a. This visit window is not applicable for Cycle 1 Day 1, could only be applied for the subsequent cycle.

b. The EOT visit should be completed prior to the initiation of the next anticancer therapy.

c. Brain scan and bone imaging will be performed at screening. Repeated at response assessment time points if metastases are identified at screening, or if metastasis is known or suspected, or as clinically indicated throughout the study.

d. If HbA1c is elevated (≥ 6.5%), refer participant to appropriate provider during Cycle 1 for glucose management. HbA1c needs to be tested in EOT evaluation as safety assessment.

e. For women of childbearing potential only. A serum pregnancy test will be performed at baseline. A urine or serum pregnancy test will then be repeated on Day 1 of each cycle prior to study drug administration, at the EOT and post-treatment follow-up visit till 6 months after the last dose of study treatment administration.

f. Not required for Cycle 1 if the assessments performed within 7 days, except for body weight, which should be measured on Day 1 of each cycle.

g. Hematology tests should be collected at the following timepoints: Screening, Cycle 1 Day 1, Cycle 1 Day 8, Cycle 1 Day 15 and Day 1 of each subsequent cycle.

h. Hematology and biochemistry tests may be collected or conducted locally up to 1 day prior to dosing. Local laboratory results must be reviewed prior to study drug administration in order to determine whether to proceed with dosing or whether dose modification is required.

i. Clinical laboratory tests at screening and on Cycle 1 Day 8 are to be performed after the participant has been fasting in order to ensure accurate interpretation of lab values such as glucose values. Fasting status will be recorded in source documents. Fasting is not necessary for laboratory tests performed at all other visits. Lipid panel (total cholesterol, LDL, HDL, and triglyceride) is only required at Screening.

j. Prior to performing 12-lead ECGs, participants should rest in supine position (or semi-recumbent, if supine is not tolerated) for 10 minutes. ECGs will be read and assessed locally.

Footnotes continued on next page

k. Repeated as clinically indicated throughout the study. Complete eye exam is required at baseline. This consists of visual acuity (VA), best corrected visual acuity (BCVA), inter ocular pressure (IOP), extra ocular movement (EOM), pupils, external exam, slit lamp exam, and dilated fundoscopic exam. Eye exams performed during the study where clinically indicated will be at the ophthalmologist's discretion. Eye exams at EOT are required for participants who experience ocular AEs during the study and this at minimum must include VA, BCVA, and slit lamp exam.

l. Include all medications taken within 28 days prior to inform consent and up until the 30-day safety follow up visit will be collected.

m. AEs will be collected from the time of informed consent through 30 days following the last dose of study treatment or until initiation of a new anticancer treatment, whichever occurs first.

n. At least 7 days must elapse between doses of enfortumab vedotin. Participants should be observed during enfortumab vedotin administration and for at least 60 minutes following the infusion for the first 3 cycles.

o. If contrast is contraindicated, see [Section 7.1 Efficacy Assessments] and [Section 10.9 Appendix 9: Scanning and Contrast Guidelines].

p. Responses will be confirmed with repeat scans at least 4 weeks after first documentation of response. Following confirmation scans, response assessments should continue with the previous scan schedule (i.e., the schedule should not be adjusted). Tumor imaging should also be performed whenever disease progression is suspected.

q. Response assessment will be performed every 8 weeks (± 1 week). After 1 year from the start of treatment, response assessments will be reduced to every 12 weeks (± 1 week). The schedule of response assessments should not be adjusted for dose delays/interruptions or other reasons for changes in the timing of a participant's study activities; timepoints for response assessments should be calculated from Cycle 1 Day 1 during treatment.

r. Participants who discontinue study treatment for reasons other than objective disease progression by RECIST V 1.1 will continue to have response assessments every 8 weeks (± 1 week) following the previous visit thereafter. After 1 year from the start of treatment, the frequency of response assessments will be reduced to every 12 weeks (± 1 week). The tumor assessments will continue until the participant has radiological disease progression per RECIST V 1.1 as determined by investigator assessment, initiates a new anticancer therapy, death, lost to follow-up, study closure, or withdrawal of consent, whichever comes first.

s. Contact participant for survival status and collection of subsequent anticancer treatment information every 12 weeks (± 1 week) (calculation from disease progression) until death, study closure, or withdrawal of consent from study, or participant is lost to follow-up, whichever occurs first. Phone contact with participant is sufficient.

1.3.1 Sample Collection Schedule

Table 2 Pharmacokinetic Sample Collection Time Points (PK Cohort)

Cycle	Day	Time Point	Collection Window
Cycle 1	1	Predose	Predose
		EOI	Within 15 min after EOI
		2 hr (Day 1)	± 15 min
		4 hr (Day 1)	± 15 min
	2	24 hr (Day 1)	± 4 hr
	3	48 hr (Day 1)	± 4 hr
	4	72 hr (Day 1)	± 4 hr
	8	Predose	Within 2 hr prior to dosing
		EOI	Within 15 min after EOI
	15	Predose	Within 2 hr prior to dosing
		EOI	Within 15 min after EOI
		2 hr (Day 15)	± 15 min
		4 hr (Day 15)	± 15 min
	16	24 hr (Day 15)	± 4 hr
	17	48 hr (Day 15)	± 4 hr
	18	72 hr (Day 15)	± 4 hr
	22	168 hr (Day 15)	± 4 hr
Cycle 2	1	Predose	Within 2 hr prior to dosing
		EOI	Within 15 min after EOI
Cycle 3	1	Predose	Within 2 hr prior to dosing
Cycle 4	1	Predose	Within 2 hr prior to dosing
Cycles 6, 8 and 10	1	Predose	Within 2 hr prior to dosing
End of Treatment		within 30–37 days of last dose	

EOI: end of infusion.

In general, the time points relative to the start of infusion, except for EOI relative to end of infusion in each corresponding cycle and day.

Table 3 Schedule and Acceptable Time Range for PK Sampling (Non-PK Cohort)

Visit		**Time**	**Window**
Cycle 1	Day 1	EOI	Within 15 min
	Day 8	Pre-dose	Within 24 hr
		EOI	Within 15 min
	Day 15	Pre-dose	Within 24 hr
		EOI	Within 15 min
Cycles 2, 4, 6, 8 and 10	Day 1	Pre-dose	Within 24 hr
End of Treatment		within 30–37 days of last dose	

EOI: end of infusion.

In general, the time points relative to the start of infusion, except for EOI relative to end of infusion in each corresponding cycle and day.

Table 4 Schedule for ATA Sampling

Visit		**Time**	**Window**
Cycle 1	Day 1	Predose	Within 24 hr
Cycle 2	Day 1	Predose	Within 24 hr
Cycle 3	Day 1	Predose	Within 24 hr
Cycle 4	Day 1	Predose	Within 24 hr
Cycles 6, 8 and 10	Day 1	Predose	Within 24 hr
End of Treatment		within 30–37 days of last dose	

ATA: antitherapeutic antibodies.

In general, the time points relative to the start of infusion.

2 INTRODUCTION

Urothelial cancer (UC) kills approximately 200,000 patients annually and is the eleventh most common cancer overall worldwide [Ferlay et al, 2018]. Enfortumab vedotin targets the cell adhesion protein Nectin-4. Nectin-4 is a type I transmembrane protein and member of a family of related immunoglobulin-like adhesion molecules implicated in cell-to-cell adhesion. Nectin-facilitated adhesion supports several biological processes, such as immune modulation, host-pathogen interaction, and immune evasion [Sakisaka et al, 2007]. Nectin-4 is highly expressed in cancer cells, particularly in urothelial cancers, breast cancer, non-small cell lung cancer (NSCLC), and other epithelial tumors, with moderate expression observed in normal human skin [Deng et al, 2019; Zhang, Chen et al, 2018; Takano et al, 2009; Fabre-Lafay et al, 2007].

Enfortumab vedotin (previously known as ASG-22CE) is a novel, fully humanized, monoclonal antibody-drug conjugate (ADC) that delivers a microtubule-disrupting agent, monomethyl auristatin E (MMAE), to cells expressing Nectin-4 [Sakisaka et al, 2007]. Enfortumab vedotin selectively binds to Nectin-4-expressing cells, initiating internalization of the ADC-Nectin-4 complex and proteolytic cleavage of the conjugated MMAE, disrupting microtubule networks and resulting in apoptotic cell death. Targeting tumors with enfortumab vedotin, which targets Nectin-4, could provide a novel approach to the treatment of certain cancers such as urothelial, lung, breast, head and neck, gastric, and esophageal cancers [Challita-Eid et al, 2016; Zhang, Zhang et al, 2018].

Enfortumab vedotin has shown activity and was approved by United States (US) Food and Drug Administration (FDA) for the treatment of adult patients with locally advanced (LA) or metastatic urothelial cancer (mUC) who have previously received a programmed cell death protein-1 (PD-1)/programmed death ligand-1 (PD-L1) inhibitor, and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, LA or metastatic setting in Dec 2019 [PADCEV™ Prescribing Information, Dec 2019].

2.1 Study Rationale

Enfortumab vedotin will be administered monotherapy at a dose of 1.25 mg/kg as an IV on Days 1, 8 and 15 of each 28-day cycle. This dose and regimen has demonstrated an acceptable safety profile and encouraging clinical activity in the Phase 1 and 2 studies in patients with urothelial cancer (Studies AGS-22M6E-11-1, EV-101, EV-102, EV-201 and EV-103).

This study is designed to assess the safety, tolerability, pharmacokinetics as well as the efficacy of enfortumab vedotin monotherapy in Chinese participants with LA or mUC. In addition, as a bridging study to global pivotal phase 2 and phase 3 studies EV-201 and EV-301, to demonstrate efficacy and safety in the Chinese population are consistent with non-Chinese population. As enfortumab vedotin has not previously been explored in the Chinese population, the other primary objective of the study is to demonstrate ethnic consistency of enfortumab vedotin monotherapy between the Chinese and non-Chinese populations through PK parameter analysis. No differences are anticipated for enfortumab vedotin based on ethnicity from the Phase 1 and 2 studies in enfortumab vedotin monotherapy up to date.

2.2 Background

A detailed description of the chemistry, pharmacology, efficacy and safety of enfortumab vedotin is provided in the Investigator's Brochure.

2.2.1 Disease and Nectin-4 Antigen Target

The International Agency for Research on Cancer has reported that urothelial cancer (UC) kills approximately 200,000 patients annually and is the 11th most common cancer worldwide [Ferlay et al, 2018]. In China, there were 82,270 new bladder cancer cases and 38,208 deaths due to bladder cancer according to The International Agency for Research on Cancer database [Ferlay et al, 2018]. First-line (1L) therapy for LA or mUC consists of cisplatin-based combinations, such as methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) and gemcitabine plus cisplatin in patients eligible for these therapies [Bellmunt et al, 2014]. In China, platinum-based first-line chemotherapies are recommended by Chinese guidelines for diagnosis and treatment of urothelial carcinoma of bladder [National Health Commission of the People's Republic of China, 2019] and are commonly used in clinical practice, similar to global standards. The reported initial response rates chemotherapy regimen in first line were approximately 50% to 70%. However, few patients have durable responses, and patients become resistant to the initial treatment. In the US and Europe, 2 PD-1/PD-L1 inhibitors (atezolizumab and pembrolizumab) are approved for treatment of cisplatin-ineligible UC patients in the front-line setting. These approvals were based on open-label, single-arm studies that showed objective response rates (ORRs) of 24% and 29%, respectively [Keytruda® Prescribing Information 2020; Tecentriq® Prescribing Information 2020]. Of note, in 2018, prescribing information for pembrolizumab and atezolizumab monotherapy in the front-line setting was revised to restrict usage to cisplatin-ineligible patients with high PD-L1 expression (present in approximately one-third of the 1L mUC population). In addition, these PD-1/PD-L1 inhibitors, both in combination regimens or monotherapy, are not currently approved in China for 1L mUC.

For second-line (2L) therapy, several PD-1/PD-L1 inhibitors such as nivolumab (PD-1 inhibitor), atezolizumab, durvalumab and avelumab (PD-L1 inhibitors) have been approved in different countries for the treatment of patients with LA or mUC that have progressed during or after platinum-containing chemotherapy. However, up-to-date there is current one PD-1 inhibitor tislelizumab approved in China, in patients with LA/mUC with PD-L1 high expression whose disease progressed during or following platinum-containing chemotherapy. The National Medical Products Administration (NMPA) approval was based on a single-arm, multi-center pivotal trial of tislelizumab showing ORR 24.8% and complete response (CR) rate 9.9%. For UC patients previously treated with a platinum-based chemotherapy and no accepted standard of care exists, although single-agent taxanes such as paclitaxel are commonly used following platinum therapies. However, the single-agent chemotherapy response rates were around 10% in the second line setting and have not demonstrated a survival advantage [McCaffrey et al, 1997, Vaughn et al, 2002].

In conclusion, novel agents are needed to treat patients with LA or mUC, especially whose disease progressed during or following platinum-containing chemotherapy and PD-1/PD-L1 inhibitor in China.

Nectin-4 is a type I transmembrane protein and member of a family of related immunoglobulin-like adhesion molecules implicated in cell-to-cell adhesion. Nectin-4 is highly expressed in cancer cells, particularly in urothelial cancers, breast cancer, non-small cell lung cancer (NSCLC), and other epithelial tumors, with moderate expression observed in normal human skin [Deng et al, 2019; Zhang, Chen et al, 2018; Takano et al, 2009; Fabre-Lafay et al, 2007].

The expression pattern and levels of Nectin-4 on tumors suggest that it would be an attractive target for ADC therapy in several solid tumors including UC. The aim of using ADCs in cancer therapy is to improve the therapeutic index of cytotoxic agents and minimize exposure to normal tissue.

2.2.2 Enfortumab Vedotin

Enfortumab vedotin (previously known as ASG-22CE) targets the cell adhesion protein Nectin-4. Enfortumab vedotin is a novel, fully humanized, monoclonal ADC that delivers a microtubule-disrupting agent, MMAE, to cells expressing Nectin-4 [Sakisaka et al, 2007]. Enfortumab vedotin selectively binds to Nectin-4-expressing cells, initiating internalization of the ADC-Nectin-4 complex and proteolytic cleavage of the conjugated MMAE, disrupting microtubule networks and resulting in apoptotic cell death.

Data from preclinical studies of brentuximab vedotin (a CD30-directed ADC comprising the same linker and MMAE payload as enfortumab vedotin), shows potential to induce immunogenic cell death (ICD), antigen presentation, and tumor immune infiltration [Gardai et al, 2015]. These results suggest that the effects are due to MMAE. Treatment with brentuximab vedotin in vitro and in preclinical models has been shown to induce hallmarks of ICD. ICD is characterized by induction of the endoplasmic reticulum stress response and subsequent surface presentation of danger-associated molecular patterns immune stimulatory molecules. These danger-associated molecular patterns induce innate immune migration and activation into the tumor cell activation [Cao et al, 2018; Cao et al, 2017].

Enfortumab vedotin has shown activity and was approved by FDA in Dec 2019 for the treatment of adult patients with LA or mUC who have previously received PD-1/PD-L1 inhibitor therapy, and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, LA or metastatic setting.

2.2.3 Nonclinical Data

2.2.3.1 ASG-22CE Nonclinical Pharmacology

ASG-22CE is the final product (enfortumab vedotin) used for clinical development and is derived from a Chinese hamster ovary (CHO) cell line, while AGS-22M6E is derived from a murine hybridoma cell line and was used in the pharmacology and toxicology studies, as well as in a completed Phase I study. These 2 molecules have identical amino acid sequences and have comparable pharmacological characteristics, such as binding affinity to Nectin-4, in vitro cytotoxicity and in vivo antitumor activity (RD12-001, RD12-002, RD12-003, RD12-004).

AGS-22M6E specifically binds to human Nectin-4 with high affinity and cross-reacts with cynomolgus monkey and rat orthologs of Nectin-4 (RD10-013, RD10-018).

AGS-22M6E does not cross-react with other Nectin family members, such as Nectin-1, -2, and -3 (RD10-015).

In *in vitro* pharmacology studies, AGS-22M6E inhibited cell survival in a cell line engineered to express human Nectin-4, as well as in a human breast carcinoma cell line endogenously positive for Nectin-4 (RD10-017). It was observed that AGS-22M6E was internalized after binding to Nectin-4 on the surface of cells (ES10-006). Intracellular release of MMAE by proteolytic cleavage induced cell death.

Antitumor activity of AGS-22M6E was evaluated in a panel of tumor xenograft models representing various cancer indications in which expression of Nectin-4 has been demonstrated. AGS-22M6E significantly inhibited the tumor growth in a xenograft model of human bladder cancer (RD10-009), as well as in xenograft models of other cancer indications such as breast, pancreatic and lung cancers (RD10-010, RD10-011, RD10-019).

2.2.3.2 ASG-22CE Nonclinical Immunogenicity and Pharmacokinetics

Toxicokinetics, immunogenicity and comparability of AGS-22M6E and AGS-22C3E bulk drug substance were evaluated in a 4-week study comparing AGS-22M6E and AGS-22C3E administered by intravenous (IV) infusion in cynomolgus monkeys with a 6-week recovery period (Charles River Laboratories [CRL] Study No. 20021751).

Maximum serum concentrations of ADC and total antibody (TAb) for both ADCs were attained at the end of the IV infusion and showed a bi-exponential decline thereafter. There were no sex-related differences observed in the toxicokinetic characteristics for ADC, TAb and small molecule metabolite for both ADCs.

Maximum concentration (C_{max}) of MMAE metabolite for both ADCs was attained between 24 - 72 hours post dose injection. The elimination half-life ($t_{1/2}$) for ADC, TAb and MMAE after administration of AGS-22M6E and AGS-22C3E (the CHO cell line-derived product) were calculated as follows; 1.70 and 1.53 days for ADC, 3.23 and 2.09 days for TAb and 4.31 days and 3.54 days for MMAE, respectively.

Overall incidences of seroconversion were 40% for both AGS-22M6E and AGS-22C3E dosed groups.

Exposure of AGS-22M6E and AGS-22C3E based on area under the concentration-time curve from time 0 to 7 days (AUC_{0-7d}) and C_{max} after first dose of AGS-22M6E and AGS-22C3E were within the pre-specified comparability criteria, and therefore, the toxicokinetics of the two materials, AGS-22M6E and AGS-22C3E were considered to be comparable.

2.2.3.3 ASG-22CE Nonclinical Toxicology

In a 4-week Good Laboratory Practice (GLP) toxicity study in rats (CRL Study No. 20005662), AGS-22M6E (ADC: 2, 5 and 10 mg/kg) and AGS-22M6 (unconjugated antibody: 10 mg/kg) were intravenously administered once every week for a total of 4 doses. One animal administered AGS-22M6E at 10 mg/kg was noted with severe abrasions and had loss of body weight, and was found dead on Day 27. AGS-22M6E-related changes mainly included skin abrasion at 5 mg/kg and 10 mg/kg, decreased body weight gain and food consumption at 10 mg/kg. Decreased indicators of red cell mass (red

blood cell, hemoglobin concentration and hematocrit) and increased reticulocyte count at 5 and 10 mg/kg, were also observed. Increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) levels at 5 and 10 mg/kg, decreased testis weight with histopathological changes (tubular epithelial degeneration) and epididymides (hypospermia/abnormal spermatids in the ducts) were observed at all dose levels. Femur bone marrow hypocellularity, and skin ulceration and/or epidermal inflammation were seen at 5 and 10 mg/kg dosing. After the 6-week recovery period, the testicular and epididymal findings were more severe. Bone marrow hypocellularity and skin ulcers/inflammation resolved in the recovery animals. There were no adverse AGS-22M6-related findings. A no observed adverse effect level (NOAEL) following administration of AGS- 22M6E for four weekly IV injections in rats was not established due to the findings noted in the testis.

In a 4-week GLP toxicity study in cynomolgus monkeys (CRL Study No. 20005664), AGS-22M6E (1, 3 and 6 mg/kg) and AGS-22M6 (6 mg/kg) were administered by IV infusion once weekly for a total of 4 doses. Administration of AGS-22M6E at 1 and 3 mg/kg was generally well tolerated, however doses of 6 mg/kg led to the unscheduled euthanasia of 3 animals on Days 11 to 13 due to severe dry skin/reddened skin and abrasions. These findings are considered a target-related effect based on the known expression of Nectin-4 in the epidermis of the skin. AGS-22M6E-related findings mainly included dry/reddened areas on the skin at all dose groups with ulceration, inflammation and hyperkeratosis in the skin at doses 3 mg/kg or more. Bone marrow suppression associated with MMAE toxicity included decreased reticulocyte count and red cell parameters, increased platelet counts, decreased neutrophils, eosinophils, and leukocyte counts at doses 3 mg/kg or more. All changes noted showed reversibility after a 6-week non-treatment period. There were no adverse AGS-22M6-related findings. The NOAEL for once weekly administration of AGS-22M6E in cynomolgus monkeys was considered to be 3 mg/kg/day.

A 4-week GLP bridging study in cynomolgus monkeys (CRL Study No. 20021751) was conducted to evaluate comparability of the hybridoma cell line-derived product (AGS-22M6E) and the CHO cell line- derived product (AGS-22C3E) when given at the same dose of 3 mg/kg/week. Administration of AGS-22M6E and AGS-22C3E by IV infusion for 4 doses over 4 weeks was well tolerated. Test article-related effects included dry skin, reddened areas of skin, decreased erythrocyte mass, reticulocytes, neutrophils and eosinophil counts, microscopic findings in bone marrow, injection site, and skin. These findings were noted in both AGS-22M6E and AGS-22C3E-dosed animals.

All test article-related effects identified in both AGS-22M6E and AGS-22C3E-dosed animals were at similar incidence and severity. After a 6-week non-treatment period, all test article-related effects returned to normal. The data support the conclusion that AGS-22M6E and AGS-22C3E demonstrate comparable toxicity profiles and toxicokinetic characteristics, when given at the same 3 mg/kg dose by IV infusion once weekly for 4 weeks to cynomolgus monkeys.

In genotoxic studies performed with other investigational compounds containing MMAE (Adcetris package insert [PI]) the MMAE was found to be genotoxic in the rat bone marrow micronucleus assay through an aneugenic mechanism. This effect is consistent

with the pharmacological effect of MMAE as a microtubule disrupting agent. MMAE was not mutagenic in the bacterial reverse mutation assay (Ames test) or mouse lymphoma assay [Adcetris PI]. Maleimide, which is a component of linker is reported to be mutagenic in Ames test and mouse lymphoma assay.

2.2.4 Clinical Data

Enfortumab vedotin is currently being tested in multiple studies including Phase 1, 2, and 3 studies, both as monotherapy and in combination with several anticancer therapies. Much of the safety and efficacy data summarized below are from monotherapy data and limited to Phase 1 and 2 studies.

EV-101 is a phase 1 study evaluating the safety and pharmacokinetics of escalating doses of enfortumab vedotin that enrolled patients with Nectin-4-expressing solid tumors (e.g., mUC, NSCLC and ovarian cancer), who progressed on ≥1 prior chemotherapy regimen, including a cohort of patients with mUC who received prior anti-PD-(L)1 therapy. Patients received escalating doses of enfortumab vedotin up to 1.25 mg/kg on Days 1, 8 and 15 of every 28-day cycle. Primary objectives were evaluation of safety/tolerability and pharmacokinetics; antitumor activity was a secondary objective. The maximum tolerated dose (MTD) was not established; however, the recommended phase 2 dose was identified as 1.25 mg/kg. Overall (data cutoff date: 27 Dec 2019), 17 of 18 (94.4%) participants with NSCLC who received at least 1 infusion of enfortumab vedotin reported at least 1 TEAE. Of these, 9 (50.0%) participants had serious TEAEs and 1 participant had a TEAE leading to death that was not considered to be drug-related. The most common TEAE in this population was nausea and the most common drug-related TEAE was alopecia. Six (33.3%) participants discontinued treatment due to one of the following TEAEs, occurring in 1 participant each: fatigue, acute respiratory failure, dyspnea, dyspnea exertional, hypoxia and rash maculopapular.

All 16 participants with OC who received at least 1 infusion of enfortumab vedotin reported at least 1 TEAE. Of these, 5 (31.3%) participants had serious TEAEs and 2 participants (12.5%) had a TEAE leading to death that was not considered to be drug-related. The most common TEAE in this population was fatigue (68.8% of participants), which was also the most common drug-related TEAE (62.5% of participants). Four (25.0%) participants discontinued treatment due to one of the following TEAEs, occurring in 1 participant each: malignant bowel obstruction, swelling, delirium and pulmonary embolism.

All 18 participants with metastatic UC and renal insufficiency who received at least 1 infusion of enfortumab vedotin reported at least 1 TEAE. Of these, 10 (55.6%) participants had serious TEAEs. No participant had a TEAE leading to death. The most common TEAE in this population was fatigue (77.8% of participants), and the most common drug-related TEAEs were alopecia and fatigue (61.1% of participants each). Decreased appetite and cerebrovascular accident led to discontinuation of study drug in 1 (5.6%) participant each.

Single agent enfortumab vedotin was generally well tolerated and responses were observed at all does levels tested but were numerically higher at a dose of 1.25 mg/kg on Days 1, 8 and 15 of each 28-day cycle. Enfortumab vedotin provided durable responses and meaningful survival results in patients after anti-PD-(L)-1 therapy in a population

with a high unmet medical need. The confirmed ORR by central review was 45% in patients with urothelial cancer [Rosenberg et al, 2019]. The median OS of 12.3 months is encouraging given the historical median OS is ≤ 10.3 months [Bellmunt et al, 2017].

EV-201 is an ongoing global, phase 2, single-arm, 2-cohort study of enfortumab vedotin (1.25 mg/kg intravenously on Days 1, 8, and 15 of every 28-day cycle) that enrolled patients with LA or mUC previously treated with anti-PD-1/L1 therapy. This study contains 2 cohorts. Cohort 1 consisted of 125 treated participants who had previously received a platinum-containing chemotherapy in the LA or metastatic setting, while Cohort 2 consisted of 27 treated participants who had not and were ineligible for cisplatin-containing therapy at the time of enrollment. Results were consistent with EV-101, for Cohort 1, enfortumab vedotin treatment led to a 44% ORR including a 12% CR rate and a 11.7-month median overall survival (OS) in addition to a 7.6-month duration of response (DOR) [Petrylak et al, 2019]. For Cohort 2, of those patients who have had a postbaseline assessment or discontinued from the study without undergoing a response assessment (i.e., Efficacy Evaluable Set), the ORR per independent review committee (IRC) assessment was 41% (9 of 22 patients) (95% CI: 20.7%, 63.6%), similar to the 44% ORR for Cohort 1. Additional initial responses are pending confirmation. The data cutoff date for the Cohort 1 primary analysis does not provide sufficient follow-up for the response duration in Cohort 2. The range of response duration among the 9 responders is 1.02 to 5.85+ months. Five of the 9 responders (56%) were censored with ongoing response.

Adverse events (AEs) in Cohort 1 (n = 125) were consistent with those previously reported in the enfortumab vedotin clinical development program. The most common TEAEs of any grade in Cohort 1 were fatigue, decreased appetite, alopecia, nausea, peripheral sensory neuropath, diarrhea and dysgeusia. The Grade 3 or higher TEAEs reported in > 5% of participants included anemia (14%), neutropenia (9%), hyperglycemia (7%), and fatigue and hyponatremia (6% each). The incidence of TEAEs leading to withdrawal of treatment was 16%, with peripheral sensory neuropathy as the most common reason for treatment withdrawal (6%). Seven participants (6%) died due to TEAEs; none of these deaths were considered treatment-related.

One participant died of interstitial lung disease that was considered related to study treatment; the event did not meet the definition of a TEAE because it occurred > 30 days after the last dose of enfortumab vedotin. This case was confounded by high dose steroid use and suspected pneumocystis jiroveci pneumonia.

In Cohort 2 (n = 27), AEs were consistent with those in Cohort 1 and as previously reported in the enfortumab vedotin clinical development program. The most common TEAEs of any grade in Cohort 2 were alopecia, anemia and fatigue, dry eye and edema peripheral. The incidence of Grade 3 or higher TEAEs was 67% and the most common ≥ Grade 3 TEAE was neutropenia (15%). SAEs were reported for 8 participants (30%); the most common were acute kidney injury (AKI) and diarrhea in 2 participants each (7%). The incidence of TEAEs leading to withdrawal of treatment was 19%; 2 participants (7%) withdrew due to acute kidney disease. There were no other AEs leading to withdrawal of treatment reported for more than 1 participant. As of the data cutoff date, 2 participants (7%) had died due to TEAEs (1 event of sepsis and 1 event of AKI).

Neither event was considered treatment-related. Enfortumab vedotin was tolerable with a manageable safety profile that was similar in both cohorts.

EV-102 is a phase 1 study evaluating safety and pharmacokinetics of enfortumab vedotin enrolling Japanese patients with LA/mUC treated with prior chemotherapy, or ineligible for cisplatin. Patients were randomized 1:1 to receive 1.0 mg/kg (arm A) or 1.25 mg/kg (arm B) enfortumab vedotin on days 1, 8 and 15 of each 28-day cycle. Seventeen patients (n = 9, arm A; n = 8, arm B) received treatment. Enfortumab vedotin was well tolerated across both doses. ORR was 35%, the antitumor activity, safety and pharmacokinetic profile were consistent with prior reports from non-Japanese patients [Takahashi et al, 2019]. The most common TEAEs in total were anemia, dysgeusia and alopecia. The most common drug-related TEAEs were dysgeusia and alopecia. Overall, 7 of 17 (41.2%) participants experienced serious TEAEs and 1 participant on 1.25 mg/kg experienced a TEAE leading to death, which was considered unrelated to the study drug. Overall, 8 (47.1%) participants had a grade 3 or above drug-related TEAE. No grade 3 or above study drug-related TEAEs were reported in more than 1 participant, with the exception of anemia and hypertension, which were reported in 2 (11.8%) participants each. Overall, the safety profile was consistent with what had been observed in other enfortumab vedotin studies and found to be manageable and tolerable.

Pharmacokinetic analyses showed that the mean exposures of enfortumab vedotin after IV infusion generally increased with increasing dose levels. In Study AGS-22M6E-11-1, a median terminal $t_{1/2}$ estimate of 2.39 days for ADC was determined in participants who received enfortumab vedotin at the 1.2 mg/kg dose level. When comparing results from Study EV-101 to results from Study EV-102, no apparent differences in exposure were observed between Japanese and North American participants.

The safety profile of enfortumab vedotin monotherapy consists of the identified risks of peripheral neuropathy, rash, extravasation site reactions, nausea, vomiting and diarrhea, considered also AE of interest (AEOI). Rash events are anticipated on-target events, as Nectin-4 is expressed in the skin. The safety and efficacy profile are consistent across all monotherapy studies (EV-101, EV-201, and EV-102), demonstrating that treatment with enfortumab vedotin as a single agent is manageable, tolerable and effective.

In addition, EV-301 is an ongoing Phase 3, multinational, open-label, randomized study to evaluate the efficacy and safety of enfortumab vedotin compared to chemotherapy in participants with LA or mUC who have received a platinum-containing chemotherapy and have experienced disease progression or relapse during or following treatment with PD-1/PD-L1 inhibitor therapy. The study completed the enrollment in January 2020 and is under study follow-up duration. Given its primary endpoint of OS, EV-301 will demonstrate whether enfortumab vedotin has a life prolong superiority compared to single agent chemotherapy in late line LA/mUC participants, and in a position of supporting enfortumab vedotin global registration in late line LA/mUC setting.

2.3 Risk/Benefit Assessment

2.3.1 Risk Assessment

The safety profile of enfortumab vedotin monotherapy consists of the known risks of peripheral neuropathy, rash, extravasation site reactions, nausea, vomiting, diarrhea,

hyperglycemia, and ocular toxicities, which are considered AEOI. Rash events are anticipated on-target events, as Nectin-4 is expressed in the skin.

Evidence of clinical activity in LA or metastatic UC has been observed in other single-arm studies of enfortumab vedotin. This may translate into an improvement in outcome for the population setting selected for this trial in a same tumor type. However, evaluation of clinical benefit is ongoing in the existing clinical studies. Final results are pending.

2.3.2 Benefit Assessment

Participants with selected for this study have LA or mUC that at least recurred or progressed following standard of care therapy in first line and have limited treatment options, especially for Chinese patients as there is only one PD-1 inhibitor (tislelizumab) approved in China to date, for patients with PD-L1 highly expressing LA/mUC whose disease progressed following or during platinum-based chemotherapy, without more options of PD-1/PD-L1 inhibitors. Enfortumab vedotin has been approved in US in Dec 2019 in LA or mUC patients who was heavily pretreated based on EV-201 study Cohort 1 results.

In addition, the safety and efficacy profiles are consistent across all monotherapy studies (EV-101, EV-201, and EV-102), demonstrating that treatment with enfortumab vedotin as a single agent is manageable, tolerable and effective in LA or mUC.

2.3.3 Overall Risk-Benefit Conclusion

Based on comprehensive evaluation and analysis of cumulative safety data and review of safety risks reported with ADC medications or other medications in the same therapeutic category, the important potential/identified risks posed by enfortumab vedotin treatment may be gastrointestinal toxicity, skin toxicity, visual/ocular toxicity, anaphylaxis or anaphylactoid signs, hyperglycemia, peripheral neuropathy and infusion-related reactions. Strict adherence to the eligibility criteria and safety assessments and close monitoring are essential to assure the safety of participants in this study.

The activity/efficacy data from the clinical studies for enfortumab vedotin, together with acceptable safety, support a favorable benefit-risk assessment for enfortumab vedotin monotherapy in treatment of patients with LA or mUC.

3 OBJECTIVES, ENDPOINTS AND ESTIMANDS

The primary and secondary objectives and endpoints for this study are listed in [Table 5].

Table 5 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• 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)	• Confirmed ORR per RECIST V1.1 by IRC
Table continued on next page	

Objectives	Endpoints
• To assess the PK of antibody-drug conjugate (ADC), total antibody (TAb) and monomethyl auristatin E (MMAE) in Chinese participants with locally advanced or metastatic urothelial cancer.	• PK variables: Selected PK parameters of ADC, TAb and MMAE are as follows: • Maximum observed concentrations (C_{max}) • Trough concentration (C_{trough}) • Time to maximum concentration (T_{max}) • Area under concentration-time curve from 0 to day 7 (AUC_{0-7d}) • Area under concentration-time curve from 0 to day 28 (AUC_{0-28d}) • Accumulation ratio of C_{max} ($R_{ac}[C_{max}]$) • Accumulation ratio of AUC_{0-7d} ($R_{ac}[AUC_{0-7d}]$) • Terminal or apparent terminal half-life ($t_{1/2}$) as appropriate • Systemic clearance (CL) and volume of distribution at steady state (V_{ss}) as appropriate
Secondary	
• To assess confirmed ORR per investigator assessment	• Confirmed ORR per RECIST V1.1 per investigator assessment
• To assess duration of response (DOR)	• DOR per RECIST V1.1 per IRC and per investigator assessment
• To assess disease control rate (DCR)	• DCR per RECIST V1.1 per IRC and per investigator assessment
• To assess progression-free survival (PFS)	• PFS per RECIST V1.1 per IRC and per investigator assessment
• To assess overall survival (OS)	• OS
• To assess the immunogenicity as defined by the incidence of antitherapeutic antibodies (ATA)	• Incidence of ATA to ADC
• To assess the safety and tolerability of enfortumab vedotin in Chinese participants with locally advanced or metastatic urothelial cancer.	• Safety variables: • Adverse events (AEs) • Laboratory tests • Vital sign measurements • 12-lead electrocardiogram (ECG) • Eastern Cooperative Oncology Group (ECOG) performance status

ADC: antibody-drug conjugate; AE: adverse event; ATA: antitherapeutic antibodies; 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; CL: clearance; C_{max}: maximum concentration; C_{trough}: trough concentration; DCR: disease control rate; DOR: duration of response; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EV: enfortumab vedotin; IRC: independent review committee; MMAE: monomethyl auristatin E; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PK: pharmacokinetic; R_{ac}(AUC): accumulation ratio calculated using AUC; $R_{ac}(C_{max})$: accumulation ratio calculated using C_{max}; $t_{1/2}$: terminal half-life; TAb: total antibody; t_{max}: time of maximum concentration; V_{ss}: volume of distribution at steady state.

Estimands

Not Applicable.

4 STUDY DESIGN AND DOSE RATIONALE

4.1 Overall 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 LA or 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 PK Chinese participants in the PK Cohort.

All participants will receive enfortumab vedotin at 1.25 mg/kg dose level administered as an IV infusion on Days 1, 8 and 15 of every 4-week (28 days) cycle. Participants will continue on study treatment until one or more of the following discontinuation criteria are met:

- Participant requests to stop treatment.
- Investigator decides it is in the participant's best interest to discontinue.
- Participant develops documented radiological disease progression per Response Evaluation Criteria in Solid Tumor (RECIST) V1.1 by investigator assessment.
- Participant starts a new anticancer therapy.
- Participant develops unacceptable toxicity.
- Female participant becomes pregnant.
- Participant is noncompliant with the protocol based on the investigator or medical monitor assessment.
- Participant did not receive study drug continuously for > 2 cycles (i.e., > 6 consecutive doses not received). Medical Monitor consultation is required after the participant was unable to receive one full cycle of study drug administration (i.e., 3 consecutive doses). Dose delays for patients who are responding to treatment may be extended beyond 8 weeks in consultation with Medical Monitor, if the patient's toxicity does not otherwise require permanent discontinuation.

The participants who discontinue study treatment for reasons other than objective disease progression per RECIST V1.1 will be followed every 8 weeks (± 1 week) for response assessments. After 1 year from the start of treatment, the frequency of response assessments will be reduced to every 12 weeks (± 1 week). The tumor assessments will continue until the participant has radiological disease progression per RECIST V 1.1 as determined by investigator assessment, initiates a new anticancer therapy, dies, withdraws study consent, or the study closes, whichever comes first. All participants are to be followed for survival status and subsequent anticancer therapy until death, lost to follow-up, withdrawal of consent from study, or study closure, whichever occurs first. The study will be closed approximately 2 years after last participant enrollment or no participants remain in long-term follow-up, whichever occurs first. A provision of drug supply to the participants who are still benefiting from treatment will be prepared prior to study closure. Additionally, the sponsor may terminate the study at any time.

One to 2 study centers will be designated as a "pharmacokinetic cohort site". Approximately 12 participants enrolled in the PK cohort will have intense PK samples collected after single and repeated doses. The other participants enrolled at non-PK cohort sites will have sparse PK samples collected. Additional participants may be enrolled in the PK cohort to compensate for participants who become unevaluable for the PK relevant

primary endpoint (PK evaluable).

Blood samples for pharmacokinetics and antitherapeutic antibodies (ATA) will be collected at time points specified in the [Table 1 Schedule of Assessments]. Validated assays will be used to measure the concentrations of ADC, TAb and MMAE in serum or plasma and to assess ATA.

After treatment discontinuation, participant will have an end of treatment (EOT) visit for a 30-day Safety Follow-up.

Safety data will be monitored closely throughout the study per the Sponsor relevant study monitoring plan.

The screening/baseline period will take place up to 28 days prior to the first dose of study treatment. In the treatment period, starting at cycle 1, participants will receive enfortumab vedotin on days 1, 8, and 15 every 28-day cycle until one of the treatment discontinuation criteria are met.

4.2 Scientific Rationale for Study Design

This is an open label, single-arm study designed to assess the safety, efficacy and pharmacokinetics of enfortumab vedotin monotherapy in Chinese participants with LA or mUC.

One of the primary endpoints is confirmed ORR (cORR) as an efficacy endpoint to explore enfortumab vedotin monotherapy's efficacy in the Chinese population, and demonstrate the consistent efficacy trend between the Chinese population and non-Chinese population. cORR is a surrogate endpoint accepted by health authorities in late line LA/mUC patients. In addition, as a primary endpoint in global pivotal Phase 2 EV-201 study and according to the Cohort 1 data, enfortumab vedotin received accelerated approval by US FDA in Dec 2019 for the treatment of adult patients with LA or mUC who have previously received a PD-1 or PD-L1 inhibitor and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, LA or metastatic setting. In regard to a single-arm design in this study, cORR assessed by IRC is implemented, to minimize bias inter-investigators and is in accordance with the recommendation from health authorities.

As enfortumab vedotin has not previously been explored in the Chinese population, the other primary objective of the study is to demonstrate ethnic consistency of enfortumab vedotin monotherapy between the Chinese and the non-Chinese populations through PK parameter analysis, even though no differences are anticipated for enfortumab vedotin based on ethnicity from the Phase 1 and 2 studies (Studies AGS-22M6E-11-1, EV-101, EV-102, EV-201) in enfortumab vedotin monotherapy to date. In Study EV-102, comparisons of Japanese and non-Japanese participants following enfortumab vedotin dosing indicate that there are no ethnic differences between Japanese and non-Japanese participants with respect to pharmacokinetics.

Therefore, the PK cohort is set in the study to collect intensive PK samplings along with sparse PK samplings in non-PK cohort participants, to address PK parameters in Chinese LA/mUC population.

Population pharmacokinetic analysis included data from 369 participants based on 3 Phase 1 studies (AGS-22M6E-11-1, EV-101 and EV-102), and 1 Phase 2 study (EV-201), demonstrated no clinically significant differences in the pharmacokinetics of enfortumab vedotin based on sex. Population pharmacokinetic analysis did not identify race (Caucasian vs. non-Caucasian) as a significant covariate on PK either. Therefore, the study is planned to enroll PK cohort participants who previously received platinum containing chemotherapy and PD-1/PD-L1 inhibitor therapy treatment regardless of sex.

A single-arm study design, with cORR by IRC being one of the primary endpoints, along with global registrational pivotal Phase 3 study EV-302 data on non-Chinese population, will support the demonstration of enfortumab vedotin monotherapy efficacy in late line LA/mUC Chinese population.

4.3 Dose Rationale

In the Phase 1 study of ASG-22CE in North America (EV-101), the Recommended Phase 2 Dose (RP2D) were established to be 1.25 mg/kg once weekly for 3 weeks of every 4-week cycle. The study tested a starting dose of 0.5 mg/kg and escalated up to a maximum dose of 1.25 mg/kg using a continual reassessment method (CRM) for dose escalation with subsequent expansion cohorts. The MTD was not reached for this study. In the dose escalation portion of this study, a total of 2 DLTs (proctalgia and blood uric acid increased) were reported in 2 participants receiving 1.0 mg/kg dose (n = 14). No DLTs were reported at 1.25 mg/kg dose (n = 6). The RP2D was determined to be 1.25 mg/kg based on both safety and efficacy data.

In this study, 1.25 mg/kg will be tested and enfortumab vedotin is dosed based on body weight. This should mitigate potential ethnic differences of ADC exposure in PK due to differences in body weight between US and Chinese participants. Thus, the dose of enfortumab vedotin as 1.25mg/kg to be tested in this study are both anticipated to be safe and active in Chinese mUC participants.

4.4 End of Study Definition

The study start is defined as the date the first participant signs informed consent. End of the study is defined as the last visit or scheduled procedure shown in schedule of assessments for the last participant in the study. The study will be closed approximately 2 years after last participant enrollment or no participants remain in long-term follow-up, whichever occurs first.

5 STUDY POPULATION

All screening assessments must be completed and reviewed to confirm the potential participant meets all eligibility criteria. Prospective approval of protocol deviations to eligibility criteria (also known as protocol waivers or exemptions) is not permitted.

5.1 Inclusion Criteria

Participant is eligible for participation in the study if all of the following apply:

1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written informed consent and privacy language as per national regulations must be

obtained from the participant prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).

2. Participant is legally 18 years or older or considered an adult according to local regulation at the time of signing the informed consent form (ICF).
3. Participant has Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
4. Participant must have histologically or cytologically documented urothelial/transitional cell carcinoma of the bladder, renal pelvis, ureter or urethra. Other histologies including adenocarcinoma, squamous differentiation or mixed are eligible.
5. Participant has locally advanced or metastatic disease that is not amenable to curative intent treatment. Participants must have measurable disease at baseline according to RECIST Version 1.1 (Eisenhauer 2009). Lesions in a prior radiation field must have progressed subsequent to radiotherapy to be considered measurable.
6. Participant must have received prior treatment with PD-1/PD-L1 inhibitor therapy in the locally advanced or metastatic urothelial cancer setting. Participants who received PD-1/PD-L1 therapy in the neoadjuvant/adjuvant setting and had recurrent or progressive disease either during therapy or within 3 months of therapy completion are eligible.
7. Participant who received prior treatment with platinum-containing chemotherapy defined as those who received platinum in the neoadjuvant/adjuvant setting and had recurrent or progressive disease within 12 months of completion or received treatment with platinum in the locally advanced (defined as unresectable with curative intent) or metastatic setting
    - Platinum based chemotherapy may include combination use with a PD-1 or PD-L1 inhibitor.
8. Participant has the following baseline laboratory data. If a participant has received a recent blood transfusion or growth factor, the hematology tests must be obtained ≥7 days after any growth factor and ≥ 28 days after any blood transfusion.
    a. absolute neutrophil count (ANC) ≥ 1.0×10^9/L
    b. platelet count ≥ 100×10^9/L
    c. hemoglobin ≥ 9 g/dL
    d. serum total bilirubin (TBL) ≤ 1.5 × upper limit of normal (ULN) or ≤ 3 × ULN for participants with Gilbert's disease
    e. creatinine clearance (CrCl) ≥ 30 mL/min as estimated per institutional standards or as measured by 24-hour urine collection (glomerular filtration rate [GFR] can also be used instead of CrCl).
    f. alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 × ULN

9. Female participant is not pregnant (see [Section 10.2 Appendix 2 Contraception Requirements]) and at least one of the following conditions apply:
    a. Not a woman of childbearing potential (WOCBP) (see [Section 10.2 Appendix 2 Contraception Requirements])
    b. WOCBP who agrees to follow the contraceptive guidance (see [Section 10.2 Appendix 2 Contraception Requirements]) from the time of informed consent through at least 6 months after the last dose of study treatment administration
10. Female participant must agree not to breastfeed starting at screening and throughout the study period and for at least 6 months after the last dose of study treatment administration.
11. Female participant must not donate ova starting at first dose of study treatment and throughout the study period and for 6 months after the last dose of study treatment administration.
12. Male participant with female partner(s) of childbearing potential (including breastfeeding partner) must agree to use contraception (see [Section 10.2 Appendix 2 Contraception Requirements]) throughout the treatment period and for 6 months after the last dose of study treatment administration.
13. Male participant must not donate sperm during the treatment period and for 6 months after the last dose of study treatment administration.
14. Male participant with pregnant partner(s) must agree to remain abstinent or use a condom for the duration of the pregnancy throughout the study period and for 6 months after the last dose of study treatment administration.
15. Participant agrees not to participate in another interventional study while receiving study treatment in the present study.
16. Participant must have had progression or recurrence of urothelial cancer during or following receipt of most recent therapy.
17. Participant must have an anticipated life expectancy of ≥ 3 months as assessed by the investigator.

5.2 Exclusion Criteria

Participant will be excluded from participation in the study if any of the following apply:

1. Participant has preexisting sensory or motor neuropathy Grade ≥ 2.
2. Participant has active central nervous system (CNS) metastases. Participants with treated CNS metastases are permitted on study if all the following are true:
    a. CNS metastases have been clinically stable for ≥ 6 weeks prior to screening
    b. If requiring steroid treatment for CNS metastases, the participant is on a stable dose ≤ 20 mg/day of prednisone or equivalent for ≥ 2 weeks
    c. Baseline imaging scans show no evidence of new or enlarged brain metastasis
    d. Participant does not have leptomeningeal disease

3. Participant has ongoing clinically significant toxicity (Grade 2 or higher with the exception of alopecia) associated with prior treatment (including systemic therapy, radiotherapy or surgery).
4. Participant with ongoing ≥ Grade 3 immunotherapy-related hypothyroidism or panhypopituitarism is excluded. Participant with ongoing immunotherapy-related colitis, uveitis, myocarditis or pneumonitis, or participants with other immunotherapy-related AEs requiring high doses of steroids (> 20 mg/day of prednisone or equivalent), is excluded. Participant with ≤ Grade 2 immunotherapy-related hypothyroidism or panhypopituitarism may be enrolled when well-maintained/controlled on a stable dose of hormone replacement therapy (if indicated).
5. Participant has a history of uncontrolled diabetes mellitus within 3 months before the first dose of study treatment. Uncontrolled diabetes is defined as hemoglobin A1c (HbA1c) ≥ 8% or HbA1c between 7% and < 8% with associated diabetes symptoms (polyuria or polydipsia) that are not otherwise explained.
6. Participant has prior treatment with enfortumab vedotin or other MMAE-based ADCs.
7. Participant has a second malignancy diagnosed within 3 years before first dose of study drug, or any evidence of residual disease from a previously diagnosed malignancy. Participants with non-melanoma skin cancer, localized prostate cancer treated with curative intent with no evidence of progression, low-risk or very low-risk (per standard guidelines) localized prostate cancer under active surveillance/watchful waiting without intent to treat, or carcinoma in situ of any type (if complete resection was performed) are allowed.
8. Participant is currently receiving systemic antimicrobial treatment for viral, bacterial or fungal infection at the time of first dose of study treatment. Routine antimicrobial prophylaxis is permitted.
9. Participants with a positive hepatitis B surface antigen and/or anti-hepatitis B core antibody and a negative polymerase chain reaction (PCR) assay at baseline should receive appropriate antiviral prophylaxis or regular surveillance monitoring as per local or institutional guidelines.
10. Active hepatitis C infection or known human immunodeficiency virus (HIV) infection. Participant who have been treated for hepatitis C infection are permitted if they have documented sustained virologic response of ≥ 12 weeks.
11. Participant has documented history of a cerebral vascular event (stroke or transient ischemic attack), unstable angina, myocardial infarction or cardiac symptoms (including congestive heart failure) consistent with New York Heart Association Class III-IV within 6 months prior to the first dose of study drug.
12. Participant had major surgery within 2 weeks or radiotherapy, chemotherapy, biologics, investigational agents, and/or antitumor treatment with immunotherapy that is not completed 2 weeks prior to first dose of study drug. Toxicities from these therapies must have resolved or adequately stabilized before starting study treatment.

13. Participant has known hypersensitivity to enfortumab vedotin or to any excipient contained in the drug formulation of enfortumab vedotin (including histidine, trehalose dihydrate and polysorbate 20) or participant has known hypersensitivity to biopharmaceuticals produced in CHO cells.
14. Participant has known active keratitis or corneal ulcerations. Participant with superficial punctate keratitis is allowed if the disorder is being adequately treated in the opinion of the investigator.
15. Participant has any condition, which, in the investigator's opinion, makes the participant unsuitable for study participation.
16. Uncontrolled tumor-related bone pain or impending spinal cord compression. Participant requiring pain medication must be on a stable regimen for at least 2 weeks at the time of first dose.

5.3 Lifestyle Considerations

Not applicable.

5.4 Screen Failures

A screen failure is defined as a potential participant who signed the ICF, but did not meet one or more criteria required for participation in the study and was not enrolled.

For screen failures, the demographic data, date of signing the ICF, inclusion and exclusion criteria, AEs up to the time of screen failure and reason for screen failure will be collected in the electronic case report form (eCRF).

5.4.1 Rescreening

Results of screening assessments that do not meet the parameters required by eligibility criteria (e.g., clinical laboratory tests, vital signs, physical examination, electrocardiogram [ECG], etc) may be repeated once within the 28-day screening period without the need to register the participant as a screen failure. If the participant meets exclusion criteria that cannot resolve during the screening period, or more than 28 days elapse from the date of signing the ICF, the participant must be documented as a screen failure. In order to re-screen after prior screen failure, a new ICF must be signed and the participant will enter into screening with a new participant identification number. Rescreening is only allowed once for an individual participant after discussion with medical monitor. The Screening/baseline and safety assessments do not need to be repeated if they still within the acceptable procedure completed time frame and all results meet inclusion and no exclusion criteria.

6 INVESTIGATIONAL PRODUCT(S)

6.1 Investigational Product(s) Administered

Table 6 Investigational Product(s)

Name	Enfortumab vedotin
Use	test product
Dosage Form	lyophilized powder for reconstitution
Physical Description	white to off-white

Unit Dose Strength	30 mg of enfortumab vedotin in a single-dose vial
Packaging and Labeling	clear single use vial
Route of Administration	intravenous infusion
Administration	Administered intravenously over 30 minutes. Refer to Section 6.1.1 for additional details.
IMP or Non-IMP	IMP
Sourcing	provided centrally by sponsor

IMP: Investigational Medicinal Product.

The investigational product, enfortumab vedotin (ASG-22CE), is a sterile, preservative-free, white to off-white lyophilized powder to be reconstituted for IV administration. The investigational product is supplied by Astellas in single-use glass vials containing 30 mg enfortumab vedotin in each vial. The investigational product should be stored at 2°C to 8°C.

Refer to the pharmacy manual, product label and package insert for detailed information regarding preparation, handling and storage of the enfortumab vedotin.

6.1.1 Investigational Product Administration

Enfortumab vedotin at a dose of 1.25 mg/kg will be administered monotherapy as an IV infusion over approximately 30 minutes on Days 1, 8, and 15 of every 28-day cycle. In the absence of infusion related reactions (IRRs), the infusion rate for all participants should be calculated in order to achieve an approximate 30-minute infusion period. Enfortumab vedotin must not be administered as an IV push or bolus. Enfortumab vedotin should not be mixed with other medications. At least 7 days must elapse between doses of enfortumab vedotin.

Participant weight must be measured during all relevant assessment time points as described in the [Table 1 Schedule of Assessments]. Weight-based dosing is calculated using the participant's actual body weight on Day 1 of each cycle. The dose does not need to be re-calculated based on actual weight on Day 8 and 15 of each cycle unless it is required by institutional standards. **An exception to weight-based dosing is made for participants weighing greater than 100.0 kg; doses will be based on 100 kg for these individuals. The maximum dose permitted on this study is 125.0 mg.**

Participants should be observed during enfortumab vedotin administration and for at least 60 minutes following the infusion for the first 3 cycles. All supportive measures consistent with optimal participant care should be given throughout the study according to institutional standards.

The injection site should be monitored closely for redness, swelling, pain, and infection during and at any time after administration. Participants should be advised to report redness or discomfort promptly at the time of administration or after infusion. Events of extravasation should be managed per institutional guidelines and precautions should be taken to prevent extravasation per institutional standards.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Packaging and Labeling

All study drug(s) used in this study will be prepared, packaged and labeled under the responsibility of qualified personnel at sponsor's designee in accordance with sponsor's designee standard operating procedures (SOPs), current Good Manufacturing Practice (GMP) guidelines, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and applicable local laws/regulations.

Each vial will bear a label conforming to regulatory guidelines, GMP and local laws and regulations that identifies the contents as investigational drug.

Refer to the pharmacy manual for detailed information regarding packaging and labeling of the enfortumab vedotin.

6.2.2 Handling, Storage and Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all enfortumab vedotin received and any discrepancies are reported and resolved before use of the enfortumab vedotin.
- Only participants enrolled in the study may receive enfortumab vedotin and only authorized study site personnel may administer enfortumab vedotin. Only study drug with appropriate expiry/retest dating may be dispensed.
- All enfortumab vedotin must be stored in a secure, environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions and access must be limited to the investigator and authorized study site personnel.
- The investigator, institution or the head of the medical institution (where applicable) is responsible for accountability, reconciliation and record maintenance (i.e., receipt, reconciliation and final disposition records).
- Further guidance and instruction on final disposition of used and unused study drug is provided in the pharmacy manual.

Refer to the pharmacy manual for detailed information regarding handling, storage and accountability of the enfortumab vedotin.

6.3 Randomization and Blinding

This is an open-label, single-arm study. 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.

6.4 Investigational Product Compliance

The dose and schedule of enfortumab vedotin administered to each participant will be recorded on the eCRF for each dose. Reasons for dose delay, reduction or omission will be documented.

6.5 Dose Modification

Intrapatient dose reduction to 1 mg/kg (dose level –1), and to 0.75 mg/kg (dose level –2) will be allowed depending on the type and severity of toxicity. Participants requiring a

dose reduction may be re-escalated by 1 dose level (e.g., participants reduced to 0.75 mg/kg may only be re-escalated to 1 mg/kg) provided the toxicity does not require study drug discontinuation and has returned to baseline or ≤ Grade 1. If the toxicity recurs, re-escalation will not be permitted. Participants with ≥ Grade 2 corneal AEs will not be permitted to dose re-escalate.

Dose modification recommendations for enfortumab vedotin associated toxicity (hematologic and non-hematologic, by National Cancer Institute-common terminology criteria for adverse event [NCI-CTCAE] v4.03 grade) are presented in Table 7 and Table 8.

If toxicities present on Day 1 of any cycle and require the enfortumab vedotin dose to be held, then the start of the cycle may be delayed. If toxicities present on Days 8 or 15 of any cycle and require the dose to be held > 2 days, then the dose(s) must be eliminated, rather than delayed. If a participant only receives enfortumab vedotin on Day 1 and needs to skip Days 8 and 15, the participant could resume the next cycle as early as Day 22 (new Day 1) if the toxicity has resolved by that time.

Treatment break, dose reduction or delay for other enfortumab vedotin associated toxicities is permitted at the discretion of the investigator. Medical Monitor consultation is required after the participant was unable to receive one full cycle of study drug administration. (i.e., 3 consecutive doses) for toxicities or any other reasons. If participant was unable to receive study drug ≥ 2 cycles (i.e., ≥ 6 consecutive doses not received) for toxicity or for any other reasons, the participant will be discontinued. Dose delays for participants who are responding to treatment may be extended beyond 8 weeks in consultation with Medical Monitor, if the participant's toxicity does not otherwise require permanent discontinuation.

Disease assessment must continue to be performed at the protocol specified frequency and will not be adjusted while participant is not receiving study treatment or any dose delay. It will continue to be timed from Cycle 1 Day 1 during treatment.

The treatment could be continued until any of the study discontinuation criteria is met.

Participants may not receive other investigational drugs and/or vaccines, radiotherapy (except palliative radiotherapy as described in Section 6.8.1), or systemic antineoplastic therapy during dose delays.

Dose modification recommendations for enfortumab vedotin associated toxicity are presented in Table 7 below.

Table 7 Recommended Dose Modifications for Enfortumab Vedotin Associated Hematologic Toxicity*

Grade 1	Grade 2	Grade 3	Grade 4
Continue at same dose level.	Continue at same dose level. For Grade 2 thrombocytopenia withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then	Withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at the same dose level or consider dose reduction by 1 dose level.	Withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then reduce dose by 1 dose level and resume treatment or discontinue at the discretion of the investigator. Transfusions or growth factors may be used as indicated per

Grade 1	Grade 2	Grade 3	Grade 4
	resume treatment at the same dose level.	Transfusions or growth factors may be used as indicated per institutional guidelines.	institutional guidelines. For anemia, treatment discontinuation should be strongly considered.
*Hematologic toxicity refers to anemia, thrombocytopenia, neutropenia and febrile neutropenia.			

Table 8 Recommended Dose Modifications for Enfortumab Vedotin Associated Non-hematologic Toxicity

Any Grade			
For suspected SJS, suspected TEN or bullous lesions, immediately withhold enfortumab vedotin and refer the subject to a dermatologist/specialist for diagnosis and specialized care. For confirmed SJS or TEN, permanently discontinue treatment. If SJS or TEN is ruled out, see recommendations provided below for skin reactions.			
Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Continue at same dose level. For Grade 1 rash or skin reactions, the subject may continue at the same dose level. See also [Section 6.5.1] for recommended management of rash. If ocular symptoms and/or changes in vision are identified, the participant should be evaluated with an ophthalmologic exam.*	Continue at same dose level, except in the event of Grade 2 neuropathy or corneal AEs. For worsening rash or skin reactions, or skin reactions with concomitant fever, withhold enfortumab vedotin until toxicity is ≤ Grade 1 or has returned to baseline, and then resume treatment at the same dose level or	Withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at the same dose level or consider dose reduction by 1 dose level.** For Grade 3 rash or skin reactions, withhold enfortumab vedotin until toxicity is ≤ Grade 1 or has returned to baseline, and then resume treatment at the same	For Grade 4 AEs, discontinue treatment.** For confirmed SJS or TEN, or Grade 4 rash or skin reactions, permanently discontinue treatment. Grade 4 vomiting and/or diarrhea that improves to ≤ Grade 2 within 72 hours with supportive management does not require discontinuation.
Table continued on next page			

Grade 1	Grade 2	Grade 3	Grade 4
	consider dose reduction by 1 level. Consider referral of the subject to a dermatologist/specialist for diagnosis and specialized care. For Grade 2 neuropathy or corneal AEs, withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, and then resume treatment at the same dose level. For the second occurrence of Grade 2 neuropathy or corneal AE's withhold dose until toxicity is ≤ Grade 1, and then reduce the dose by 1 dose level and resume treatment. If ocular symptoms and/or changes in vision are identified, the participant should be evaluated with an ophthalmologic exam.*	dose level or consider dose reduction by 1 level. Consider referral of the subject to a dermatologist/specialist for diagnosis and specialized care. Subjects who have confirmed SJS or recurrent ≥ Grade 3 rash events should have therapy permanently discontinued. For Grade 3 neuropathy or corneal AEs, discontinue treatment. For Grade 3 hyperglycemia/elevated blood glucose, withhold study treatment. Resume treatment once hyperglycemia/elevated blood glucose has improved to ≤ Grade 2 and participant is clinically and metabolically stable. If ocular symptoms and/or changes in vision are identified, the participant should be evaluated with an ophthalmologic exam.*	For Grade 4 hyperglycemia/elevated blood glucose, withhold enfortumab vedotin treatment and undertake a full evaluation of the hyperglycemia event. Once the blood glucose levels return to Grade 2 drug dosing may be resumed with close monitoring after consultation with medical monitor.

AEs: adverse events; SJS: Stevens-Johnson Syndrome; TEN: toxic epidermal necrolysis

* Ophthalmologic exam should be performed by an ophthalmologist. If optometrists can perform exams and prescribe medications, an optometrist may be used instead.

** Grade 3/4 electrolyte imbalances/laboratory abnormalities that are not associated with clinical sequelae and/or are corrected with supplementation/appropriate management within 72 hours of their onset do not require discontinuation (e.g., Grade 4 hyperuricemia). Grade 3 or 4 elevations of amylase or lipase, if asymptomatic do not require treatment delay or treatment discontinuation.

6.5.1 Enfortumab Vedotin-Related Rash

Enfortumab vedotin is a Nectin-4 directed antibody drug conjugate. Nectin-4 is a cell adhesion molecule that is highly expressed in urothelial carcinoma. Low to moderate levels of Nectin-4 are also expressed on normal tissues, including skin keratinocytes, sweat glands and hair follicles; thus, skin reactions are anticipated events. As such, skin reactions are AEs of interest in all clinical studies with enfortumab vedotin.

A cumulative review of post-marketing safety data from 18 Dec 2019 (the approval date of enfortumab vedotin in the US) through 22 Oct 2020 identified reports of severe cutaneous adverse reactions in 15 subjects receiving enfortumab vedotin, some of whom had fatal outcomes. These reactions occurred predominantly during the first cycle of

treatment. AEs reported in these cases included Stevens-Johnson Syndrome (SJS) (5 cases), blister (3 cases), dermatitis bullous (3 cases), symmetrical drug-related intertriginous and flexural exanthema (SDRIFE; 2 cases), and 1 case each of dermatitis exfoliative, exfoliative rash, epidermal necrosis, oropharyngeal blistering, stomatitis and toxic epidermal necrolysis (TEN).

In enfortumab vedotin monotherapy studies of urothelial carcinoma, SAEs of severe cutaneous adverse reactions were reported in 11 of 749 subjects (1.5%) and included dermatitis bullous (0.4%), drug eruption (0.4%), blister (0.1%), conjunctivitis (0.1%), SJS (0.1%), stomatitis (0.1%) and toxic skin eruption (0.1%).

Subjects should be informed that rash and severe skin reactions have occurred after administration of EV, and to contact the Investigator immediately if they have signs and symptoms of skin reactions, oral mucosal and ocular abnormalities including mucositis or conjunctivitis. Starting in the first cycle and throughout treatment, closely monitor subjects for skin reactions. For mild to moderate skin reactions, consider appropriate treatment, such as topical corticosteroids and antihistamines as clinically indicated. For recommendations regarding dose modifications for skin reactions due to EV, refer to [Table 8].

6.5.2 Management of Hyperglycemia

Investigators should monitor blood glucose levels and are advised to perform additional assessments if any symptoms of hyperglycemia are observed, including a thorough evaluation for infection. In addition, if steroids are used to treat any other condition, blood glucose levels may require additional monitoring. If elevated blood glucose levels are observed, participants should be treated according to local standard of care and referral to endocrinology may be considered.

Participants, especially those with a history of or ongoing diabetes mellitus or hyperglycemia, should be advised to immediately notify their physicians if their glucose level becomes difficult to control or if they experience symptoms suggestive of hyperglycemia such as frequent urination, increased thirst, blurred vision, fatigue, and headache. Participants who enter the study with an elevated HbA1c (≥ 6.5%) at baseline should be referred to an appropriate provider during Cycle 1 for glucose management. Blood glucose should be checked prior to each dosing and dose should be withheld for blood glucose > 250 mg/dL (13.9 mmol/L) (Grade 3 or higher). Dosing may continue once the participant's blood glucose has improved to ≤ Grade 2 and participant is clinically and metabolically stable. Blood glucose > 500 mg/dL (27.8 mmol/L) (Grade 4) considered related to enfortumab vedotin requires treatment discontinuation. If a participant experiences new onset of diabetes mellitus, evaluate participants with a metabolic panel, urine ketones, HbA1c, and C-peptide to assess for new onset diabetes.

6.5.3 Management of Enfortumab Vedotin Infusion Related Reactions

An IRR may occur during the infusion of study treatment. The infusion should be administered at a site properly equipped and staffed to manage anaphylaxis should it occur. All supportive measures consistent with optimal participant care should be given throughout the study according to institutional standards. Supportive measures may include administering medications for IRRs.

Participants who experience an IRR may be premedicated for subsequent infusions. Premedication may include pain medication (e.g., acetaminophen or equivalent), an antihistamine (e.g., diphenhydramine hydrochloride), and a corticosteroid administered approximately 30 to 60 minutes prior to each infusion or according to institutional standards. Should a participant experience IRRs in the setting of premedication, continued treatment with enfortumab vedotin must be discussed with the medical monitor prior to the next planned dose.

If anaphylaxis occurs, study treatment administration should be immediately and permanently discontinued.

6.6 Continued Access to Investigational Product After the End of the Study

Options to provide enfortumab vedotin to participants who are continuing to receive treatment and are benefiting will be determined at the time of study closure.

6.7 Treatment of Overdose

Neither the effects of overdose of enfortumab vedotin nor an antidote to overdose are known. In the case of an overdose, the participant should be closely monitored for adverse reactions and supportive treatment should be administered.

Weight-based dosing for enfortumab vedotin is based on the participant's actual body weight, with the exception of participants weighing greater than 100 kg; doses will be based on 100 kg for these individuals. The maximum dose calculated per cycle in this study is 125 mg.

In the event of an overdose of enfortumab vedotin >10%, study personnel should:

Care for and medically stabilize the participant until there is no immediate risk of complications or death, if applicable. There is currently no known antidote for an overdose of enfortumab vedotin.
Notify the Medical Monitor as soon as they become aware of the overdose, to discuss details of the overdose (e.g., exact amount of enfortumab vedotin administered, participant weight) and AEs, if any.

Refer to [Section 10.3.7 Reporting Procedures for Special Situations] for reporting requirements for suspected overdose or other medication error.

6.8 Concomitant Therapy

Medications taken within 28 days prior to inform consent and up to the first dose of study medication will be documented on the appropriate case report form (CRF) as a prior medication.

Medications taken after the first dose of study medication up until the 30-day safety follow-up visit (EOT visit in [Table 1 Schedule of Assessments]) will be documented on the appropriate CRF as concomitant medication.

6.8.1 Allowed Concomitant Therapy

Concomitant chronic prednisone (or equivalent) may be used at a dose of ≤20 mg/day. Higher doses of prednisone (or equivalent) are permitted for limited duration to treat acute

conditions that arise during the study as medically indicated. The use of anti-emetics is permitted. Premedications for IRRs per Section 6.5.3 are permitted.

Therapies to manage enfortumab vedotin-associated toxicity as recommended in Section 6.5 are permitted, including growth factors, and transfusions.

Participants who are receiving strong CYP3A4 inhibitors or P-glycoprotein (P-gp) inhibitors concomitantly with enfortumab vedotin should be closely monitored for adverse reactions.

Routine prophylaxis with vaccines is permitted; it is recommended that vaccines used do not contain live micro-organisms. Antimicrobial prophylaxis or ongoing treatment of resolving and/or controlled infection is permitted during the study.

Participants with a positive hepatitis B surface antigen and/or anti-hepatitis B core antibody and a negative PCR assay at baseline should receive appropriate antiviral prophylaxis or regular surveillance monitoring as per local or institutional guidelines.

Participants with treated CNS metastases are permitted on study conditionally; participant with uncontrolled tumor-related bone pain or impending spinal cord compression requiring pain medication on a stable regimen is permitted as per Section 5.2.

Palliative radiotherapy on a non-target bone lesion that is not progressing is allowed after 3 cycles of treatment; must be administered after the initial response assessment and repeat scans described in Section 7.1. This will not be considered a subsequent anticancer therapy, but must not interfere with the assessment of tumor target lesions. Treatment with enfortumab vedotin should be interrupted during palliative radiotherapy.

6.8.2 Prohibited Concomitant Therapy

If the investigator determines that any of the following medications are necessary to provide adequate medical support to the participant, the participant must be withdrawn from further administration of the study treatment:

a. Other investigational drugs and/or vaccines

b. Chemotherapy or other medications intended for antitumor activity. This does not apply to participants on endocrine therapy, or to participants on agents intended for the treatment of bone metastasis where participants should be on a stable dose of bone targeting agents for at least 2 weeks prior to first dose of study drug (e.g., bisphosphonates, or receptor activator of nuclear factor kappa-B [RANK] ligand inhibitors).

c. Radiation therapy except palliative radiation for non-target lesions (as described in Section 6.8.1) that is approved by the sponsor. Note: Radiation therapy to a preexisting symptomatic solitary lesion or to the bone may be considered on an exceptional case-by-case basis after consultation with the sponsor.

7 STUDY PROCEDURES AND ASSESSMENTS

- Study procedures and their timing are summarized in the [Table 1 Schedule of Assessments]. Adherence to the study design requirements, including those specified in the schedule of assessments, is essential and required for study conduct. Prospective protocol waivers or exemptions are not allowed.

- Any change, divergence or departure from the study design or procedures identified in the protocol is considered a protocol deviation. All deviations from the protocol are to be recorded.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the schedule of assessments.

7.1 Efficacy Assessments

Measures of anticancer activity will be assessed by computed tomography (CT) scans with contrast approximately every 8 weeks (± 1 week). After 1 year on study, response assessments will be reduced to every 12 weeks (± 1 week). The schedule of response assessments should not be adjusted for dose delays/interruptions or other reasons for changes in the timing of a participant's study activities; timepoints for response assessments should be calculated from Cycle 1 Day 1. A CT scan with contrast (chest, abdomen, and pelvis) is the preferred modality for tumor assessment. Magnetic resonance imaging (MRI) is acceptable if CT scans are contraindicated in a participant (e.g., participant is allergic to contrast media). Participants must be evaluated using the same imaging method throughout the study for efficacy assessments. Other regions should be scanned if the participant has known or suspected disease in that region. Brain and/or bone scans should also be repeated at response assessment timepoints if bone metastases were identified at baseline, or if metastasis is known or suspected. Responses (CR or partial response [PR]) will be confirmed with repeat scans at least 4 weeks after first documentation of response. The schedule for response assessments should not be adjusted after the confirmatory scan (e.g., CR at Week 8, confirmatory scans at Week 12, next assessment due at Week 16). Tumor imaging should also be performed whenever disease progression is suspected. The determination of antitumor activity will be based on confirmed objective response assessments by IRC as defined by RECIST V 1.1. The investigator could make treatment decisions based on site assessments of scans by RECIST V 1.1.

Participants who discontinue study treatment for reasons other than objective disease progression by RECIST V 1.1 will continue to receive CT scans with contrast 8 weeks (±1 week) after the previous response assessment scan and every 8 weeks (±1 week) following the previous scan thereafter. After 1 year on study the frequency of response assessments will be reduced to every 12 weeks (±1 week). The tumor assessments will continue until the participant has radiological disease progression per RECIST V 1.1 as determined by investigator, initiates a new anticancer therapy, dies, withdraws study consent, lost to follow-up or the study closes, whichever comes first. The determination of

antitumor activity will be based on confirmed objective response assessments as defined by RECIST V 1.1. Participants who do not have at least 2 (initial response and confirmation scan) post-baseline response assessments will be counted as non-responders. Clinical response of CR, PR, SD, or progressive disease (PD) will be determined at each assessment. Response and progression will also be assessed by IRC and investigator independently.

Survival status will be updated every 12 weeks (±1 week) (calculated from disease progression) until death, study closure, lost to follow-up or withdrawal of consent from study, whichever occurs first.

Participants' clinical data must be available for CRF source verification. Tumor images will be submitted to a central imaging laboratory.

7.1.1 Evaluation of Target Lesions

7.1.1.1 Complete Response

CR is defined as disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm from baseline measurement.

7.1.1.2 Partial Response

PR is defined as at least a 30% decrease in the sum of diameters (longest for nonnodal lesions, short axis for nodal lesions) of target lesions taking as reference to the baseline sum of diameters.

7.1.1.3 Progressive Disease

PD is defined as at least a 20% increase in the sum of diameters (longest for nonnodal lesions, short axis for nodal lesions) of the target lesions taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (Note: the appearance of 1 or more new lesions is also considered progression).

7.1.1.4 Stable Disease

SD is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters while on study drug.

7.1.2 Evaluation of Non-target Lesions

To achieve unequivocal progression on the basis of non-target lesions, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR of target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of 1 or more non-target lesions is usually not sufficient to qualify for unequivocal progression.

7.1.2.1 Complete Response

For CR of non-target lesions, participants must have disappearance of all non-target lesions and all lymph nodes must be nonpathological in size (< 10 mm short axis).

7.1.2.2 Non-CR/Non-PD

Non-CR/Non-PD of non-target lesions is defined as persistence of 1 or more non-target lesions.

7.1.2.3 Progressive Disease

PD of non-target lesions is defined as unequivocal progression of existing non-target lesions or the appearance of 1 or more new lesions.

7.1.3 New Lesions

New lesion is defined as the new finding in an anatomical location on the follow-up scan assessment, exclude the impact of differences of scan technique. Such lesion that was not scanned at baseline is also considered a new lesion. The appearance of 1 or more new lesions is also considered progression.

7.1.4 Time Point for Response Evaluation

The overall response status at each time point for participants with measurable disease at baseline will be reported according to the [Table 1 Schedule of Assessments].

7.2 Safety Assessments

7.2.1 Laboratory Assessments

- See [Section 10.6 Appendix 6: Laboratory Assessments] for the list of clinical laboratory tests (including hematology, biochemistry, urinalysis and HbA1c) to be performed and refer to [Table 1 Schedule of Assessments] for timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- Clinical significance of out-of-range laboratory findings is to be determined and documented by the investigator or subinvestigator who is a qualified physician. Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.

Laboratory tests will be sent to the local laboratory for analysis and entered into eCRF. Clinical laboratory tests will be performed locally prior to dosing. Tests will be obtained as indicated in the [Table 1 Schedule of Assessments]. If hematology and biochemistry tests were performed within 7 days prior to the first day of dosing, they do not need to be repeated on Cycle 1 Day 1. Clinical laboratory tests at screening, at screening and on Cycle 1 Day 8 are to be performed after the participant has been fasting in order to ensure accurate interpretation of lab test values such as glucose values. Participant can take food after fasting blood samples are obtained. Fasting status will be recorded in source documents. Fasting is not necessary for laboratory tests performed at all other visits. HbA1c will be obtained at screening/baseline and EOT visits. If HbA1c is elevated (≥ 6.5%), refer participant to appropriate provider during cycle 1 for glucose management. Lipid panel, including total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglyceride tests, will be only obtained at screening.

Additional assessments may be done to monitor AEs or as required by dose modification requirements. Additional laboratory tests should be performed according to institutional standard of care.

For women of childbearing potential only, a serum pregnancy test will be performed at baseline. A urine or serum pregnancy test will then be repeated on Day 1 of each cycle prior to study drug administration at the EOT and follow-up visits till 6 months after the last dose of study treatment administration. Adequate contraception should be used by study participants during or after the last dose of study treatment administration per the requirement stated in [Section 10.2 Appendix 2 Contraception Requirements].

7.2.2 Vital Signs

Vital signs, including systolic and diastolic blood pressure (mmHg), pulse rate (beats/minute) and temperature will be obtained as indicated in the [Table 1 Schedule of Assessments]. All vital sign measures will be taken prior to dosing with the participant in the sitting or supine position.

If clinically significant vital sign changes from screening/baseline are noted, the changes will be documented as AEs on the AE page of the eCRF. Clinical significance will be defined as a variation in vital signs that has medical relevance as deemed by the investigator that could result in an alteration in medical care.

7.2.3 Physical Examination

Standard, full physical examinations will be performed to assess general appearance, skin, eyes, ears, nose, throat, neck, cardiovascular, chest and lungs, abdomen, musculoskeletal, neurologic status, mental status, and lymphatic systems. Physical examinations will be conducted at visits as outlined in the [Table 1 Schedule of Assessments]. Height measurement is only required at screening/baseline. Weight measurement will also be performed as indicated in the [Table 1 Schedule of Assessments]. If physical examination except for weight was performed within 7 days prior to the first day of dosing, it does not need to be repeated on Cycle 1 Day 1.

If clinically significant worsening of findings from baseline is noted at any study visit, the changes will be documented as AEs on the AE eCRF. Clinical significance is defined as any variation in physical findings, which has medical relevance that could result in an alteration in medical care. The investigator will continue to monitor the participant until the parameter returns to Grade ≤ 1, or to the baseline condition, or until the investigator determines that follow-up is no longer medically necessary.

7.2.4 Electrocardiogram

Routine 12-lead ECGs will be performed and assessed using local standard procedures as indicated in the [Table 1 Schedule of Assessments]. If clinically significant worsening of a finding from baseline is noted, the abnormality will be documented as AEs on the AE eCRF. Prior to performing 12-lead ECGs, participants should rest in supine position (or semi-recumbent, if supine is not tolerated) for 10 minutes. ECGs will be read and assessed locally.

7.2.5 ECOG Performance Status

ECOG performance status [Section 10.7 Appendix 7: ECOG Performance Status Scale] will be evaluated at protocol-specified timepoints.

7.2.6 Ophthalmology Examination

Participants will have a complete eye examination at baseline performed by a qualified ophthalmologist or optometrist, including but not limited to: visual acuity (VA), best corrected visual acuity (BCVA), inter ocular pressure (IOP), extra ocular movement (EOM), pupils, external exam, slit lamp exam, and dilated fundoscopic exam. Eye exams performed during the study where clinically indicated will be at the ophthalmologist's discretion. Eye exams at EOT are required for participants who experience ocular AEs during the study and this at minimum must include VA, BCVA, and slit lamp exam.

7.2.7 Order of Assessments

Not applicable.

7.3 Adverse Events and Other Safety Aspects

The definitions of an AE or SAE can be found in [Sections 10.3.1 and 10.3.2], respectively.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study drug, or that caused the participant to discontinue the study drug and/or study (see [Section 10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting]).

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in [Section 10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting].

7.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All SAEs will be collected from the signing of the ICF until 30 days following the last dose of study treatment or until initiation of a new anticancer treatment, whichever occurs first, at the time points specified in the schedule of assessments [Section 1.3] and reported on the eCRF.

All AEs will be collected from the signing of the ICF until the follow up visit at the time points specified in the schedule of assessments [Section 1.3] and reported on the eCRF.

If the NCI-CTCAE grade of an SAE/AE changes, the event should be relisted on the eCRF with the new NCI-CTCAE grade and new onset date.

If the NCI-CTCAE grade decreases, the SAE/AE should be relisted on the eCRF with the new NCI-CTCAE grade and new onset date. The exception is ongoing pre-dose events that continue post-dose and improve post-dose. Such events should not be re-listed.

If the NCI-CTCAE grade of an SAE reduces, the details of the AE should be provided on the SAE worksheet for the medical assessor to be able to assess the course of the event.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in [Section 10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting]. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the investigator must promptly notify the sponsor.

7.3.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

7.3.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in [Section 8.3]). Further information on follow-up procedures is provided in [Section 10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting].

If after the protocol-defined AE collection period (see [Section 7.3.1 Time Period for Collecting Adverse Event and Serious Adverse Event Information]), an AE progresses to an SAE, or the investigator learns of any (S)AE (serious adverse event or adverse event) including death, where he/she considers there is reasonable possibility it is related to the study drug or study participation, the investigator must promptly notify the sponsor.

7.3.4 Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study drug under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

- An investigator who receives an investigator safety report describing a SUSAR or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

7.3.5 Disease-related Events and/or Disease-related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

Under this protocol, the following event(s) will not be considered as an (S)AE:

- Disease progression: events that are clearly consistent with the expected pattern of progression of the underlying disease are not to be recorded as (S)AEs. If there is any uncertainty as to whether an event is due to anticipated disease progression and/or if there is evidence suggesting a causal relationship between the study drug and the event, it should be reported as an (S)AE. All deaths up to 30 days after the final administration of study drug must be reported as an SAE, even if attributed to disease progression.

7.3.6 Special Situations

Certain special situations observed in association with the study drug, such as incorrect administration (e.g., wrong dose of study drug or background therapy) are reported as protocol deviations and/or may require special reporting, as described below. These special situations are not considered AEs, but do require to be communicated to Astellas as per the timelines defined below.

If a special situation is associated with, or results in, an AE, the AE is to be assessed separately from the special situation and captured as an AE in the eCRF. If the AE meets the definition of an SAE, the SAE is to be reported as described in [Section 10.3.6 Reporting Procedures for Serious Adverse Events] and the details of the associated special situation are to be included in the clinical description on the special situation worksheet or pregnancy reporting form.

The special situations are:

- Pregnancy
- Lactation
- Medication error, overdose and use outside protocol
- Misuse/abuse
- Occupational exposure
- (Suspicion of) Transmission of infectious agent
- Suspected drug-drug interaction

Instructions and procedures for reporting special situations are provided in [Section 10.3.7 Reporting Procedures for Special Situations].

7.4 Pharmacokinetics

Approximately 12 participants enrolled at the PK cohort site(s) will participate in 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 (PK evaluable). Blood samples (7 mL/sample) for the analysis of ADC, TAb and MMAE will be collected as indicated in the [Table 1 Schedule of Assessments], [Table 2

Pharmacokinetic Sample Collection Time Points (PK Cohort)] and [Table 3 Schedule and Acceptable Time Range for PK Sampling (Non-PK Cohort)] for the evaluation of pharmacokinetics. Blood samples should be collected via a peripherally placed IV cannula or by direct venipuncture, which should always be performed on the opposite arm of the enfortumab vedotin infusion line. Only in the case where venous access cannot be gained from the opposite arm of the study drug infusion line, then the arm of the study drug infusion line should be used. In the event that blood cannot be drawn by venipuncture, the central line may be used. If blood is collected from central line, use the lumen that was not used to administer the study drug.

Bioanalysis of ADC, TAb and MMAE in serum or plasma will be performed using validated methods at bioanalytical laboratories specified by the sponsor. The actual date and time of each blood sample collection will be documented. Blood sampling, processing, storage and shipment instructions will be provided in the Laboratory Manual. Samples will be shipped to and analyzed by a Sponsor designated analytical laboratory.

7.5 Immunogenicity Assessments

Blood samples will be collected during the study treatment period till the EOT visit for determination of ATA concentrations [Table 4 Schedule for ATA Sampling]. Blood samples (4 mL/sample) will be collected at the time points indicated in [Table 1 Schedule of Assessments]. Blood samples should be collected via a peripherally placed IV cannula or by direct venipuncture, which should always be performed on the opposite arm of the enfortumab vedotin infusion line. Only in the case where venous access cannot be gained from the opposite arm of the study drug infusion line, then the arm of the study drug infusion line should be used. In the event that blood cannot be drawn by venipuncture, the central line may be used. If blood is collected from central line, use the lumen that was not used to administer the study drug. Bioanalysis of ATA in serum will be performed using validated methods at bioanalytical laboratories specified by the sponsor.

Blood sampling, processing, storage and shipment instructions will be provided in the laboratory manual. Samples will be shipped to and analyzed by a sponsor designated analytical laboratory.

7.6 Total Amount of Blood

The total amount of blood for each participant will vary depending on the course of their disease, duration on treatment and local laboratory requirements. At any time during the study, if any laboratory abnormalities are found for a participant, additional blood may be drawn for safety monitoring.

The maximum amount of blood collected within 24 hours is approximately 70 mL for participant in the PK cohort and 40 mL for participant in Non-PK cohort on Cycle 1 Day 1.

8 PARTICIPANT DISCONTINUATION

Refer to [Section 10.1.9 Study and Site Start and Closure] regarding discontinuation of study sites or of the study as a whole.

8.1 Discontinuation of Individual Participant(s) from Study Treatment

A discontinuation from treatment is defined as a participant who enrolled in the study and for whom study treatment is permanently discontinued for any reason.

The participant is free to withdraw from the study treatment and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to discontinue the participant from study treatment or to terminate a participant's involvement in the study at any time if the participant's clinical condition warrants it.

The reason for discontinuation from study treatment must be documented in the participant's medical records.

A participant must discontinue study treatment for any of the following reasons:

- Participant requests to stop treatment.
- Investigator decides it is in the participant's best interest to discontinue.
- Participant develops documented radiological disease progression per RECIST V1.1 by investigator assessment.
- Participant starts a new anticancer therapy.
- Participant develops unacceptable toxicity.
- Female participant becomes pregnant.
- Participant is noncompliant with the protocol based on the investigator or medical monitor assessment.
- Participant did not receive study drug continuously for > 2 cycles (i.e., > 6 consecutive doses not received). Medical Monitor consultation is required after the participant was unable to receive one full cycle of study drug administration. (i.e., 3 consecutive doses). Dose delays for participants who are responding to treatment may be extended beyond 8 weeks in consultation with medical monitor, if the participant's toxicity does not otherwise require permanent discontinuation.

8.2 Discontinuation of Individual Participant(s) from Study

All participants who discontinue study treatment will remain in the study and must continue to be followed for protocol-specific follow-up procedures as outlined in [Table 1 Schedule of Assessments]. The only exception to this is when the participant specifically withdraws consent for any further contact with him/her or persons previously authorized by the participant to provide this information. A participant may be discontinued from the study for any of the following reasons:

- Lost to follow-up
- Death
- Participant withdrawal of consent
- Participant termination by sponsor

8.3 Lost to Follow-up

Every reasonable effort is to be made to contact any participant lost to follow-up during the course of the study to complete study-related assessments, record outstanding data and

retrieve study drug. These contact attempts should be documented in the participant's medical record.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The statistical hypothesis is that ORR will be superior to 10% historical control.

9.2 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 (PK evaluable).

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.

9.3 Populations for Analyses

The number and percentage of participants will be characterized for all enrolled participants and by each population.

The following populations are defined:

Population	Description
Enrolled	All participants who signed the informed consent form, met the inclusion and exclusion criteria, and enrolled into the study.
Full Analysis Set (FAS)	All participants who are enrolled and receive any amount of study drug in the study. The FAS population will be used for primary analysis of efficacy endpoints.
Safety Analysis Set	All participants who are enrolled and take any amount of study drug. The safety analysis set will be used for all safety analyses.
Pharmacokinetic analysis set (PKAS)	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 and 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. Inclusion of participants in the pharmacokinetic analysis set with missing data or major protocol deviations will be considered by the pharmacokineticist on a case-by-case basis.

9.4 Statistical Analyses

A statistical analysis plan (SAP) will be written to provide details of the analysis, along with specifications for tables, listings and figures to be produced. Changes from the planned analyses in the final SAP that impact the statistical analyses will be justified in the clinical study report (CSR).

9.4.1 General Considerations

In general, data will be summarized with descriptive statistics for continuous endpoints, and frequency and percentage for categorical endpoints, unless otherwise specified. Percentages by categories will be based on the number of participants with no missing data (i.e., 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.

Demographics and baseline characteristics will be summarized overall for all enrolled participants.

The number and percentage of participants who completed and discontinued treatment and reasons for treatment discontinuation will be presented for all enrolled participants and for participants in the Safety Analysis Set (SAF) overall. Similar tables for investigational period disposition and follow-up disposition will also be presented for all enrolled participants overall. All disposition details and dates of first and last evaluations for each participant will be listed.

Previous and concomitant treatment and medical history will be listed. Investigational product exposure will be summarized by descriptive statistics and will be listed.

9.4.2 Analysis of Efficacy

9.4.2.1 Analysis of Primary Endpoint

9.4.2.1.1 Primary Analysis

Efficacy analysis will be conducted on the FAS. The interpretation of results from statistical tests and the study efficacy conclusion will be based on the FAS.

The primary efficacy endpoint of this study is the confirmed ORR per IRC. The ORR is defined as the proportion of participants with confirmed CR or PR according to RECIST V 1.1. Participants who do not have at least 2 (initial response and confirmation scan) post-baseline response assessments will be counted as non-responders.

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.

9.4.2.1.2 Sensitivity Analysis

Sensitivity may be conducted for selected endpoints as deemed appropriate. Details will be specified in the SAP.

9.4.2.1.3 Subgroup Analysis

Subgroup analyses may be conducted for selected endpoints as deemed appropriate. Details will be specified in the SAP.

9.4.2.2 Analysis of Secondary Endpoints

9.4.2.2.1 DOR per IRC

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

The median DOR and DOR at 6 and 12 months will be estimated using the Kaplan-Meier method and reported along with the corresponding 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. Details on the definition of censoring will be provided in the SAP. This analysis will be conducted using the FAS.

9.4.2.2.2 DCR per IRC

Disease control rate (DCR) per IRC is defined as the proportion of participants whose best overall response is a CR, PR or SD according to RECIST V 1.1 based on IRC. Responses do not need to be confirmed to be scored as responders for the purpose of determining DCR.

DCR will be summarized for the FAS, and the 2-sided 95% CI will be calculated.

9.4.2.2.3 PFS per IRC

Progression-free survival (PFS) per IRC is defined as the time from start of study treatment to first documentation of objective tumor progression (PD per RECIST V 1.1) based on IRC assessment, or to death due to any cause, whichever comes first.

The median PFS and PFS at 6 and 12 months will be estimated using the Kaplan-Meier method and will be reported along with the corresponding 95% CI. Details on the definition of censoring will be provided in the SAP. This analysis will be conducted using the FAS.

9.4.2.2.4 Confirmed ORR per Investigator Assessment

Confirmed ORR per investigator assessment is defined as the proportion of participants with confirmed CR or PR according to RECIST V 1.1 based on investigator's assessment. Participants who do not have at least 2 (initial response and confirmation scan) post-baseline response assessments will be counted as non-responders.

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

9.4.2.2.5 DOR per Investigator Assessment

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

The same analysis as described in [Section 9.4.2.2.1 DOR per IRC] will be conducted using the FAS.

9.4.2.2.6 DCR per Investigator Assessment

Disease control rate (DCR) per investigator assessment is defined as the proportion of participants whose best overall response is a CR, PR or SD according to RECIST V 1.1 based on investigator assessment. Responses do not need to be confirmed to be scored as responders for the purpose of determining DCR.

The same analysis as described in [Section 9.4.2.2.2 DCR per IRC] will be conducted using the FAS.

9.4.2.2.7 PFS per Investigator Assessment

Progression-free survival (PFS) per investigator assessment is defined as the time from start of study treatment to first documentation of objective tumor progression (PD per RECIST V 1.1) based on investigator assessment, or to death due to any cause, whichever comes first.

The same analysis as described in [Section 9.4.2.2.3 PFS per IRC] will be conducted using the FAS.

9.4.2.2.8 Overall Survival

Overall survival (OS) is defined as the time from start of study treatment to date of death due to any cause.

The median OS and OS at 6 and 12 months will be estimated using the Kaplan-Meier method and will be reported along with the corresponding 95% CI. Details on the definition of censoring will be provided in the SAP. This analysis will be conducted using the FAS.

9.4.2.2.9 Tumor shrinkage

Best percent change from baseline in sum of diameters in target lesion(s) will be plotted as a waterfall plot for the participants with both baseline and at least 1 post-baseline measurements.

9.4.3 Analysis of Safety

Safety analysis is secondary endpoint in this study. The SAF will be used for the safety analysis. All participants who are enrolled and received study drug will be included in the SAF. The frequency of AEs and the SAEs will be summarized by MedDRA system organ class (SOC) and preferred term. In addition, summary statistics will be provided for the following safety parameters:

- Laboratory values
- Vital sign measurements
- 12-lead ECG
- ECOG performance status

9.4.3.1 Adverse Events

AEs will be coded using MedDRA.

An TEAE is defined as an AE observed after starting administration of the study drug and up to 30 days after the final administration of study drug. A study drug-related TEAE is defined as any TEAE with a causal relationship assessed as “yes” by the investigator.

The number and percentage of participants with TEAEs, drug-related TEAEs, serious TEAEs, drug-related serious TEAEs, TEAEs leading to withdrawal of treatment and drug-related TEAEs leading to withdrawal of treatment, TEAEs excluding SAEs will be summarized as deemed appropriate. The number and percentage of TEAEs by severity will also be summarized. The worst severity will be summarized if the same AE is recorded more than once for a participant.

AE data will be listed.

9.4.3.2 Laboratory Assessments

For quantitative clinical laboratory measurements (hematology, biochemistry and urinalysis analysis), descriptive statistics will be used to summarize results and change from baseline by visit.

Laboratory data will be listed.

9.4.3.3 Vital Signs

Descriptive statistics will be used to summarize vital sign results and changes from baseline for participants in the SAF by visit and time point.

Vital signs data will be listed.

9.4.3.4 Electrocardiogram

12-lead ECG data interpretations will be listed.

9.4.3.5 ECOG Performance Status

ECOG status will be summarized for each visit. Shifts from baseline to the best and worst postbaseline score may be tabulated.

9.4.3.6 Ophthalmology Examination

The analysis for ophthalmological assessment will be described in SAP in details.

9.4.4 Analysis of Pharmacokinetics

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.

9.4.4.1 Pharmacokinetic Concentrations

Descriptive statistics will be used to summarize plasma or serum concentrations of ADC, TAb and 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.

9.4.4.2 Estimation of Pharmacokinetic Parameters

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 who are also part of PKAS will have pharmacokinetic parameter estimates for each of the 3 analytes (ADC, TAb and MMAE), the following PK parameters will be calculated if data permit:

- C_{max} after first dose and third dose
- C_{trough} after first dose and third dose.
- T_{max} after first dose and third dose
- $AUC_{0\text{-}7d}$ after first dose and third dose
- $AUC_{0\text{-}28d}$ in Cycle 1
- $R_{ac}(C_{max})$
- $R_{ac}(AUC_{0\text{-}7d})$
- $t_{1/2}$ as appropriate
- CL and V_{ss} as appropriate

Descriptive statistics will be used to summarize plasma or serum pharmacokinetic parameters of ADC, TAb and MMAE separately.

9.4.5 Analysis of Pharmacodynamics | Immunogenicity

ATA to ADC will be listed, number and percentage of participants with positive ATA will be summarized.

9.4.6 Other Analyses

Not applicable.

9.5 Interim Analysis

No formal interim analysis is planned.

9.6 Additional Conventions

As a general principle, no imputation of missing data will be done. Exceptions are the start and stop dates of AEs and concomitant medications, the detailed imputation rules will be specified in the SAP. The imputed dates will be used to assess if the AEs or concomitant medications are treatment emergent or concomitant, respectively. Listings of the AEs and concomitant medications will present the actual partial dates; imputed dates will not be shown.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Ethical, Regulatory and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation

536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2 Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed Consent of Participants

10.1.3.1 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

10.1.3.2 Supply of New and Important Information Influencing the Participant's Consent and Revision of the Written Information

- The investigator or his/her representative will immediately inform the participant verbally whenever new information becomes available that may be relevant to the participant's consent or may influence the participant's willingness to continue participating in the study (e.g., report of serious adverse drug reaction). The communication must be documented in the participant's medical records and whether the participant is willing to remain in the study or not must be confirmed and documented.
- The investigator must update the participant's ICF and submit it for approval to the IRB/IEC. The investigator or his/her representative must obtain written informed consent from the participant on all updated ICFs throughout their participation in the study. The investigator or his/her designee must reconsent participants with the updated ICF even if relevant information was provided verbally. The investigator or his/her representative who obtained the written informed consent and the participant should sign and date the ICF. A copy of the signed ICF will be given to the participant and the original will be placed in the participant's medical record. An entry must be made in the participant's records documenting the reconsent process.

10.1.4 Data Protection

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited unless the participant provides written consent or approval. Additional medical information may be given only after approval of the participant to the investigator or to other appropriate medical personnel responsible for the participant's well-being.

The sponsor shall not disclose any confidential information on participants obtained during the performance of their duties in the study without justifiable reasons.

Even though any individuals involved in the study, including the study monitors and auditors, may get to know matters related to a participant's privacy due to direct access to source documents, or from other sources, they may not disclose the content to third parties.

The sponsor affirms the participant's right to protection against invasion of privacy. Only a participant identification number will identify participant data retrieved by the sponsor. However, the sponsor requires the investigator to permit the sponsor, sponsor's representative(s), the IRB/IEC and when necessary, representatives of the regulatory health authorities to review and/or to copy any medical records relevant to the study.

The sponsor agrees to comply and process personal data in accordance with all applicable privacy laws and regulations, including, without limitation, the Personal Information Protection Law in Japan and privacy laws in the US. If the services will involve the collection or processing of personal data (as defined by applicable data protection legislation) within the European Economic Area (EEA), then the sponsor shall serve as the controller of such data, as defined by the EU Data Protection Directive (DPD), and investigator and/or third party shall act only under the instructions of the sponsor in regard to personal data. If the sponsor is not based in the EEA, the sponsor must appoint a third party to act as its local data protection representative or arrange for a co-controller established in the EU for data protection purposes in order to comply with the DPD.

10.1.5 Committee(s) Structure

Sponsor will provide the imaging IRC charter including the organization, responsibility and procedure as an independent document before site initiation.

10.1.6 Dissemination of Clinical Study Data

ICH E3 guidelines recommend and EU Directive 2001/83/EC requires that a final CSR that forms part of a marketing authorization application, be signed by the representative for the coordinating investigator(s) or the principal investigator(s). The representative for the coordinating investigator(s) or the principal investigator(s) will have the responsibility to review the final study results to confirm to the best of his/her knowledge it accurately describes the conduct and results of the study. The representative for the coordinating investigator(s) or the principal investigator(s) will be selected from the participating investigators by the sponsor prior to database lock.

10.1.7 Data Quality Assurance

- All participant data relating to the study will be recorded on the eCRF unless transmitted to the sponsor or designee electronically in an external data file (e.g.,

central laboratory data). The investigator is responsible for verifying that data entries on the eCRF are accurate and correct by physically or electronically signing the eCRF.

- Guidance on completion of CRFs will be provided in a separate eCRF Completion Guideline.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations [CROs]).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator according to ICH or applicable local regulatory requirements, whichever is longer, after study completion. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8 Source Documents

1. Source data must be available at the study site to document the existence of the participants and to substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the participant.

2. The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

3. The investigator is responsible for ensuring the source data are attributable, legible, contemporaneous, original, accurate and complete whether the data are handwritten on paper or entered electronically. If source data are created (first entered), modified, maintained, achieved, retrieved or transmitted electronically via computerized systems (and/or other kind of electronic devices) as part of regulated study activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records, protocol-related assessments, AE tracking, electronic clinical outcome assessment (eCOA) and/or drug accountability.

4. Paper records from electronic systems used in place of electronic format must be certified copies. A certified copy must be an exact copy and must have all the same attributes and information as the original. Certified copies must include signature and date of the individual completing the certification. Certified copies must be a complete and chronological set of study records (including notes, attachments, and

audit trail information, if applicable). All printed records must be kept in the participant file and be available for archiving.

5. Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9 Study and Site Start and Closure

The study start date is the date the first participant signs the ICF for the study.

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study test product development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the sponsor or designee shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10 Arrangement for Use of Information and Publication of the Study

Information concerning the test product, patent applications, processes, unpublished scientific data, the Investigator’s Brochure and other pertinent information is confidential and remains the property of the sponsor. Details should be disclosed only to the persons involved in the approval or conduct of the study. The investigator may use this information for the purpose of the study only. It is understood by the investigator that the sponsor will use the information obtained during the study in connection with the development of the product and therefore may disclose it as required to other clinical investigators or to regulatory agencies. In order to allow for the use of the information

derived from this study, the investigator understands that he/she has an obligation to provide the sponsor with all data obtained during the study.

Publication of the study results is discussed in the study agreement.

10.1.11 Quality Assurance

The sponsor is implementing and maintaining quality assurance (QA) and quality control (QC) systems with written SOPs to ensure that studies are conducted and data are generated, documented, recorded, and reported in compliance with the protocol, GCP and applicable regulatory requirement(s). Where applicable, the QA and QC systems and written SOPs of the CRO will be applied.

The sponsor or sponsor's designee may arrange to audit the study at any or all study sites and facilities. The audit may include on-site review of regulatory documents, CRFs and source documents. Direct access to these documents will be required by the auditors.

To support quality around participant safety and reliability of study results, quality tolerance limits (QTLs) are defined and monitored. QTLs represent the acceptable variation of study data, taking into consideration the current state of medical and statistical knowledge about the variables to be analyzed, as well as the statistical design of the study. It is a level, point, or value associated with a parameter that should trigger an evaluation if a deviation is detected to determine if there is a possible systematic issue (i.e., a trend has occurred). The QTLs defined for this study are provided below.

Table 9 Quality Tolerance Limits

QTL #: Name and Parameter	Definition	Parameter Justification
QTL1: Eligibility	Proportion % of enrolled participants who do not meet critical inclusion/ exclusion criteria	A high number of participants not meeting the entrance criteria can have a negative impact on interpretation of the primary endpoint and overall validity of the study results.
QTL2: Tumor Scan Compliance	Proportion (%) of enrolled participants who do not have all imaging scans collected per study protocol requirements.	A high number of participants with missing tumor imaging data can have a negative impact on interpretation of the primary endpoint and overall validity of the study results.
QTL3: Safety Data	Proportion (%) of enrolled participants with outliers or trends in AE reporting rates.	Possible over or under reporting of safety information can impact subject safety.
QTL4: Pharmacokinetic Data	Proportion (%) of enrolled participants with missing data in actual sampling times or dosing, major protocol deviations, or dose adjustment.	A high number of participants with missing PK data/dose adjustment can have a negative impact on interpretation of the primary endpoint and overall study validity.

AE: adverse event; QTL: quality tolerance limit.

QTL Management Activities:

For control of risks associated with QTL 1: Eligibility, refer to [Section 5 Study Population, Section 7.1 Efficacy Assessments and Study Monitoring Plan].

For control of risks associated with QTL2 Tumor Scan Compliance, refer to [Section 7.1 Efficacy Assessments and Study Monitoring Plan].

For control of risks associated with QTL3 Safety Data, refer to [Section 7.2 Safety Assessments, Section 7.3 Adverse Events and Other Safety Aspects, Section 10.3 Appendix 3 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting, and Study Monitoring Plan].

For control of risks associated with QTL4 Pharmacokinetic Data, refer to [Section 7.4 Pharmacokinetics and Study Monitoring Plan].

10.2 Appendix 2: Contraception Requirements

WOCBP who are eligible for participation in the study, including those who choose complete abstinence, must have pregnancy tests as specified in the schedule of assessments. Pregnancy test results must confirm that the participant is not pregnant.

WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION DEFINITIONS

A female is considered fertile (i.e., WOCBP) following menarche and until becoming postmenopausal unless permanently sterile.

Females in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal with one of the following (i.e., permanently sterile):
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
- Postmenopausal

A postmenopausal state is defined as at least 12 months after last menstrual bleeding without an alternative medical cause.

In case the last menstrual bleeding cannot be clearly determined, confirmation with more than one follicle-stimulating hormone (FSH) measurement of at least > 40 IU/L (or higher per local institutional guidelines) is required.

Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status by repeated FSH measurements before study enrollment.

Documentation of any of these categories can come from the study site personnel's review of the female participant's medical records, medical examination or medical history interview.

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILDBEARING POTENTIAL

Female participants of childbearing potential are eligible for participation in the study if they agree to use a condom plus one of the highly effective methods of contraception listed below from the time of signing the ICF and until the end of relevant systemic exposure, defined as 6 months after the final study drug administration.[a]

Highly effective methods of contraception (failure rate of < 1% per year when used consistently and correctly)[b]:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation
  - Oral
  - Injectable
  - Implantable
- Other combined (estrogen- and progesterone-containing) methods
  - Vaginal ring
  - Injectable
  - Implantable
  - Intrauterine hormone-releasing system or intrauterine device
  - Bilateral tubal occlusion

Male is sterile due to a bilateral orchiectomy or radical cystoprostatectomy/removal of seminal vesicles

- Vasectomized partner
  A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
- Sexual abstinence
  Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the test product. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant. It is not necessary to use any other method of contraception when complete abstinence is elected.

[a] Local laws and regulations may require use of alternative and/or additional contraception methods.

[b] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILDBEARING POTENTIAL.

Male participants with female partners of childbearing potential are eligible for participation in the study if they agree to the following during treatment and until the end of relevant systemic exposure defined as 6 months after final study drug administration.[a]

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator
- Use a condom
- Female partners of male participants who have not undergone a vasectomy with the absence of sperm confirmed or a bilateral orchiectomy should require use of one form of highly effective methods of contraception

[a] Local laws and regulations may require use of alternative and/or additional contraception methods.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

10.3.1 Definition of Adverse Events

AE Definition:

An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study drug, whether or not considered related to the study IP.

"Adverse event" means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study IP. This includes events related to the comparator and events related to the (study) procedures.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study IP administration even though it may have been present before the start of the study.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.1.1 Abnormal Laboratory Findings

Any abnormal laboratory test result (e.g., hematology, biochemistry) or other safety assessment (e.g., vital signs, physical examination, ECGs or radiographic scans), including those that worsen from baseline, that is considered to be clinically significant in the medical and scientific judgment of the investigator and not related to underlying disease, is to be reported as an (S)AE.

Any clinically significant abnormal laboratory finding or other abnormal safety assessment, which is associated with the underlying disease, does not require reporting as an (S)AE, unless judged by the investigator to be more severe than expected for the participant's condition.

Repeating an abnormal laboratory test or other safety assessment, in the absence of any of the above criteria, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

10.3.1.2 Potential Cases of Drug-induced Liver Injury (DILI)

Refer to [Section 10.4 Appendix 4: Liver Safety Monitoring and Assessment] for detailed instructions on drug induced liver injury. Abnormal values in AST and/or ALT concurrent or with abnormal elevations in TBL that meet the criteria outlined in [Section 10.4 Appendix 4: Liver Safety Monitoring and Assessment], in the absence of other causes of liver injury, are considered potential cases of drug-induced Liver Injury (DILI) (potential Hy's Law cases) and are always to be considered important medical events and reported per [Section 10.3.6 Reporting Procedures for Serious Adverse Events].

10.3.2 Definition of Serious Adverse Events

An SAE is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening

  The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization
  - In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during

hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
    - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in persistent or significant disability/incapacity
    - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
    - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
- Other situations:
    - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

If an event is not an AE per definition in Section 10.3.1, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

10.3.3 Assessment of Causality

- The investigator is obligated to assess the relationship between study IP and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study IP administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Following a review of the relevant data, the causal relationship between the IP and each (S)AE will be assessed by answering "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the IP?"

When making an assessment of causality, the following factors are to be considered when deciding if there is evidence and/or arguments to suggest there is a "reasonable possibility" that an (S)AE may have been caused by the IP (rather than a relationship cannot be ruled out) or if there is evidence to reasonably deny a causal relationship:

- Has the participant been administered IP?
- Plausibility (i.e., could the event been caused by the suspect IP? Consider biologic and/or pharmacologic mechanism, half-life, literature evidence, drug class, preclinical and study data, etc.)
- Dechallenge/dose reduction/rechallenge:
  - Dechallenge: Did the (S)AE resolve or improve after only stopping the dose of the suspect drug without any treatment?
  - Dose reduction: Did the (S)AE resolve or improve after reducing the dose of the suspect drug?
  - Rechallenge: Did the (S)AE reoccur if the suspected drug was reintroduced after having been stopped?
- Laboratory or other test results: a specific lab investigation supports the assessment of the relationship between the (S)AE and the IP (e.g., based on values pre-, during and post-treatment)
- Available alternative explanations independent of IP exposure; such as other concomitant drugs, past medical history, concurrent or underlying disease, risk factors including medical and family history, season, location, etc., and strength of the alternative explanation
- Temporal relationship between exposure to the IP and (S)AE onset and/or resolution. Did the (S)AE occur in a reasonable temporal relationship to the administration of the IP?
- Finally, judging which are more likely based on all the above contents, factors of reasonable possibility or confounding factors, comprehensive judgment of plausible will be provided.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. While it is very important that the investigator always assesses causality for every event before the initial transmission of the SAE data to the sponsor, the initial report should be submitted without delay (i.e., within 24 hours of awareness). With limited or insufficient information about the event to make an informed medical judgment and in absence of any indication or evidence to establish a causal relationship, a causality assessment of "no" is to be considered. In such instance, the investigator is expected to obtain additional information regarding the event as soon as possible and to re-evaluate the causality upon receipt of additional information.

The medically qualified investigator may revise his/her assessment of causality in light of new information regarding the SAE and shall send an SAE follow-up report and update the eCRF with the new information and updated causality assessment.

10.3.4 Assessment of Severity

AEs, including abnormal clinical laboratory values, will be graded using the National Cancer Institute-common terminology criteria for adverse event (NCI-CTCAE) guidelines Version 4.03. The items that are not stipulated in the NCI-CTCAE Version 4.03 will be assessed according to the criteria below and entered into the eCRF:

Table 10 Grading Scale Defining the Severity of an Adverse Event

Grade	Assessment Standard
1 - Mild	Asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated
2 - Moderate	Minimal local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL†
3 - Severe	Medically significant but not immediately life threatening, hospitalization or prolonged hospitalization indicated; disabling; limiting self-care ADL‡
4 - Life-threatening	Life threatening consequences, urgent intervention indicated
5 - Death	Death related to AE

ADL: activities of daily living; AE: adverse event

†Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

‡Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden.

10.3.5 Recording and Follow-Up of AEs and/or SAEs

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the eCRF.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the eCRF.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Follow-Up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any post mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.6 Reporting Procedures for Serious Adverse Events

The investigator must complete and submit an SAE worksheet containing all information that is required by local and/or regional regulations to the sponsor by fax or email immediately (within 24 hours of awareness).

The investigator must complete and submit the reports as required by local regulation, containing all necessary information, to the competent authority.

The SAE worksheet must be signed by a medically qualified investigator (as identified on delegation of authority log). Signature confirms accuracy and completeness of the SAE data, as well as the investigator causality assessment including the explanation for the causality assessment.

For contact details, see [Contact Details of Sponsor's Key Personnel]. Fax or email the SAE/special situations/product defect worksheet to:

Astellas Pharma Global Development Inc.
Pharmacovigilance
International Fax: +44-800-471-5263
Alternative fax number: +1-888-396-3750
Email: safety-us@astellas.com*
*Please use email in general.

If there are any questions, or if clarification is needed regarding the SAE, please contact the sponsor's medical monitor/study physician or their designee [Contact Details of Sponsor's Key Personnel].

Follow-up information for the event should be sent promptly (as soon as available but no longer than within 7 days of the initial notification).

Full details of the SAE should be recorded on the medical records, SAE/special situation worksheet and on the eCRF.

The following minimum information is **required**:

- International study number/study number
- Participant number, sex and age
- Date of report
- Description of the SAE (event and seriousness criteria)
- Causal relationship to the IP (including reason)
- Drug provided (if any)

The sponsor or sponsor's designee will medically evaluate the SAE and determine if the report meets the requirements for expedited reporting based on seriousness, causality, and expectedness of the events (e.g., SUSAR reporting) according to current local/regional

regulatory requirements. The sponsor or sponsor's designee will submit expedited safety reports to competent authorities and concerned ethics committee per current local regulations, and will inform the investigators of such regulatory reports as required. Investigators must submit safety reports as required by their IRB/IEC within timelines set by regional regulations where required. Documentation of the submission to and receipt by the IRB/IEC of expedited safety reports should be retained by the study site.

The sponsor will notify all investigators responsible for ongoing clinical studies with the test product of all SUSARs and all SAE line listings, which require submission per local requirements IRB/IEC.

The investigators should provide written documentation of IRB/IEC notification for each report to the sponsor.

The investigator may contact the sponsor's medical monitor/study physician for any other problem related to the rights, safety or well-being of the participant.

10.3.7 Reporting Procedures for Special Situations

10.3.7.1 Contraceptive Guidance and Collection of Pregnancy Information

If a female participant becomes pregnant during the study dosing period or within 6 months from the discontinuation of dosing, the investigator is to report the information to the sponsor according to the timelines in [Section 10.3.6 Reporting Procedures for Serious Adverse Events] using the SAE worksheet as a special situation and in the eCRF.

The investigator will attempt to collect pregnancy information on any female partner of a male participant who becomes pregnant during the study dosing period or within 6 months from the discontinuation of dosing and report the information to the sponsor according to the timelines in [Section 10.3.6 Reporting Procedures for Serious Adverse Events] using the special situation worksheet or pregnancy form.

The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result and neonatal data, etc., should be included in this information.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or termination (including elective termination) of a pregnancy is to be reported for a female participant as an AE in the eCRF or SAE per [Section 10.3.6 Reporting Procedures for Serious Adverse Events]. Participant pregnancy outcomes listed below are to be reported as SAEs:

- Spontaneous abortion/miscarriage, abortion and missed abortion
- Death of a newborn or infant within 1 month after birth is to be reported as an SAE regardless of its relationship with the IP.
- If an infant dies more than 1 month after the birth, it is to be reported if a relationship between the death and intrauterine exposure to the IP is judged as *"possible"* by the investigator.
- Congenital anomaly (including anomaly in miscarried fetus)
- Benign hydatidiform mole
- Blighted ovum

Unless a congenital anomaly is identified prior to spontaneous abortion or miscarriage, the embryo or fetus should be assessed for congenital defects by visual examination or other means as appropriate. (S)AEs experienced by the newborn/infant should be reported via the pregnancy reporting form. Generally, follow up will be no longer than 6 to 8 weeks following the estimated delivery date.

10.3.7.2 Lack of Efficacy

Not Applicable.

10.3.7.3 Medication Error, Overdose and "Off-label Use"

If a medication error (defined as an unintended failure in the treatment process that leads to, or has the potential to lead to, harm to the participant), overdose or "off-label use" (i.e., use outside of the target disease defined in the protocol) is suspected, refer to [Section 6.7 Treatment of Overdose]. Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of an SAE, the SAE is also to be reported as described in [Section 10.3.6 Reporting Procedures for Serious Adverse Events] together with the details of the medication error, overdose and/or "off-label use."

10.3.7.4 Misuse/Abuse

Definition of misuse: Situations where the IP is/are intentionally and inappropriately used not in accordance with the intended use as defined in the protocol.

Definition of abuse: Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.

If misuse or abuse of the IP is suspected, the investigator must forward the special situation worksheet to the sponsor by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of an SAE, the SAE is also to be reported as described in [Section 10.3.6 Reporting Procedures for Serious Adverse Events] together with details of the misuse or abuse of the IP.

10.3.7.5 Occupational Exposure

If occupational exposure (e.g., inadvertent exposure to the IP of study site personnel while preparing it for administration to the participant) to the IP occurs, the investigator must forward the special situation worksheet to the sponsor by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs occurring to the individual associated with or resulting from the special situation are to be reported on the special situations worksheet.

10.3.7.6 (Suspicion of) Transmission of Infectious Agent

If transmission of an infectious agent associated with the IP is suspected, the investigator must forward the special situation worksheet to the sponsor by fax or email immediately (within 24 hours of awareness) and any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of an SAE, the SAE is also to be reported as described in [Section 10.3.6 Reporting Procedures for Serious Adverse Events] together with the details of the suspected transmission of infectious agent.

10.3.7.7 Suspected Drug-drug Interaction

If a drug-drug interaction associated with the IP is suspected, the investigator must forward the special situation worksheet to the sponsor by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of an SAE, the SAE is also to be reported as described in [Section 10.3.6 Reporting Procedures for Serious Adverse Events] together with details of the suspected drug-drug interaction.

10.3.8 Supply of New Information Affecting the Conduct of the Study

When new information becomes available that is necessary for conducting the study properly, the sponsor will inform all investigators involved in the study as well as the appropriate regulatory authorities. Investigators should inform the IRB/IEC of such information when needed.

The investigator will also inform the participants, who will be required to sign an updated ICF in order to continue in the study.

10.3.9 Urgent Safety Measures

An urgent safety measure (USM) is an intervention that is not defined by the protocol and can be put in place with immediate effect without needing to gain prior approval by the sponsor, relevant competent authorities (CA), IRB/IEC, where applicable, in order to protect participants from any immediate hazard to their health and/or safety. Either the investigator or the sponsor can initiate a USM. The cause of a USM can be safety-, product- or procedure-related.

10.3.10 Reporting Urgent Safety Measures

In the event of a potential USM, the investigator must contact the study physician (within 24 hours of awareness). Full details of the potential USM are to be recorded in the participant's medical records. The sponsor may request additional information related to the event to support their evaluation.

If the event is confirmed to be a USM, the sponsor will take appropriate action to ensure the safety and welfare of the participants. These actions may include but are not limited to a change in study procedures or study treatment, halting further enrollment in the study, or stopping the study in its entirety. The sponsor or sponsor's designee will notify the relevant competent authorities and concerned ethics committee within the timelines required per current local regulations, and will inform the investigators, as required. When required, investigators must notify their IRB/IEC within timelines set by regional regulations.

10.4 Appendix 4: Liver Safety Monitoring and Assessment

The purpose of this appendix is to provide guidance for the monitoring of DILI during the course of the study. It should be noted that this section does not specify the end-of-study analyses of liver enzymes. The end-of-study liver enzymes analyses will be described in the SAP. Any participant enrolled in a study with active drug therapy and who reveals an increase of serum aminotransferases (AT) to > 3 × ULN (to > 5 × ULN in participants with liver metastases) or TBL> 2 × ULN should undergo detailed testing for liver enzymes (including at least ALP, ALT, AST and TBL). Testing should be repeated within 72 hours of

notification of the test results. Participants should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

Confirmed abnormalities will be characterized as moderate and severe where ULN is as shown below.

Table 11 Moderate and Severe Liver Abnormalities

	ALT or AST		TBL
Moderate	> 3 × ULN (in participants without liver metastases), > 5 × ULN (in participants with liver metastases)	or	> 2 × ULN
Severe	> 3 × ULN	and†	> 2 × ULN

ALT: alanine aminotransferase; AST: aspartate aminotransferase; TBL: total bilirubin; ULN: upper limit of normal

†Samples taken simultaneously or within maximum 24 hours.

In addition, the participant should be considered to have severe hepatic abnormalities for any of the following:

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks (in the absence of liver metastases)
- ALT or AST > 3 × ULN and† TBL > 2 × ULN or international normalized ratio (INR) > 1.5 (If INR testing is applicable/evaluated)
- ALT or AST > 5 × ULN and† (TBL > 2 × ULN in participants with liver metastases)
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%)

† Samples taken simultaneously or within a maximum of 24 hours.

The investigator may determine that abnormal liver function results, other than those described above, may qualify as moderate or severe abnormalities and require additional monitoring and follow-up.

Follow-up Procedures

Confirmed moderate and severe abnormalities in hepatic functions should be thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination and clinical laboratory tests. The study site personnel are to complete the liver abnormality case report form (LA-CRF). Participants with confirmed abnormal liver function testing should be followed as described below.

Confirmed moderately abnormal liver function tests should be repeated 2 to 3 times weekly, and then weekly or less if abnormalities stabilize or the IP has been discontinued and the participant is asymptomatic.

Severe hepatic liver function abnormalities as defined above, in the absence of another etiology may be considered an important medical event and may be reported as an SAE. The sponsor should be contacted and informed of all participants for whom severe hepatic liver function abnormalities possibly attributable to IP are observed.

To further assess abnormal hepatic laboratory findings, the investigator is expected to:

- Obtain a more detailed history of symptoms and prior or concurrent diseases. Symptoms and new-onset diseases are to be recorded as AEs in the eCRF. Illnesses and conditions such as hypotensive events and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Nonalcoholic steatohepatitis is seen in obese hyperlipoproteinemic and/or diabetic participants and may be associated with fluctuating AT levels. The investigator should ensure that the medical history form captures any illness that predates study enrollment that may be relevant in assessing hepatic function.
- Obtain a history of concomitant drug use (including nonprescription medication, complementary and alternative medications), alcohol use, recreational drug use and special diets. Medications, including dose, are to be entered in the eCRF. Information on alcohol, other substance use and diet should be entered on the LA-CRF or an appropriate document.
- Obtain a history of exposure to environmental chemical agents.
- Based on the participant's history, other testing may be appropriate including:
  - Acute viral hepatitis (A, B, C, D, E or other infectious agents)
  - Ultrasound or other imaging to assess biliary tract disease
  - Other clinical laboratory tests including INR, direct bilirubin
- Consider gastroenterology or hepatology consultations.
- Submit results for any additional testing and possible etiology on the LA-CRF or an appropriate document.

Study Treatment Discontinuation

In the absence of an explanation for increased liver function tests, such as viral hepatitis, preexisting or acute liver disease, presence of liver metastases, or exposure to other agents associated with liver injury, the participant may be discontinued from study treatment. The investigator may determine that it is not in the participant's best interest to continue study treatment. Discontinuation of study treatment should be considered if:

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks (in participants without liver metastases
- ALT or AST > 3 × ULN and† TBL > 2 × ULN or INR > 1.5 (If INR testing is applicable/evaluated)
- ALT or AST > 5 × ULN and† (TBL > 2 × ULN in participants with liver metastases)
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%)

† Samples taken simultaneously or within a maximum of 24 hours.

In addition, if close monitoring for a participant with moderate or severe hepatic laboratory tests is not possible, study treatment should be discontinued.

Hy's Law Definition:

- Evidence that a drug can cause hepatocellular-type injury, generally shown by a higher rate than control of people with 3 × AT elevations over the ULN (2 × elevations are too common in treated and untreated participants to be discriminating).
- Cases of increased bilirubin (to at least 2 × ULN) in people with concomitant AT elevation to at least 3 × ULN (but it is almost invariably higher) and no evidence of

intra-or extra-hepatic bilirubin obstruction (elevated ALP) or Gilbert's syndrome [Temple, 2006].

FDA Guidance for Industry titled "Drug-induced Liver Injury: Premarketing Clinical Evaluation" issued by the FDA on July 2009:

FDA Guidance for Industry:

- The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo.
- Among participants showing such AT elevations, often with AT levels much greater than 3 × ULN, one or more also show elevation of serum TBL to > 2 × ULN, without initial findings of cholestasis (elevated serum ALP).
- No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.

10.5 Appendix 5: List of Excluded Concomitant Medications

The following list describes medications and foods that are common strong inhibitors/inducers of CYP3A, CYP2C8 and p-glycoprotein (P-gp) inhibitors that should be avoided, used with caution, or closely monitored. This list should not be considered all inclusive; consult individual drug labels for specific information. If there are concerns or questions about concomitant use of any drugs listed below, discussion with the sponsor is encouraged. Refer to Section 6.8 for concomitant therapies.

P-gp Inhibitors	**Strong CYP3A Inhibitors**	**Strong CYP3A4 Inducers**	**Strong CYP2C8 Inhibitors**	**Strong CYP2C8 Inducers**
amiodarone	boceprevir	carbamazepine	clopidogrel	rifampin
carvedilol	cobicistat	enzalutamide	gemfibrozil	
clarithromycin	conivaptan	mitotane		
drenedarone	danoprevir/ ritonavir	phenytoin		
itraconazole	elvitegravir/ ritonavir	rifampin		
lapatinib	grapefruit juice	St John's wort		
lopinavir/ritonavir	indinavir/ ritonavir			
propafenone	itraconazole			
quinidine	ketoconazole			
ranolazine	lopinavir/ritonavir			
saquinavir/ritonavir	paritaprevir/ ritonavir/ (ombitasvir and/or dasabuvir)			
telaprevir	posaconazole			
tipranavir/ritonavir	ritonavir			
verapamil	saquinavir/ ritonavir			
	telaprevir			
	tipranavir/ritonavir			
	troleandomycin			
	voriconazole			

Note: Any additional strong inhibitors/inducers of CYP3A, CYP2C8, and p-glycoprotein (P-gp) inhibitors that are identified or become commercially available while the clinical trial in ongoing are also applicable.

P-gp: p-glycoprotein

10.6 Appendix 6: Clinical Laboratory Assessments

Laboratory tests will be performed according to the schedule of assessments. Except for PK and PD related testing, all the other laboratory tests will be sent to a local laboratory for analysis.

Table 12 Clinical Laboratory Tests

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.

10.7 Appendix 7: ECOG Performance Status Scale

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

***Reference**

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649 55.

10.8 Appendix 8: RECIST Version 1.1

Table 1 – Time point response: patients with target (+/– non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Table 2 – Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.
a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Response Evaluation Criteria in Solid Tumors

Term	Definition
Complete response (CR)	Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to <10 mm.
Partial response (PR)	A ≥30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 0.5 cm. The appearance of one or more new lesions is also considered progression.
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
Measurable lesion	Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of 10 mm by CT scan (CT slice thickness no greater than 5 mm). A lymph node must be ≥15 mm in short axis when assessed by CT scan to be considered measurable.

From RECIST Version 1.1 (Eisenhauer 2009)

A response (CR or PR) will be considered confirmed if the following disease assessment (at least 4 weeks after the initial response) still shows response (CR or PR). In cases where the initial response is followed by SD, it will be considered as confirmed if the SD is later followed by PR or CR. For example, if a participant had PR in Week 8, SD in Week 12, and PR in Week 16, this PR will be considered as confirmed.

10.9 Appendix 9: Scanning and Contrast Guidelines

In decreasing order of preference

Brain Scan
Brain MRI with gadolinium
If gadolinium is medically contraindicated:
Brain MRI without gadolinium
Brain CT with IV contrast
Brain CT without IV contrast

Chest-Abdomen-Pelvis Scans:
Chest-Abdomen-Pelvis CT with IV contrast
If iodine media is medically contraindicated:
Chest CT without IV contrast and Abdomen-Pelvis MRI with gadolinium
Chest-Abdomen-Pelvis CT without IV contrast (oral contrast is recommended)
Chest-Abdomen-Pelvis MRI with gadolinium

CT Oral Contrast
Radio opaque agents (e.g., iodine and barium based agents)
Radio-lucent agents (whole milk, VoLumen®, water)

Important: Imaging modality, anatomical coverage and acquisition parameters should remain consistent across all imaging visits for each patient.

10.10 List of Abbreviations and Definition of Key Study Terms

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
BCVA	best corrected visual acuity
BMI	body mass index
BUN	blood urea nitrogen
CA	competent authority
CHO	Chinese hamster ovary
CI	confidence interval
CIOMS	council for international organizations of medical sciences
C_{max}	maximum concentration
CNS	central nervous system
CrCl	creatinine clearance
CR	complete response
CRF	case report form
CRL	Charles River Laboratories
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

Abbreviations	Description of abbreviations
DPD	Data Protection Directive
ECG	electrocardiogram
eCOA	electronic clinical outcome assessment
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EEA	European Economic Area
EOM	extra ocular movement
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
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
IOP	inter ocular pressure
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
LA-CRF	liver abnormality case report form
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
IV	intravenous
MMAE	monomethyl auristatin E
MRI	magnetic resonance imaging

Abbreviations	Description of abbreviations
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	objective 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
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
SJS	Stevens-Johnson Syndrome
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reactions
$t_{½}$	terminal elimination half-life
TAb	total antibody
TEAE	treatment-emergent adverse event
TBL	total bilirubin
TEN	toxic epidermal necrolysis
t_{max}	time of maximum concentration

Abbreviations	Description of abbreviations
ULN	upper limit of normal
UC	urothelial cancer
US	United States
USM	urgent safety measure
VA	visual acuity
V_{ss}	volume of distribution at steady state
WOCBP	woman of childbearing potential

Definition of Key Study 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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