CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761137Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	BLA
Application Number	761137
Priority or Standard	Priority
Submit Date	July 15, 2019
Received Date	July 15, 2019
PDUFA Goal Date	March 15, 2020
Division/Office	DO1/OOD/OND/CDER
Review Completion Date	December 17, 2019
Established Name	enfortumab vedotin-ejfv
(Proposed) Trade Name	PADCEV™
Pharmacologic Class	Nectin-4-directed antibody and microtubule inhibitor conjugate
Code name	
Applicant	Astellas Pharma US, Inc.
Formulation	injection, powder, lyophilized for solution
Dosing Regimen	1.25 mg/kg (up to a maximum dose of 125 mg) given as an IV infusion over 30 minutes on Days 1, 8, and 15 of a 28-day cycle until disease progression or unacceptable toxicity
Applicant Proposed Indication(s)/Population(s)	(b) (4) [redacted]
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor, and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

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Glossary

ADC	antibody-drug conjugate
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AEOI	AEs of interest
AST	aspartate aminotransferase
ATA	anti-therapeutic antibody
AUC	area under the plasma concentration time curve
BICR	blinded independent central review
BLA	biologics license application
BMI	body mass index
BOR	best overall response
BSEP	bile salt export pump
BTD	breakthrough therapy designation
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
CPI	checkpoint inhibitor
CR	complete response
CrCl	creatinine clearance
COA	clinical outcome assessment
DDI	drug-drug interaction
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eTMF	electronic trial master file
EE	efficacy evaluable
EORTC	European Organization for the Research and Treatment of Cancer
EOT	end of treatment
FAS	full analysis set

FDA	Food and Drug Administration
FGFR	fibroblast growth factor receptor
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practice
HbA1c	hemoglobin A1C
hERG	human ether-à-go-go
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IND	Investigational New Drug
INR	international normalized ratio
IPD	important protocol deviation
IRR	infusion-related reaction
ISS	integrated summary of safety
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	monomethyl auristatin E
MTD	maximum tolerated dose
NA	not available
N/A	not applicable
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NE	not evaluable
OPQ	Office of Pharmaceutical Quality
ORR	objective response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	progressive disease
PD-1	programmed death receptor-1
PD-L1	programmed death ligand-1
PFS	progression-free survival
PK	pharmacokinetics

PR	partial response
PRO	patient reported outcome
QLQ-C30	EORTC Quality of Life Questionnaire
QTcF	Fridericia's QT correction formula
RECIST	Response Evaluation Criteria in Solid Tumor
REMS	risk evaluation and mitigation strategy
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SOC	system organ class
TAb	total antibody
TEAE	treatment-emergent adverse event
TK	toxicokinetics
t_{max}	time to reach maximum observed plasma concentration
UC	urothelial cancer
ULN	upper limit of normal
UTI	urinary tract infection

1 Executive Summary

1.1. Product Introduction

Enfortumab vedotin is a Nectin-4-directed antibody-drug conjugate that is a new molecular entity and that has not previously received marketing approval for any indication by any regulatory body. Approval of enfortumab vedotin also represents the first approval of a drug that specifically targets the Nectin-4 pathway.

Enfortumab vedotin is comprised of a fully human IgG1-kappa antibody (AGS-22C3) conjugated to the microtubule-disrupting agent, monomethyl auristatin E, via a protease-cleavable maleimidocaproyl valine-citrulline linker (SGD-1006). The Applicant submitted nonclinical studies and cross-referenced data from nonclinical pharmacology, pharmacokinetic and toxicology studies in support of the approval of enfortumab vedotin for the proposed indication. The established pharmacological class is Nectin-4-directed antibody and microtubule inhibitor conjugate. Enfortumab vedotin demonstrated antitumor activity in nectin-4 expressing cell lines and animal models.

The proposed indication is (b) (4)

The dosing regimen proposed by the Applicant was 1.25 mg/kg (up to a maximum dose of 125 mg) given as an IV infusion over 30 minutes on Days 1, 8, and 15 of a 28-day cycle until disease progression or unacceptable toxicity.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness for this application is obtained from Cohort 1 of the single arm, multicenter study SGN22E-001 (EV-201) that enrolled patients with locally advanced or metastatic urothelial cancer who previously received systemic therapy with a platinum-based combination regimen and a PD-1/PD-L1 inhibitor. These patients all received enfortumab vedotin at the proposed dose. The confirmed objective response rate (ORR) in the 125-patient efficacy population was 44% (95% CI:35.1,53.2) and the median duration of response (DoR) was 7.6 months (95% CI: 6.3, NE) as determined by the Blinded Independent Central Review (BICR). The median follow-up duration was 10.2 months.

Patients with locally advanced or metastatic urothelial cancer previously treated with a platinum-containing regimen and immunotherapy have limited therapeutic options. Recently, erdafitinib received accelerated approval by the FDA for patients with susceptible FGFR3 or

FGFR2 genetic alterations in the post-platinum setting; however, only approximately 20% of patients with metastatic UC have these FGFR alterations. There are no other approved therapies for the proposed patient population. In post-platinum setting, trials report ORR less than 15% for single agent therapy.

Patients were not selected based on levels of Nectin-4 expression in Study EV-201. Out of the 125 patients enrolled, 120 patients had sufficient tumor sample available for testing of Nectin-4 expression by immunohistochemistry. In all of these patients, the tumor expressed detectable levels of Nectin-4.

The final agreed upon indication for enfortumab vedotin is (b) (4)

Accelerated approval of enfortumab vedotin is recommended. Submission of the interim overall survival (OS) analysis and final OS reports from clinical trial EV-301 titled; "An Open-Label, Randomized Phase 3 Study to Evaluate Enfortumab Vedotin vs Chemotherapy in Subjects with Previously Treated Locally Advanced or Metastatic Urothelial Cancer" results will be a postmarketing requirement (PMR) as a condition of approval for enfortumab vedotin.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Patients with locally advanced or metastatic urothelial cancer have a poor prognosis despite the high response rate seen with standard platinum/gemcitabine chemotherapy. While pembrolizumab has received regular approval in the second-line setting, patients who progress on this therapy or on another approved PD-1/PD-L1 inhibitor have limited treatment options. This represents a population of patients for which an unmet medical need exists.

Enfortumab vedotin is a breakthrough-therapy designated antibody-drug conjugate targeting Nectin-4. EV was evaluated in the single-arm phase 2 study EV-201, which enrolled patients with locally advanced or metastatic UC. Cohort 1, which forms the basis for the primary efficacy and safety evaluation, enrolled 125 patients who previously received platinum-based chemotherapy and a PD-1/PD-L1 inhibitor. Efficacy was assessed via independently-determined confirmed response rate and duration of response in patients, who received enfortumab vedotin at a dose of 1.25 mg/kg, which is the proposed dose for approval. In the overall development program 310 subjects were treated at the dose of 1.25 mg/kg, and data from the additional 185 patients in this larger cohort were also reviewed for a comprehensive safety evaluation of the dose under review.

The BICR-assessed response rate was 44% with a median duration of 7.6 months. A companion diagnostic was not submitted as Nectin-4 is highly expressed in bladder cancers and responses were seen even among patients with lower levels of Nectin-4 expression across the enfortumab clinical development program. Nectin-4 expression was not a criterion for enrollment in study EV-201. The safety profile of EV is acceptable in this setting. Deaths due to an adverse event occurred in 3.2% of patients while permanent treatment discontinuation occurred in 16%. Grade 3-4 adverse events occurred in 73% of patients and the most common (> 15%) all grade adverse events were fatigue, peripheral neuropathy, decreased appetite, rash, alopecia, nausea, dysgeusia, diarrhea, dry eye, pruritus and dry skin. Hyperglycemia, Peripheral Neuropathy, Ocular Disorders, Skin Reactions, Infusion Site Extravasations, and Embryo-Fetal Toxicity are labeled as warnings and precautions for enfortumab vedotin.

Approval of enfortumab vedotin is recommended by all disciplines. Results of the ongoing randomized phase 3 trial EV-301 will serve as a PMR

to confirm the clinical benefit of enfortumab vedotin.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Patients with locally advanced or metastatic urothelial cancer who have previously received platinum chemotherapy and immunotherapy with PD-1/PD-L1 targeting agents have limited treatment options and a poor prognosis.	Patients with locally advanced or metastatic urothelial cancer who have received prior platinum-based chemotherapy and immunotherapy have a serious and life-threatening condition with limited treatment options.
Current Treatment Options	• Erdafitinib has received accelerated approval for patients who have progressed on prior platinum-based chemotherapy and whose tumors harbor susceptible FGFR3 or FGFR2 alterations, although this only represents approximately 20% of patients in this setting. Other chemotherapeutic agents, including taxanes, may be used in this setting. None of other single agent therapies are curative and ORR is low. These patients eventually progress on such therapies.	Patients with locally advanced or metastatic urothelial cancer who have received prior platinum-based chemotherapy and immunotherapy currently may be treated off-label with chemotherapeutic agents. However, ORR is low. Relatively few (~20%) patients, whose tumors harbor susceptible FGFR3 or FGFR2 genetic alterations, may be treated with erdafitinib
Benefit	• In a single-arm trial, the confirmed response rate by Blinded Independent Central Review for enfortumab vedotin in patients at the proposed dose and line of therapy was 44% (95% CI 35.1, 53.2). This included 15 patients with complete responses (12%). The median duration of response was 7.6 months (95% CI 6.3, NE).	Enfortumab vedotin has demonstrated a good response rate with a median duration of response of approximately two thirds of a year and an acceptable safety profile

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• No REMS will be required. • The most commonly reported treatment emergent adverse events (TEAEs) were fatigue (56%), peripheral neuropathy (56%), decreased appetite (52%), rash (52%), alopecia (50%), and Nausea (45%). Hyperglycemia, Peripheral Neuropathy, Ocular Disorders, Skin Reactions, Infusion Site Extravasations, and Embryo-Fetal Toxicity are labeled as warnings and precautions. • The Applicant will be required to complete and to submit the final report of clinical trial EV-301 to confirm the clinical benefit of enfortumab vedotin in urothelial cancer. In addition to confirmation of efficacy in a randomized setting, data from EV-301 will more fully inform the complete safety profile of enfortumab vedotin	The risk-benefit profile of enfortumab vedotin is acceptable in the approved patient population. A randomized trial EV-301 is ongoing and will provide further data on the efficacy and safety of enfortumab vedotin in locally advanced or metastatic urothelial cancer.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

					Section where discussed, if applicable
✓	The patient experience data that was submitted as part of the application, include:				
	✓	Clinical outcome assessment (COA) data, such as			
			✓	Patient reported outcome (PRO)	8.1.2 Efficacy Results – Secondary or exploratory COA (PRO) endpoints, 8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability
			□	Observer reported outcome (ObsRO)	
			✓	Clinician reported outcome (ClinRO)	8.2 Review of Safety

	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that was not submitted in the application, but was considered in this review.	

X X X

X

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Bladder cancer is the sixth most common cancer in the United States (US), with an estimated 77,000 new cases diagnosed and more than 16,000 patient deaths from the disease in 2016 [National Cancer Institute, 2016]. Bladder cancer occurs mainly in people over the age of 55 years with an average age at the time of diagnosis of 73 years. Overall, approximately 1 in 27 men will develop this cancer in contrast to approximately 1 in 89 women. Whites are more likely to be diagnosed with bladder cancer than African Americans or Hispanic Americans. Urothelial cancer is strongly associated with smoking and increased dietary fat. Because these are also factors that predispose to other medical conditions, including cardiovascular, cerebrovascular, and pulmonary disease, patients with urothelial cancer often have significant comorbidities [American Bladder Cancer Society Statistics, 2019]. Approximately 90% of bladder cancers are urothelial cancer (UC) and, when advanced, the prognosis of these cancers is poor [Simeone, et al., 2019]. Most UCs are diagnosed at the non-muscle invasive stage, at which time management involves resection with or without intravesicular therapy. Despite such treatment, patients often develop more advanced disease that is incurable, ultimately leading to death. In addition, approximately 12% of patients have locally advanced or metastatic disease at diagnosis [National Cancer Institute, 2016].

First-line therapy for locally advanced or metastatic UC is cisplatin-based combination therapy, which is associated with a median overall survival (OS) of ~12.7 months in patients able to tolerate the therapy [Simeone, et al., 2019]. However, many patients are unable to tolerate cisplatin-based therapy due to comorbidities such as moderate/severe renal dysfunction, poor performance status or hearing loss, all of which are common among elderly patients who represent the population most affected by UC. In this regard, 75% of patients are over age 65 at diagnosis, and almost half of all patients are unable to tolerate cisplatin-based chemotherapy [National Cancer Institute, 2016]. For these patients, carboplatin-based therapy may be used instead, but is less effective, with a median overall survival of ~9 months.

Metastatic UC has, until recently, had a 5-year mortality rate exceeding 85%. Since 2016, the number of treatment options for patients with locally advanced or metastatic UC who progress after platinum-based chemotherapy have increased. These treatment options are described in Section 2.2. Although these agents are associated with durable responses that may contribute to prolonged survival, ~70% to 80% of patients do not benefit based on response to treatment and require additional therapeutic options. Locally advanced or metastatic UC is a serious, life threatening condition with significant unmet need once approved therapy classes are exhausted.

The FDA's Assessment:

The FDA agrees with the Applicant's position above.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

There are limited treatment options for patients following disease progression during or after PD-1/PD-L1 inhibitors and platinum. Recently, erdafitinib was also approved in the post-platinum setting; however, only 10% to 20% of patients with metastatic UC have susceptible FGFR mutations [Siefker-Radtke et al, 2018]. Other treatment options for these patients include chemotherapeutic agents such as taxanes (typically given as single agent), or participation in a clinical trial [NCCN, 2019]. Most of these chemotherapy options are associated with significant toxicity (e.g., febrile neutropenia and myelosuppression) that negatively impact quality of life in a patient population that is characterized by advanced age, low performance status, and multiple comorbidities. In the post-platinum setting, taxanes were shown to have objective response rates (ORRs) of 11.4% and 13.4% in 2 large phase 3 studies comparing PD-1/PD-L1 inhibitors to chemotherapy (paclitaxel, docetaxel, or vinflunine) [Bellmunt et al, 2018; Powles et al, 2018]. Consistent with the ORRs reported in the post-platinum setting, data from a small subgroup analysis of a recent phase 3 trial showed that subjects treated with docetaxel after both platinum and a PD-1/PD-L1 inhibitor had an ORR of 10.5% (n=2/19) [Drakaki et al, 2018].

There is a significant unmet medical need for effective therapies for patients with locally advanced or metastatic UC who have received a PD-1 or PD-L1 inhibitor and have received a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting. In clinical studies, enfortumab vedotin has been shown to be effective with a tolerable and manageable safety profile in this patient population.

provides a summary of potential treatments for patients with locally advanced or metastatic UC who have previously received a PD-

1/PD-L1 inhibitor and platinum-containing chemotherapy.

Product (s) Name	Relevant Indication	Year of Approval And Type of Approval [a]	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments						
Erdafitinib BALVERSA™	Monotherapy for adults with locally advanced or metastatic UC that have susceptible FGFR3 or FGFR2 genetic alterations and progressed during or following at ≥1 prior platinum-containing chemotherapy including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.	Initial US Accelerated Approval: 2019	Recommended starting dose of 8 mg (two 4 mg tablets) orally once daily, with a dose increase to 9 mg (three 3 mg tablets) once daily based on serum phosphate (PO_4) levels and tolerability at 14 to 21 days	Study BLC2001(NCT02365597): multicenter, open-label, single-arm study ORR: 32.2% by BICR, including non-responders to PD-L1/PD-1 therapy Median DOR: 5.4 months by BICR	• Ocular disorders (central serous retinopathy/retinal pigment epithelial detachment) • Hyperphosphatemia • Embryo-fetal toxicity [Erdafitinib (Balversa™) Prescribing Information, Janssen Pharmaceutical Companies, Apr 2019]	
Other Treatments						
Taxanes	No relevant indications for UC.	N/A	No labeled dosing guidelines in this setting. However, in the KEYNOTE-045, IMvigor211, and RANGE studies, the	KEYNOTE-045 (included investigator's choice of docetaxel, paclitaxel or vinflunine): ORR: 11.4% by BICR DOR: 4.3 months (4)	Docetaxel: • Toxic deaths in patients with hepatic impairment • Neutropenia and febrile neutropenia • Enterocolitis and neutropenic colitis	NCCN guidelines: a non-preferred recommended regimen for la/mUC post-platinum or post-checkpoint inhibitor (1)

			following doses were used for the chemotherapy control arms: Docetaxel: 75mg/m^2 as an IV infusion every 3 weeks. Paclitaxel: 175 mg/m^2 as an IV infusion every 3 weeks. (2-4)	IMvigor211 (included investigator's choice of docetaxel, paclitaxel or vinflunine): ORR by investigator: 13.4% DOR: 7.4 months (2) RANGE (docetaxel) ORR by BICR: 12.7% DOR: 4.2 months (3)	• Hypersensitivity reactions • Fluid retention • Neuropathy [Docetaxel Prescribing Information, Hospira, Inc, Mar 2019] Paclitaxel: • Anaphylaxis and severe hypersensitivity • Neutropenia, leukopenia, thrombocytopenia, and anemia • Peripheral neuropathy [Paclitaxel Prescribing Information, Mylan Institutional LLC, Dec 2018]	
Vinflunine (Javlor™)	Monotherapy for adults with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen.	Marketing authorization throughout EU: 21 Sept 2009	recommended dose: 320 mg/m^2 as 20-minute IV infusion every 3 weeks.	Median OS 6.9 months Median PFS 3.0 months Vinflunine (Javlor™) EPAR-Product Information, Jun 2018]	• Hematological toxicology • Gastrointestinal disorders • Cardiac disorders • Posterior reversible encephalopathy syndrome • Hyponatremia • Hepatic impairment • Renal impairment [Vinflunine (Javlor™) EPAR-Product Information, Jun 2018]	Not available in the US

IV: intravenous; la/muC: locally advanced or metastatic urothelial carcinoma; UC: urothelial cancer
a Accelerated approval or full approval

The FDA's Assessment:
The FDA generally agrees with the applicant's assessment.

Gemcitabine monotherapy is also included as a treatment option in guidelines based on a Phase II study of single-agent gemcitabine in 40 previously untreated patients with metastatic urothelial cancer. ORR from that trial was 28% (95% CI 16, 43), and median DOR was 5 months (Stadler et. al., JCO 1997). There were 10/40 (25%) with grade 3 hematologic toxicities and 2/40 (5%) with grade 4 toxicities. We note that this study was in an earlier line of therapy, and ORR is likely to be lower in later lines of treatment.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:
Enfortumab vedotin is not currently approved or marketed in the US or any other country globally. The clinical development program for enfortumab vedotin is being conducted under Investigational New Drug (IND) 116360 with Division of Oncology Products 1, and the relevant regulatory history is included in Section 3.2.

The FDA's Assessment:
The FDA agrees with the above assessment.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:
The initial drug substance process (b) (4) utilized (b) (4) and the antibody-drug conjugate (ADC) produced by this process is referred to as AGS-22M6E. An IND (b) (4) was opened to initiate the first in human phase 1 study AGS-22M6E-11-1. During this study, expression of (b) (4) (b) (4) a well characterized Chinese Hamster 0vary (CHO) cell expression system and the ADC produced by this process is enfortumab vedotin. At the request of FDA, a new IND 116360, was opened (28 Dec 2012) and all subsequent clinical trials have been conducted under this IND.

A summary of relevant regulatory correspondence with the Agency for enfortumab vedotin under IND 116360 is provided in Table 1.

Table 1: Summary of Regulatory Communications

Regulatory Event	Date	Description
Study May Proceed	28 Dec 2012	The sponsor submitted a new IND (116360) for enfortumab vedotin on 29 Nov 12 along with Protocol AGS-22M6E-11-1, Amendment 2 which incorporated a bridging design (b) (4) to CHO-derived ADC.
Face-to-Face Type B EOP1 Meeting	21 Apr 2017	The FDA acknowledged that the locally advanced or metastatic UC patient population post-programmed death receptor-1(PD-1)/programmed death-ligand 1 (PD-L1) inhibitor therapy represents a population with significant unmet medical need. The FDA provided feedback on the patient population, study endpoints and dose regimen for Phase 2 study EV-201. The Agency

Regulatory Event	Date	Description
		indicated that the accelerated approval pathway may be possible pending review of Study EV-201 results and the primary endpoint of confirmed ORR may predict clinical benefit.
Face-to-Face Type B Pre-Phase 3 Meeting	09 Nov 2017	The FDA provided advice on the study design, eligibility criteria, comparator, statistical design, endpoints, stratification factors and role of phase 3 study EV-301 as a confirmatory trial. The Agency supported the sponsors' proposed study design and positioning as a confirmatory study for both platinum-treated patients and patients without prior platinum treatment.
BTD Granted	22 Mar 2018	Enfortumab vedotin was granted a breakthrough therapy designation (BTD) for the treatment of patients with locally advanced or metastatic UC whose disease has progressed during or following checkpoint inhibitor therapy.
Face-to-Face Type B CMC Meeting	16 Apr 2018	The Agency provided feedback on the proposed process validation plan and DP stability data package to support the BLA and as single shelf-life for the 20mg and 30 mg/vial DP. A follow up meeting was recommended to discuss comparability data for the 20 mg/vial and 30 mg/vial strengths.
Type C Clinical Pharmacology Meeting	07 May 2018	The Agency noted that the proposed clinical pharmacology assessment plan provided in the briefing book was generally acceptable. The meeting was cancelled.
Initial Pediatric Study Plan Agreement	15 May 2018	FDA agreed with the initial Pediatric Study Plan (iPSP) with a full waiver for the use of enfortumab vedotin in pediatric patients with metastatic UC, from birth to 18 years.
Initial Comprehensive Multidisciplinary BTD Type B Meeting	20 Sep 2018	The sponsor provided a summary of the enfortumab vedotin development plan and gained agreement with the FDA that it is acceptable to submit data from Cohort 1 from Study EV-201 as the primary support for the BLA using the accelerated approval pathway.
Face-to-Face: Type B CMC Meeting	02 Nov 2018	The FDA provided feedback on the planned BLA submission package and pre-license inspection schedule. FDA also agreed to accept limited CMC information within 30-days of the BLA filing date.
Written Responses: Type B Pre-BLA Content and Format Meeting	14 Dec 2018	The FDA provided written responses on the proposed content and format for the BLA submission, the timing of data cutoff for the primary efficacy analysis of Study EV-201, and the strategy and presentation of safety analyses within the BLA.
Pre-BLA Type B CMC Meeting – Preliminary comments	26 Mar 2019	The FDA provided preliminary comments on CMC topics including DL intermediate specification, DP release and stability specifications, DS stability specification, and pre-license inspection schedule. The sponsor cancelled the meeting after receiving FDA's preliminary comments.
Pre-BLA Type B Clinical Meeting – Preliminary comments	03 May 2019	The sponsor provided a summary of the topline clinical results from Study EV-201 and the FDA provided preliminary comments regarding the proposed clinical content of the BLA submission, 30-day CMC amendment, 90-day safety update report, and communication plan. The sponsor cancelled the meeting after receiving FDA's preliminary comments.

BTD: Breakthrough Therapy Designation; CHO: Chinese hamster ovary; CMC: Chemistry, Manufacturing and Controls; DP: drug product; DS: drug substance; EOP1: end of phase 1; IND: investigational new drug; ORR: objective response rate; UC: urothelial cancer

The FDA's Assessment:

The FDA generally agrees with the above assessment, with the following additional rows to the table:

Regulatory Event	Date	Description
Granted priority review (BLA 761137)	13 Sept 2019	FDA letter documented 1) No filing review issues identified, 2) Review classification is Priority, and 3) User fee goal date is March 15, 2020
Written Responses	30 Sept 2019	FDA's advice to sponsor regarding adequacy of the (b) (4) patient sample size to support an indication (b) (4) was that : it is premature (b) (4) FDA recommended providing (b) (4) when data is available..

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The clinical team requested that OSI verify the integrity of the submitted clinical data from SGN22E-001 (Study EV-201). Three study sites (10030, 10008, and 10003) and the contract research organization (Seattle Genetics, Inc.), were selected for inspection. The inspections occurred between August and October 2019. All three clinical study sites had relatively high enrollment, with a cumulative enrollment of 30. Two of the three sites were associated with a higher ORR than the reported overall ORR of 44% for Cohort 1.

The inspections verified the Applicant's submitted clinical data with source documents at the three clinical investigator sites and evaluated the CRO's practices and procedures. There were no significant Good Clinical Practice (GCP) compliance deficiencies in the conduct of this study at these sites. Based on the results of these inspections, the data reported by these three investigator sites and the CRO appear to be acceptable and supportive of this BLA and the respective indication.

For details, see Clinical Inspection Summary from OSI.

4.2. Product Quality

Refer to separate Product Quality review.

4.3. Clinical Microbiology

Refer to separate Clinical Microbiology review.

4.4. Devices and Companion Diagnostic Issues

The applicant did not submit an application for an *in vitro* diagnostic device (IVD). FDA agrees that the use of an IVD is not essential to the safe and effective use of enfortumab vedotin.

There was no diagnostic device used to identify Nectin-4 expression or to select patients for the trial. Out of the 125 patients enrolled, 120 patients had sufficient tumor sample available for testing. In all of these patients, the tumor expressed Nectin-4. As responders were seen in patients with all levels of Nectin-4 expression, FDA agrees that the use of an IVD is not essential to the safe and effective use of enfortumab vedotin.

PD-L1 expression (combined positive score [CPS] <10 vs. ≥ 10) does not appear to impact the

benefit-risk ratio.

See Clinical Pharmacology (Figure 7 and associated discussion) and Clinical (Table 66 and associated discussion) sections for further discussion.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The FDA's Assessment:

Enfortumab vedotin is Nectin-4-directed antibody-drug conjugate (ADC, AGS-22C3E). The ADC is comprised of a fully human IgG1-kappa antibody (AGS-22C3) conjugated to the microtubule-disrupting agent, monomethyl auristatin E (MMAE), via a protease-cleavable maleimidocaproyl valine-citrulline (vc) linker (SGD-1006). Astellas and Seattle Genetics are co-development partners for enfortumab vedotin (BLA # 761137). The Applicant submitted nonclinical studies and cross-referenced data from nonclinical pharmacology, pharmacokinetic and toxicology studies from INDs 116360 and (b) (4) (Agensys Inc. owned, an affiliate of Astellas Pharma) in support of enfortumab vedotin (ASG-22C3E, AGS-22M6E, PADCEV) approval for the proposed indication. The established pharmacological class is Nectin-4-directed antibody and microtubule inhibitor conjugate.

During the product development of the antibody portion of the ADC, the Applicant changed the cell line used for the antibody production from (b) (4) (AGS-22M6) to CHO cells (AGS-22C3). Both ADCs (AGS-22M6E and AGS-22C3E) were used in the nonclinical studies to support the development of this product. In *in vitro* and *in vivo* pharmacology bridging studies, AGS-22C3E and AGS-22M6E demonstrated comparable binding affinity, cytotoxicity and *in vivo* activity (IND 116360). Furthermore, in a 4-week repeat-dose bridging toxicology study in cynomolgus monkeys, the toxicity profiles of AGS-22M6E and AGS-22C3E (3 mg/kg via weekly intravenous infusion) were similar in incidence and severity, and both showed comparable toxicokinetic profiles (IND 116360).

Primary Pharmacology: In a peer-reviewed publication authored by Agensys [1], the authors reported that Nectin-4 is a type I transmembrane protein that belongs to the Nectin family of related immunoglobulin-like adhesion molecules. Nectin-4 is expressed in multiple cancers, particularly urothelial, breast, lung, pancreatic, and ovarian cancer [1]. Higher levels of expression of Nectin-4 were associated with disease progression and/or poor prognosis (Agensys Inc. publication) [2].

In vitro and *in vivo* pharmacology studies were performed to characterize the pharmacology of enfortumab vedotin. In vitro, enfortumab vedotin and AGS-22M6 (unconjugated antibody)

[1] *Challita-Eid PM, et al. Enfortumab vedotin antibody-drug conjugate targeting Nectin-4 is a highly potent therapeutic agent in multiple preclinical cancer models. Cancer Res. 2016;76:3003-13.*

[2] *Fabre-LaFay S, et al. Nectin-4 is a new histological and serological tumor associated marker for breast cancer. BMC Cancer. 2007;7:73.*

bound to the Nectin-4 expressed on the surface of various human cancer cells and wide number of normal human tissues, though the expression in the normal human tissues was generally reported at low levels. Enfortumab vedotin and AGS-22M6 bound to cells engineered to express Nectin-4 but did not cross react with cells expressing Nectin-1, Nectin-2 and Nectin-3. Orthologs of Nectin-4 share >99%, ~94%, and ~92% homology to the human protein in cynomolgus monkeys, rats, and mice, respectively. Binding affinity of enfortumab vedotin to Nectin-4 was similar between humans, cynomolgus monkeys, and rats, but enfortumab vedotin bound to murine Nectin-4 at 10-fold lower affinity, thus supporting the use of the rat and monkey in the nonclinical toxicology studies.

Confocal and fluorescence microscopy evaluation demonstrated that subsequent to binding of enfortumab vedotin to cancer cells expressing Nectin-4 (e.g. bladder carcinoma cell line [T24-Nectin-4]), the enfortumab vedotin-Nectin-4 complex internalized and was catabolized by the cancer cells in the intracellular lysosomal compartment, beginning 2 hours post incubation. In a peer-reviewed publication authored by Seattle Genetics, the authors reported that following internalization of the enfortumab vedotin complex, MMAE was released via proteolytic cleavage of the vc-linker [3]. Mass spectrometry revealed high levels of intracellular free MMAE concentrations delivered by enfortumab vedotin in a Nectin-4 positive bladder carcinoma cell line model (T24-Nectin-4), while MMAE was not increased in cells that did not express Nectin-4. Higher cytotoxic cell killing correlated with higher levels of intracellular MMAE released. No cytotoxicity activity was reported with the unconjugated antibody (AGS-22M6). In a peer-reviewed publication authored by Seattle Genetics, the authors reported that intracellular release of MMAE into the cytosol induced growth arrest in G2/M phase followed by apoptotic cell death [4]. Neither AGS-22C3 (unconjugated antibody) nor enfortumab vedotin (complete ADC) promoted ADCC or CDC activity when tested against BT-483 (breast cancer cells) and PC3-AGS22 cells (prostate cancer cells) expressing human Nectin-4. On the other hand, enfortumab vedotin showed antibody-dependent cellular phagocytosis (ADCP) activity at concentrations ≥200 ng/mL in PC-3-Nectin-4^{+} and MDA-MB-468 breast carcinoma cells, which express Nectin-4. In a competition assay using flow cytometry, it was demonstrated that Nectin-1-Fc (a binding competitor of enfortumab vedotin) does not inhibit the cytotoxicity or binding of enfortumab vedotin to Nectin-4. In vivo, enfortumab vedotin administration to AG-B1 and AG-B8 (cells expressing human Nectin-4) patient-derived human bladder cancer xenograft mouse models resulted in >75% tumor growth inhibition relative to the unconjugated antibody and the control (5% dextrose).

Safety Pharmacology: Safety pharmacology parameters were evaluated as part of the general

[3] *Doronina SO, Toki BE, Torgov MY, Mendelsohn BA, Cerveny CG, Chace DF, et al. Development of potent monoclonal antibody auristatin conjugates for cancer therapy. Nat Biotechnol. 2003;21:778-84.*

[4] *Francisco JA, et al. cAC10-vcMMAE, an anti-CD30-monomethyl auristatin E conjugate with potent and selective antitumor activity. Blood. 2003;102:1458-65.*

toxicology studies with enfortumab vedotin. No effect was reported on ECG, heart rate, blood pressure, respiratory or CNS endpoints. MMAE alone did not significantly inhibit the human ether-à-go-go-related gene (hERG) channel. The data suggested that enfortumab vedotin and free MMAE would pose little or no risk for QT interval effects. QTc prolongation was not reported clinically.

ADME Studies: Systemic exposure of enfortumab vedotin (C_{max} and AUC) following a repeat intravenous dosing increased in approximately dose-proportional manner in rats and monkeys. No significant gender differences in systemic exposure were reported. Exposure to the naked antibody was higher than the enfortumab vedotin concentrations, due to release of MMAE component. MMAE exposure showed a similar pattern to enfortumab vedotin exposure in the rat and the monkey. In monkeys and rats, the half-life of enfortumab vedotin was 1.72 and 1.2 days, respectively. Decreases in systemic exposure levels were reported in rats and monkeys following repeat dosing (Day 85 or 22, respectively), due to the presence of anti-drug antibodies (ADAs).

Distribution- In a whole-body autoradiography in male rats, radioactivity of [^{3}H]MMAE was reported in most tissues of the rat at concentrations that were higher than blood during the 24 hours post dose. The highest concentrations were reported in the bile and urinary bladder, suggesting that both were routes of elimination of [^{3}H]MMAE. Elimination of radioactivity from most tissues was observed at 96 hours post dose, except for the eye uveal tract (t½ = 672 hours post dose), indicating that [^{3}H]MMAE likely bound melanin.

Metabolism- MMAE undergoes metabolism primarily by cytochrome P450 enzymes. In an in vitro cross species study, the metabolism was generally similar between the species (i.e. rat, monkey and human). Metabolites were formed by hydroxylation, demethylation, dehydrogenation or hydrolysis. Furthermore, MMAE was reported to be an inhibitor of CYP3A4/5 but not an inducer of CYP1A2, CYP2B6, or CYP3A4/5.

Excretion- A mass balance study was conducted in rats. Following a single intravenous dose of [^{3}H]-MMAE, the major route of excretion in rats was determined to be via the feces (≥96%), with urinary excretion accounting for ≤15% of the dose. Unchanged MMAE was excreted in both urine and feces.

Repeat-dose toxicology: The Applicant conducted GLP intravenous repeat-dose (weekly) general toxicology studies in rats (4 and 13-week) with enfortumab vedotin, and the unconjugated antibody (AGS-22M6); and in monkeys (4-week) with enfortumab vedotin, AGS-22M6 and MMAE alone. In addition, the effects of enfortumab vedotin on male reproductive system was investigated in a dedicated 4-week rat repeat-dose study. In the repeat-dose studies, the toxicity profile of enfortumab vedotin in the rat and monkey showed overlap. Mortalities were reported in the rat and monkey studies. In the 4-week rat study, death was

reported on Day 27 at the highest dose (10 mg/kg) of enfortumab vedotin (AUC 3920 µg.hr/mL; 4-fold higher than the $AUC_{0\text{-}168hours}$ of 914.4 µg*hr/mL in human at the clinical recommended dose of 1.25 mg/kg). The cause of death was attributed to skin, bone marrow (hypocellularity) and liver toxicities. No mortalities were reported in the 13-week study in rats administered enfortumab vedotin at doses up to 5 mg/kg once weekly (at 0.94-fold the exposure in human at the clinical recommended dose). In the 4-week repeat-dose study in monkeys, monkeys received doses of 1, 3, and 6 mg/kg enfortumab vedotin or 0.1093/0.0545 mg/kg MMAE once weekly. There were 5 early deaths in the study, three at a dose of 6 mg/kg enfortumab vedotin (Day 8; 6.7-fold the exposure in human at the clinical recommended dose) and two in the MMAE-only group (Day 8; at exposures lower than the exposure in human at the clinical recommended dose). The cause of death was attributed to skin, bone marrow, gastrointestinal (GI) tract, and liver toxicities. Prior to the moribund sacrifice/death, the monkeys were lethargic and hypoactive. Enfortumab vedotin administration to all the remaining monkeys at 6 mg/kg was ceased following the administration of only two doses (Days 1 and 8).

The predominant target organs of toxicities in both species included skin, injection site, bone marrow, liver and the ocular system (cornea, lacrimal gland). Additional target organs of toxicities were reported only in the rat that included sex organs (testes, epididymis and mammary gland) and GI tract in the monkey. Skin and injection site toxicities included abrasions, sores, reddened/dry skin, coupled with inflammation, epidermal hyperplasia, hyperkeratosis, ulcers, single-cell necrosis of the epidermis and/or adnexa. Bone marrow toxicity was associated with bone marrow hypocellularity and reductions in RBC, hemoglobin, hematocrit, neutrophils and eosinophils. Liver toxicity was associated with elevated AST, ALT, GGT, reduced albumin, and total protein; and microscopically with single-cell hepatocellular necrosis/abnormal mitosis. Eye toxicity in the rat was associated with increased mitotic figures in the corneal epithelium; and in the monkey, histopathological findings of lymphocyte infiltration in the lacrimal gland, accompanied by observations of ptosis, eye discharge, and periorbital swelling. Despite these observations, there were no significant findings in the in-life ophthalmologic examinations (slit lamp) in rats and monkeys. The ocular findings in the rat were reported only in the 13-week study. GI tract toxicity in the monkey was associated with microscopic findings of lymphatic dilation (ileum and jejunum), hemorrhage and coagulative necrosis in the cecum and colon. Male sex organ toxicities (rats) were associated with decreases in testes and epididymis weights, and histopathological findings in the testes (seminiferous tubule degeneration, spermatid/spermatocyte depletion), epididymis (cell debris, sperm granuloma and hypospermia/abnormal spermatids), seminal vesicle (glandular hypoplasia) and prostate (glandular hypoplasia) at doses ≥2mg/kg (at exposure approximately similar to the human systemic exposure at the clinical recommended dose). Seminal vesicle and prostate effects were not reported in the 13-week rat study. In male and female rats, mammary gland findings were reported and included atrophy, abnormal mitotic figures and single cell necrosis. The mammary gland findings were only reported in the 13-week study. In monkeys, a decrease in testes and increase in prostate weights were reported following

administration of MMAE alone. The sex organ weight changes in the monkeys were not correlated with histopathology findings. In both species, the majority of the lesions reported were either resolved or partially resolved, with the exception of findings in rat testes and epididymis. Cumulatively, the effects in the male reproductive system indicate a potential for impact on fertility in male patients. In rat and monkey studies, findings (hematology, organ weight changes and/or histopathology) were reported at the lowest enfortumab vedotin dose tested (0.19-fold [0.5 mg/kg] and 0.51-fold [1 mg/kg], respectively, the exposure in human at the clinical recommended dose).

The toxicities observed in animals were consistent with target-mediated enfortumab vedotin, as well as target-independent effects of MMAE. The eye and skin were identified in tissue cross reactivity studies in human and/or monkey (skin) as Nectin-4 expressing tissues, as such they were considered target-mediated toxicities. Bone marrow, GI-tract, and liver toxicities were observed in the monkey with both the ADC and MMAE. Bone marrow, liver, and sex organ toxicities were observed with the ADC only in rats. The toxicities in the nonclinical studies (skin, injection site, bone marrow, eye, intestine and axonal degeneration) correlated with clinically observed toxicities. No adverse toxicities were reported with the unconjugated antibody in either species, suggesting minimal impact from antigen binding alone.

Genetic toxicology: Using the standard core battery of genetic toxicology studies recommended in the ICH S2 guidance, MMAE was reported to be genotoxic in the in vivo rat bone marrow micronucleus assay through an aneugenic mechanism. MMAE was not shown to be mutagenic in the bacterial reverse mutation assay (Ames test) or the L5178Y mouse lymphoma forward mutation assay.

Other toxicology studies (phototoxicity, glucose uptake and insulin secretion): MMAE and linker-MMAE had no absorption in the range of 290-700 nm and do not present a direct phototoxicity concern. Studies were performed to determine if MMAE induced hyperglycemia, by evaluating the peripheral glucose uptake, islet viability and insulin secretion. There was significant increase in glucose uptake in human skeletal muscle cells at MMAE concentration of 100 ng/mL (26-fold higher than the C_{max} reported in human at the clinical recommended dose), while MMAE did not inhibit glucose uptake at lower concentrations tested (< 30 ng/mL; 7.7-fold the C_{max} reported in human at the clinical recommended dose). Loss in human islet viability was reported at concentrations ≥0.1 ng/mL (0.03-fold lower than the C_{max} reported in human at the clinical recommended dose) and a decline in insulin secretion (not dose dependent) from human islets incubated with MMAE was reported. The data suggested that enfortumab vedotin and free MMAE can pose risk for hyperglycemia in patients. Hyperglycemia occurred in patients treated with enfortumab vedotin. There were no indications of altered glucose homeostasis in the repeat-dose toxicology studies in rats and monkeys.

Reproductive toxicology: In the preliminary embryo-fetal study, enfortumab vedotin was

administered intravenously at 2 mg/kg and 5 mg/kg during the period of organogenesis to time mated female rats. Total litter loss (100%) was reported at a maternal toxic dose of 5 mg/kg (3-fold the human exposures at the clinical dose of 1.25 mg/kg). A dose of 2 mg/kg (at approximately similar to the human exposures at the clinical dose) resulted in maternal toxicity (decrease in body weight), embryo-fetal lethality (post implantation loss, early and late resorptions and fetal loss), and malformations that included gastroschisis, malrotated hindlimb, absent forepaw, malpositioned internal organs, and fused cervical arch. Additionally, skeletal anomalies (asymmetric, fused, incompletely ossified, and misshapen sternebrae, misshapen cervical arch and unilateral ossification of the thoracic centra) and decreases in fetal body weights were reported. A maternal and developmental NOAEL could not be reliably established due to limitations of the preliminary study design. In the definitive embryo-fetal development study, intravenous administration of MMAE alone at 0.2 mg/kg intravenously during the period of organogenesis to time mated female rats, resulted in maternal toxicity (decrease in body weight), abortion, embryo-fetal lethality (post implantation loss, early and late resorptions and fetal loss), malformations that included protruding tongue, malrotated hindlimbs, gastroschisis, agnathia, situs inversus, malformed mandible, caudal vertebrae (misaligned, fused and/or absent), split sternebrae, and shortened fibula. The reported findings following the administration of MMAE occurred at exposures approximately similar to the human exposures at the clinical recommended dose. MMAE was transferred across the placenta and was found in fetal serum, suggesting a possible direct effect of MMAE on the embryo and fetus. The similarity in embryo-fetal effects reported with enfortumab vedotin and MMAE suggests that the reported effects may be MMAE mediated.

The embryo-fetal toxicity studies indicated a potential risk to the fetus when enfortumab vedotin is administered to a pregnant woman. As such, it is recommended to advise females of reproductive potential to use effective contraception throughout treatment and for 2 months after the final dose (5 X $T_{1/2}$ [3.4 days] + 1 month) and to advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 4 months after the last dose (5 X $T_{1/2}$ [3.4 days] + 3 months). The recommendations for duration of contraception are based on the FDA guidance, Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations, for drugs that are aneugenic. Because of the potential for serious adverse reactions in a breastfed child from enfortumab vedotin, the label will advise women not to breastfeed during treatment and for at least 3 weeks after the last dose (5 x $T_{1/2}$ [3.4 days]).

The submitted nonclinical pharmacology and toxicology data support approval of PADCEV for the proposed indication.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:
N/A

The FDA's Assessment:
IND's 116360 and (b) (4) are owned by Agensys Inc (affiliate of Astellas Pharma).

5.3. Pharmacology

The FDA's Assessment:

Primary pharmacology

The Applicant conducted in vitro and in vivo pharmacology studies with ASG-22M6E.

The following studies (RD10-018, ES10-002, ES10-001) were reviewed by the FDA under IND # (b) (4) for ASG-22M6E (Agensys, Inc. an affiliate of Astellas Pharma). The following are summaries of the findings from each study, as presented in the original IND.

- **Study title: AGS-22M6E and AGS-22M6 Bind to Recombinant Human, Cynomolgus Monkey, Rat and Murine Orthologs of Nectin-4 Expressed on PC-3 Cells (Study # RD10-018)**

Results
Orthologs of Nectin-4 share >99%, ~94%, and ~92% homology to the human protein in cynomolgus monkeys, rats, and mice, respectively. Binding affinity to Nectin-4 was similar between humans, cynomolgus monkeys, and rats. AGS-22M6E also bound murine Nectin-4, though at a 10-fold lower affinity. Both the rat and the cynomolgus monkey are potentially relevant species for toxicology.

- **Study title: Immunohistochemical Evaluation of the Tissue Cross Reactivity of AGS- 22M63 with Normal Cynomolgus Monkey Tissues (Study # ES10-002)**

Results
Single tissue samples from normal cynomolgus monkeys were obtained, and immunohistochemistry staining was performed with either AGS-22M6E or an irrelevant control antibody. Specific staining was only observed in the skin, tonsil, and esophagus.

- **Study title: Immunohistochemical Evaluation of Nectin-4 Expression in Normal Human Tissues (Study # ES10-001)**

Results

Test tissues used in this study were from a normal human tissue microarray. Three human tissue microarrays were obtained with a total of 294 samples representing 36 human organs. Positive staining for Nectin-4 was seen in a wide number of tissues, though generally at low levels. Positive staining was reported in the bladder, breast, esophagus, larynx, pituitary gland, placenta, salivary gland, skin, stomach, testis, ureter, uterus, kidney, liver, lung, pancreas, prostate, thymus and tonsil.

During development, the Applicant changed the cell line used for the antibody production from (b) (4) *(AGS-22M6) to CHO cells (AGS-22C3). The following studies (RD12-004 & RD12-002) were conducted to bridge the ADCs (AGS-22M6E and AGS-22C3E) and reviewed by the FDA under IND # 116360 for ASG-22C3E (Agensys, Inc. an affiliate of Astellas Pharma). The following are summaries of the findings from each study as presented in the original IND.*

- **Study title: Determination of AGS-22C3E and AGS-22M6E Cytotoxicities on PC3-AGS22 cells (Study # RD12-004)**

Results

- Both ADCs induced specific cytotoxic activity to Nectin-4.
- The percent average potency for AGS-22C3E when compared to AGS-22M6E was 91.4%.
- Both ADCs have similar specific cytotoxic potencies.

Table 2: Average % relative potency of AGS-22C3E when compared to AGS-22M6E

Table 1. Average % Relative Potency of AGS-22C3E when compared to AGS-22M6E

EC_{50} Value Comparison using plates containing PC3-AGS22 Cells							
	Assay 1	*Assay 2*	*Assay 3*		*Average*	*SD*	*% CV*
AGS-22M6E	*1.535*	1.466	1.568		1.523	0.052	3%
AGS-22C3E	*1.701*	*1.604*	*1.716*		1.674	0.061	4%
% Relative Potency	90.2%	91.4%	91.4%		*91.0%*		

PC3 cells engineered to express human Nectin-4 (PC3-AGS22)
(Excerpted from Applicant's report)

- **Study title: Efficacy Study Comparing** (b) (4) **AGS- 22M6E and CHO Cell Line-Derived AGS-22C3E in a Subcutaneously Established Xenograft Model of Human Breast Cancer AG-Br7 in SCID Mice (Study # RD12-002)**

Results

AGS-22M6E and AGS-22C3E at 2 mg/kg resulted in comparable tumor regression and growth inhibition.

- **Study title: AGS-22M6E and AGS-22M6 Bind to Nectin-4 Expressed on the Surface of Cancer**

Cells (Study # RD10-013)

Methods and Results

The binding and affinity of AGS-22M6E (ADC) and AGS-22M6 (unconjugated antibody) to Nectin-4 expressed on the surface of Panc02-03 (pancreatic adenocarcinoma), HT-1376 (bladder carcinoma), NCI-H322M (non-small cell lung carcinoma), AG-OV1-XCL (ovarian carcinoma) and T47D (breast carcinoma) cancer cells were assessed at concentrations of 1, 3 and 10 µg/mL, by fluorescence-activated cell sorting (FACS).

AGS-22M6E (ADC) and AGS-22M6 (unconjugated mAb) bound Nectin-4 expressed on the surface of the different cancer cells at higher mean fluorescence intensity (MFI) relative to the negative control groups (H3-1.4.1.2 and H3-1.4.1.2-vcE), with a fold difference range between 3 to 62.

Table 3: Binding of AGS-22M6 and AGS-22M6E to cancer cells

Table 1. Binding of AGS-22M6 and AGS-22M6E to Cancer Cells

Sample ID	Average MFI ± SE (n=3)			Fold-difference			Cell ID
	10µg/ml	3µg/ml	1µg/ml	10µg/ml	3µg/ml	1µg/ml	
H3-1.4.1.2	3.9 ± 0.15	3.7 ± 0.11	3.7 ± 0.10	-	-	-	PANC02-03
AGS-22M6	16.3 ± 0.67	18.6 ± 0.61	17.3 ± 0.36	4	5	5	
H3-1.4.1.2-vcE	4.2 ± 0.08	3.9 ± 0.08	3.8 ± 0.07	-	-	-	
AGS-22M6E	13.0 ± 0.29	15.7 ± 0.08	15.9 ± 0.41	3	4	4	
H3-1.4.1.2	8.9 ± 0.33	8.3 ± 0.14	8.0 ± 0.20	-	-	-	HT-1376
AGS-22M6	399.7 ± 7.1	397.3 ± 14.2	411.7 ± 11.6	45	48	52	
H3-1.4.1.2-vcE	8.9 ± 0.13	7.3 ± 0.76	6.7 ± 0.90	-	-	-	
AGS-22M6E	365.2 ± 30.0	401.1 ± 2.5	409.9 ± 5.4	41	55	61	
H3-1.4.1.2	5.0 ± 0.07	4.8 ± 0.02	4.7 ± 0.01	-	-	-	NCI-H322M
AGS-22M6	261.6 ± 7.3	275.4 ± 3.06	292.1 ± 2.43	52	58	62	
H3-1.4.1.2-vcE	5.3 ± 0.02	4.9 ± 0.04	4.8 ± 0.1	-	-	-	
AGS-22M6E	248.3 ± 3.7	260.3 ± 7.3	274.3 ± 4.9	47	54	57	
H3-1.4.1.2	22.7 ± 0.75	19.4 ± 0.79	17.5 ± 0.19	-	-	-	AG-OV1-XCL
AGS-22M6	256.3 ± 0.33	303.9 ± 6.5	299.3 ± 13.7	11	16	17	
H3-1.4.1.2-vcE	23.3 ± 0.57	21.1 ± 0.30	18.1 ± 0.07	-	-	-	
AGS-22M6E	149.3 ± 6.6	196.8 ± 4.5	231.3 ± 4.5	6	9	13	
H3-1.4.1.2	25.1 ± 1.5	22.1 ± 0.54	21.0 ± 0.72	-	-	-	T47D
AGS-22M6	764.7 ± 35.6	907.2 ± 14.2	883.1 ± 5.3	31	41	42	
H3-1.4.1.2-vcE	30.9 ± 1.6	24.6 ± 0.43	21.0 ± 0.32	-	-	-	
AGS-22M6E	564.2 ± 20.5	706.8 ± 29.8	782.0 ± 6.21	18	29	37	

(Excerpted from Applicant's report)

AGS-22M6E and AGS-22M6 binding (B_{max}) and affinity (K_d) to human Nectin-4 on the surface of T47D breast cancer cells were approximately similar.

Table 4: Apparent affinity of AGS-22M6 and AGS-22M6E to nectin-4 expressed on T47D cells

Table 2. Apparent Affinity of AGS-22M6 and AGS-22M6E to Nectin-4 Expressed on T47D Cells

	AGS-22M6E	AGS-22M6
Bmax (MFI)	**215.1**	**243.2**
K_D (nM)	**0.011**	**0.011**
Std. Error		
Bmax (MFI)	6.7	4.8
K_D (nM)	0.002	0.001
95% Confidence Intervals		
Bmax (MFI)	201.3 to 228.9	233.5 to 253.0
K_D (nM)	0.006748 to 0.01572	0.008556 to 0.01425

(Excerpted from Applicant's report)

- **Study title: AGS-22M6E and AGS-22M6 Do Not Cross react With Other Nectin Family Members - Nectin-1, Nectin-2 and Nectin-3 (Study # RD10-015)**

Methods and results

The purpose of this study was to determine the specificity of binding of anti-Nectin antibodies, AGS-22M6, and AGS-22M6E to Nectin-4 and three other Nectin family members, Nectin-1, Nectin-2, and Nectin-3 using FACS analysis. The following recombinant cell lines were used: Rat1(E)-Nectin-1, Rat1(E)-Nectin- 2, Rat1(E)-Nectin-3, Rat1(E)-Nectin-4, and Rat1(E)-Neo control.

AGS-22M6E and AGS-22M6 bound with a high mean fluorescence intensity (MFI of 684.07 and 761.23) to Rat1(E) cells engineered to express Nectin-4 but not to Rat1(E) cells expressing Nectin-1, Nectin-2, or Nectin-3.

Table 5: Summary of FACS analysis of AGS-22M6E and AGS-22M6 and Nectin-specific Abs to recombinant Rat1 cells expressing Nectins 1, 2, 3 and 4

Table 1. Summary of FACS analysis of AGS-22M6E and AGS-22M6 and Nectin-specific Abs to recombinant Rat1(E) cells expressing Nectins 1, 2, 3, and 4.

Cell lines	1st Ab	2nd Ab	Mean Fluorescence			Avg	SE
Rat1(E)-neo control	anti-Nectin-1	anti-Mouse	5.11	5.32	5.27	5.23	0.06
Rat1(E)-neo control	anti-Nectin-2	anti-Mouse	5.11	5.38	5.15	5.21	0.08
Rat1(E)-neo control	anti-Nectin-3	anti-Mouse	6.47	5.88	6.57	6.31	0.22
Rat1(E)-neo control	AGS-22M6	anti-Human	9.28	8.69	8.13	8.70	0.33
Rat1(E)-neo control	AGS-22M6E	anti-Human	12.76	9.32	8.89	10.32	1.22
Rat1(E)-Nectin-1	anti-Nectin-1	anti-Mouse	1616.17	1715.51	1742.94	1691.54	38.51
Rat1(E)-Nectin-1	AGS-22M6	anti-Human	10.31	9.63	8.14	9.36	0.64
Rat1(E)-Nectin-1	AGS-22M6E	anti-Human	6.8	6.75	6.64	6.73	0.05
Rat1(E)-Nectin-2	anti-Nectin-2	anti-Mouse	962.8	1047.72	992.66	1001.06	24.87
Rat1(E)-Nectin-2	AGS-22M6	anti-Human	8.58	7.18	8.15	7.97	0.41
Rat1(E)-Nectin-2	AGS-22M6E	anti-Human	5.99	6.05	6.8	6.28	0.26
Rat1(E)-Nectin-3	anti-Nectin-3	anti-Mouse	1124.53	1111.37	1099.58	1111.83	7.21
Rat1(E)-Nectin-3	AGS-22M6	anti-Human	9.77	6.81	7.66	8.08	0.88
Rat1(E)-Nectin-3	AGS-22M6E	anti-Human	7.37	7.14	8.03	7.51	0.27
Rat1(E)-Nectin-4	AGS-22M6	anti-Human	779.45	768.99	735.24	761.23	13.34
Rat1(E)-Nectin-4	AGS-22M6E	anti-Human	698.25	692.67	661.29	684.07	11.50

(Excerpted from Applicant's report)

- **Study title: Confocal Microscopy Evaluation of AGS-22M6E Internalization in T47D and PC3-AGS-22 Cells (Study # ES10-006)**

Methods and results

The purpose of this study was to evaluate the internalization of AGS-22M6E in Nectin-4 endogenously-expressing T47D breast cancer cells and over-expressing PC3-AGS-22 recombinant prostate cancer cells, using immunofluorescence and confocal imaging at 0, 4, 8 and 18 hours post incubation with AGS-22M6E.

T47D cells:

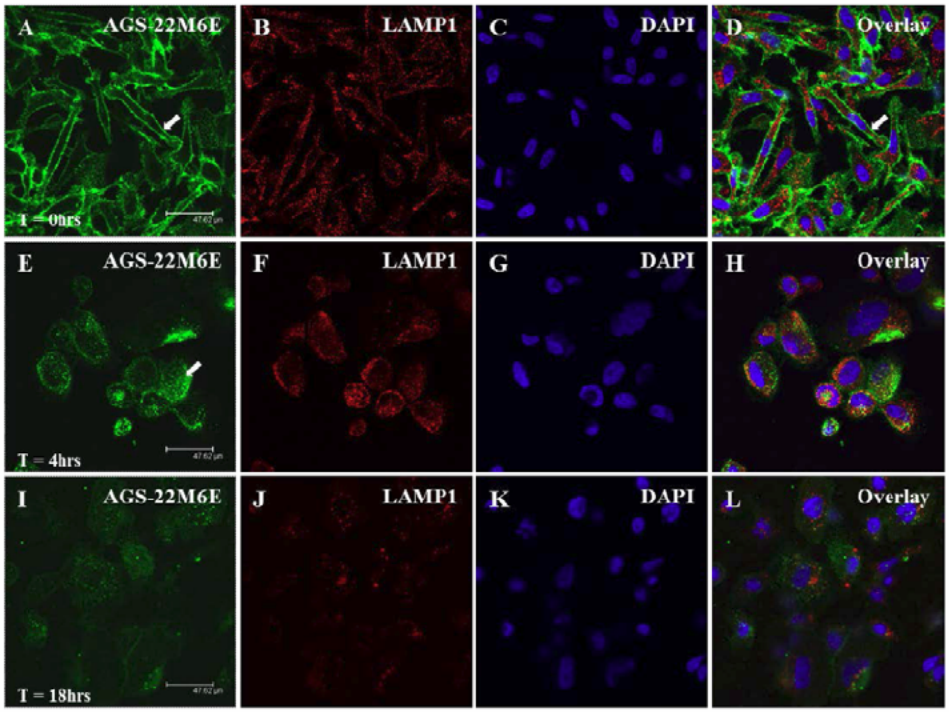
- At t=0 hours, AGS-22M6E was predominantly localized at the plasma membrane of cell to cell membrane junctions with minimal expression of AGS-22M6E in the intracellular regions.
- After 4 hours of incubation, AGS-22M6E was expressed in the cytosol of T47D cells. Labeling of AGS-22M6E with lysosomal marker LAMP1 showed a strong correlation between the lysosomal marker and intracellular AGS-22M6E, indicating that AGS-22M6E trafficked into the cytosolic compartment by a lysosomal internalization mechanism.
- Eight hours of incubation resulted in reduced expression of AGS-22M6E. Labeling of AGS-22M6E with LAMP1 showed no co-localization in the overlay images, indicating the absence of AGS-22M6E in the intracellular lysosomal compartments.

PC3-AGS-22 cells:

- At t=0 hours, AGS-22M6E was predominantly localized to the surface membrane with minimal expression of AGS-22M6E in the intracellular regions.
- At t=4 hours, AGS-22M6E was expressed in the cytosolic area of PC3-AGS-22 cells. Labeling of AGS-22M6E with LAMP1 revealed little to no correlation between the lysosomal marker and intracellular AGS-22M6E. This data suggested that internalization of AGS-22M6E in PC3-AGS-22 cells is not accomplished through the lysosomal pathway.
- At t=18 hours, images showed reduction in cell population and weak expression of AGS-22M6E in the cytosol. Labeling of AGS-22M6E with LAMP1 revealed no co-localization, indicating no AGS-22M6E in the intracellular lysosomal compartment.

Figure 1: Time course distribution of AGS-22M6E in PC3-AGS-22 cells

Figure 2. Time Course Distribution of AGS-22M6E in PC3-AGS-22 Cells



PC3-AGS-22 cells concurrently labeled with AGS-22M6E (**A, E, I,** green), lysosomal marker LAMP1 (**B**, **F**, **J**, red), and DAPI nuclear stain (**C**, **G**, **K**, blue). Image overlay of 3 concurrent labels (**D**, **H**, L). PC3-AGS-22 cells were incubated with AGS-22M6E and fixed after T=0 hours (top row), T=4 hours (middle row), and T=18 hours (bottom row). At T=0, AGS-22M6E was strongly observed at the plasma membrane of PC3-AGS-22 (top row, white arrows) with limited cytosolic expression. At T=4 hours, cell density was reduced and the previously observed spindle-shaped morphology of PC3-AGS-22 cells became more rounded. Additionally at T=4 hours, cell surface labeling was drastically reduced and intracellular expression increased (E, white arrow). Cytosolic AGS-22M6E did not co-localize with LAMP1 suggesting internalization of AGS-22M6E from the cell surface was not via lysosomal internalization. At T=18 hours, cell density was further reduced and overall expression of AGS-22M6E was significantly weaker in the remaining cells (**I**).

(Excerpted from Applicant's report)

- **Study title: Fluorescence microscopy evaluation of AGS-22C3E internalization and lysosomal trafficking in a Nectin-4 positive bladder carcinoma cell line model (Study # TRN-5257-NCR-EN)**

Methods and results

The objective of the study was to determine the internalization and trafficking kinetics of AGS-22C3E (ADC) in a human bladder carcinoma cell line engineered to express human Nectin-4 protein (T24 hNectin-4 [clone: 1A9]). T24 hNectin-4 (clone: 1A9) cells were evaluated by indirect immunofluorescence following treatment with AGS-22C3E, AGS-22C3 (unconjugated

antibody) or hIgG-vc-MMAE (non-binding negative control ADC) at final concentration of 2 µg/mL at 0, 2, 4, 8 and 18 hours post incubation.

- At t=0, AGS-22C3E was predominately localized to the cell surface membrane.
- At t=2hrs, AGS-22C3E was at punctate structures within the cells, that colocalized with the lysosomal marker LAMP1. AGS-22C3E staining continued on the plasma membrane but decreased relative to the t=0 timepoint and was enriched at cell-cell junctions.
- At t=4hrs, AGS-22C3E showed a greater reduction in the membrane staining intensity, but there were fewer cells that showed obvious colocalization with LAMP1 vesicles.
- At t=24hrs, there was significant reduction in AGS-22C3E detected on both the plasma membrane and within intracellular vesicles.
- The Applicant stated that the unconjugated antibody (AGS-22C3) showed a similar pattern to the ADC, while the non-binding negative control ADC (hIgG-vc-MMAE) did not show any fluorescent signal. No data was submitted in the report to support this conclusion.

In conclusion, the data suggested that AGS-22C3E was internalized and catabolized by the cells starting 2 hours post incubation with AGS-22C3E.

- **Study title: Measurement of intracellular release of MMAE by AGS-22C3E in a Nectin-4 positive bladder carcinoma cell line model (Study # TRN-5260)**

Methods and results

The objective of the study was to measure the intracellular concentration of free MMAE drug delivered by AGS-22C3E (ADC) in Nectin-4 positive bladder carcinoma cells. T24 human bladder carcinoma cell line was transduced with human Nectin-4 lentiviral particles (T24-hNectin-4). Cells were treated with the ADC for 24 hours at 100 and 1000 ng/mL. Mass spectrometry was used to determine the intracellular concentrations of MMAE.

- In T24-Nectin-4 cell line, intracellular MMAE concentrations at 100 ng/mL and 1,000 ng/mL, were 95 nM and 249 nM respectively, while, in T24 parental cells the MMAE levels were up to 0.6 nM.

Table 6: Intracellular MMAE concentrations in AGS-22C3E treated cells

Table 2. Intracellular MMAE concentrations in AGS-22C3E treated cells

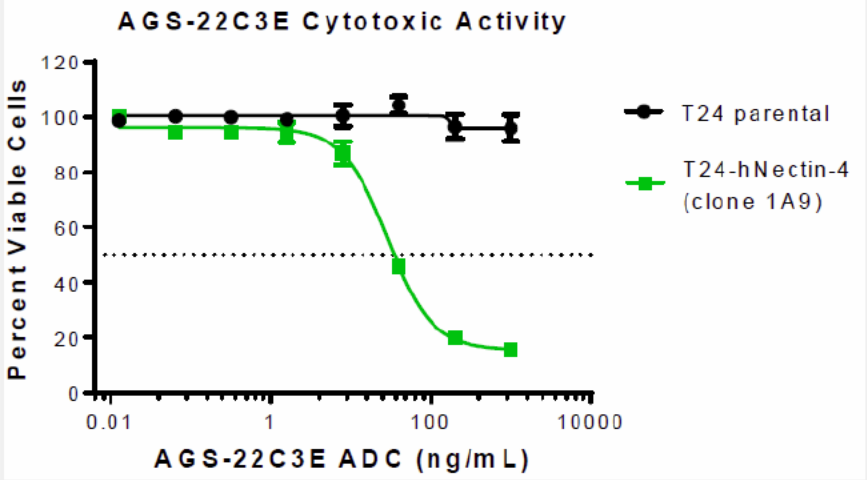
Cell Line	Drug	Nectin-4 Surface Expression (copies per cell)	Treatment Concentration	Intracellular MMAE (nM)
T24 parental	AGS-22C3E	<2000	100 ng/mL	BLLQ*
T24 parental	AGS-22C3E	<2000	1,000 ng/mL	0.6 ± 0.25
T24-Nectin-4 (clone: 1A9)	AGS-22C3E	650,000	100 ng/mL	94.9 ± 14.8
T24-Nectin-4 (clone: 1A9)	AGS-22C3E	650,000	1,000 ng/mL	248.8 ± 15

*Below lower limit of quantification (3.2 fmol MMAE)

(Excerpted from Applicant's report)

- In the T24-hNectin-4 cells, a higher cytotoxic cell killing was reported than the T24 parental cells. This increase in cytotoxicity was correlated with higher level of intracellular MMAE released reported in T24-hNectin-4 cells.

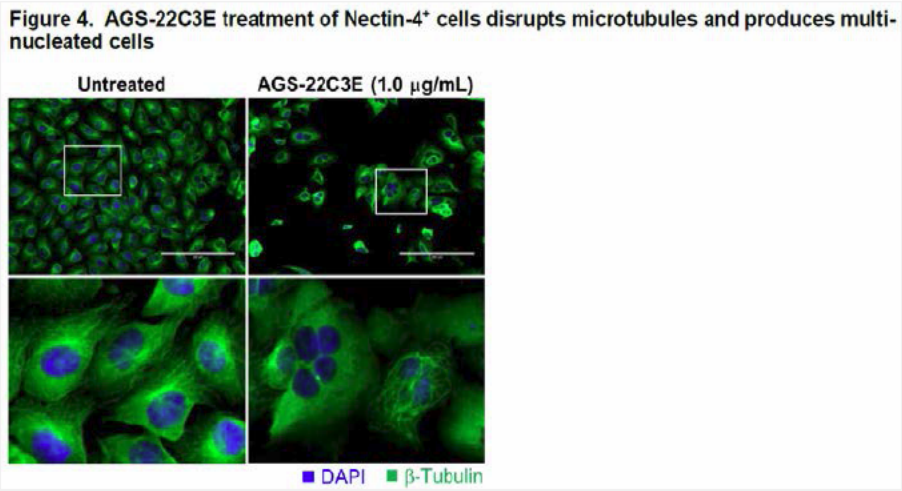
Figure 2: AGS-22C3E cytotoxic activity



(Excerpted from Applicant's report)

- AGS-22C3E dosed at 1,000 ng/mL for 48 hours resulted in multi-nucleated cells with disrupted microtubule networks at a higher frequency than the untreated cells.

Figure 3: AGS-22C3E treatment of nectin-4 cells disrupts microtubules and produces multinucleate cells



(Excerpted from Applicant's report)

In conclusion, AGS-22C3E released MMAE in the T24-hNectin-4 bladder carcinoma cells that express a high level of human Nectin-4, and in turn, MMAE caused disruption in the cell microtubule networks that resulted in cell death.

- **Study title: AGS-22M6E is cytotoxic to Nectin-4 expressing cells (endogenously positive for Nectin-4 and engineered to express human/cynomolgus/rat/murine orthologs of Nectin-4). (Study # RD10-017)**

Methods and results

The objective of the study was to evaluate the activity of AGS-22M6E and AGS-22M6 to induce cell death in a panel of PC3 cell lines engineered to express Nectin-4 antigen of human, cynomolgus monkey, rat, and mouse origin. Additionally, the activity of AGS-22M6E to induce cytotoxicity was evaluated in T47D breast carcinoma cell line that endogenously expresses Nectin-4.

AGS-22M6E induced a cytotoxicity effect in PC3 and T47D cells with IC_{50} ranging from 0.008 to 0.28 nM. No cytotoxicity activity was reported with the unconjugated antibody (AGS-22M6) on these cells (PC3 and T47D).

Table 7: IC_{50} values of inhibition of cell survival by AGS-22M6E in various cell lines

Table 3 IC_{50} Values of Inhibition of Cell Survival by AGS-22M6E in Various Cell Lines

Cell Line	IC_{50} (nmol/L)
PC3-human Nectin-4	0.008
PC3-cyno Nectin-4	0.02
PC3-rat Nectin-4	0.03
PC3-mouse Nectin-4	0.20
T47D	0.28

(Excerpted from Applicant's report)

- **Study title: AGS-22M6E and AGS-22M6 compete with Nectin-1-Fc for binding to Nectin-4 on the surface of Rat1(E)-Nectin-4 cells (Study # RD10-016)**

Methods and results

The objective of this study was to investigate that both AGS-22M6E and AGS-22M6 compete with Nectin-1 for binding to Nectin-4. The competition between AGS-22M6E, AGS-22M6 and Nectin-1-Fc-Biotin for binding to the Nectin-4 on the surface of the Rat1(E)-Nectin-4 cells was determined by FACS. Rat1(E)-Nectin-4 recombinant cell line was generated. Rat1(E)-Neo cells infected with empty retroviral construct was used as negative control.

Both AGS-22M6E and AGS-22M6 bound to Rat1(E)- Nectin-4 cells. In addition, Nectin-1-Fc fusion protein bound to the surface of Rat1(E)-Nectin-4 cells.

Table 8: MFI values of 3 test agents and controls on Rat1 (E) neo and Rat1 (E) nectin-4 cells

Rat1 (E) neo

Sample ID (ng/ml)	Detection	Rat1(E)neo			Average MFI	Std Dev	CV (%)	Std. Error
		X Geo MFI 1	X Geo MFI 2	X Geo MFI 3				
Nectin-1-fc-Bio(300)	Strep-PE	6	6	6	6	0	2	0.1
AGS22M6(1000)	anti-hIgG-PE	3	3	3	3	0	1	0.0
AGS22M6E(1000)	anti-hIgG-PE	3	4	4	4	0	4	0.1

Rat1 (E) nectin-4 cells

Sample ID (ng/ml)	Detection	Rat1(E) Nectin-4			Average MFI	Std Dev	CV (%)	Std. Error
		X Geo MFI 1	X Geo MFI 2	X Geo MFI 3				
Nectin-1-fc-Bio(300)	Strep-PE	118	152	110	127	23	18	13.1
AGS22M6(1000)	anti-hIgG-PE	296	197	431	308	118	38	67.9
AGS22M6E(1000)	anti-hIgG-PE	413	49	235	232	182	78	105.1

(Excerpted from Applicant's report)

Binding of Nectin-1-Fc to Rat(E)-Nectin-4 cells was decreased by the presence of increasing concentrations of both AGS-22M6E and AGS22M6.

Table 9: AGS-22M6 and AGS-22M6E compete with nectin-1-Fc for binding to nectin-4 on the surface of Rat1(E)-nectin-4 cells

Table 2. AGS-22M6 and AGS-22M6E compete with Nectin-1-Fc for binding to Nectin-4 on the surface of Rat1(E)-Nectin-4 cells

AGS-22M6/AGS-22M6E Conc.	Nectin-1-Fc MFI s (n=3)			
(ng/ml)	Competed by AGS-22M6	SE	Competed by AGS-22M6E	SE
1000	8	0.5	8	0.3
333.3	9	0.3	9	0.7
111.1	13	0.4	13	0.3
37.0	28	1.5	29	1.5
12.3	79	9.4	71	4.8
4.1	116	4.4	113	4.7
1.4	126	3.3	142	13.4
0.46	142	11.0	159	11.9
0.15	159	6.5	159	9.3
0.05	182	3.1	162	6.4
0.02	180	5.3	164	5.8

(Excerpted from Applicant's report)

In conclusion, AGS-22M6E, AGS-22M6 and Nectin-1-Fc bound to Nectin-4 expressing cells and AGS-22M6E and AGS-22M6 displace Nectin-1-Fc in a competition assay.

- **Study title: Effect of Nectin-1-Fc Protein on Enfortumab Vedotin Cytotoxicity against PC-3 Cells Overexpressing Nectin-4 Protein (Study # 7465-HP-0001)**

Methods and results

The objective of the study was to investigate the effect of Nectin-1-Fc protein on enfortumab vedotin cytotoxicity against PC-3 cells overexpressing Nectin-4 protein.
PC-3 were plated and Nectin-1-Fc protein was added to the well at 1 or 0 µg/mL. Subsequently, enfortumab vedotin was added to the well at concentrations of 40, 20, 10, 5.0, 2.5, 1.3, 0.63, 0.31 and 0 ng/mL. Cell viability was assessed using CellTiter Glo® assay.

Enfortumab vedotin induced cytotoxicity with or without the addition of Nectin-1-Fc protein to the well, indicating that Nectin-1 does not modulate the cytotoxicity of enfortumab vedotin.

Table 10: EC_{50} values of enfortumab vedotin on PC3 cells overexpressing nectin-4 protein

EC_{50} Values of Enfortumab Vedotin on PC-3 Cells Overexpressing Nectin-4 Protein

Condition	EC_{50} (ng/mL) (95% confidence interval)
with 1 µg/mL Nectin-1-Fc	2.4 (1.5-3.9)
without Nectin-1-Fc	2.4 (1.5-3.8)

(Excerpted from Applicant's report)

- **Study title: Evaluation of Antibody Dependent Cell-Mediated Cytotoxicity (ADCC) of AGS-22C3 and ASG-22CE on BT-483 and PC3-AGS22 Cells (Study # ES16-046)**
- **Study title: Evaluation of Complement-Dependent Cytotoxicity (CDC) of AGS-22C3 and ASG-22CE on BT-483 and PC3-AGS22 Cells (Study # ES16-047)**

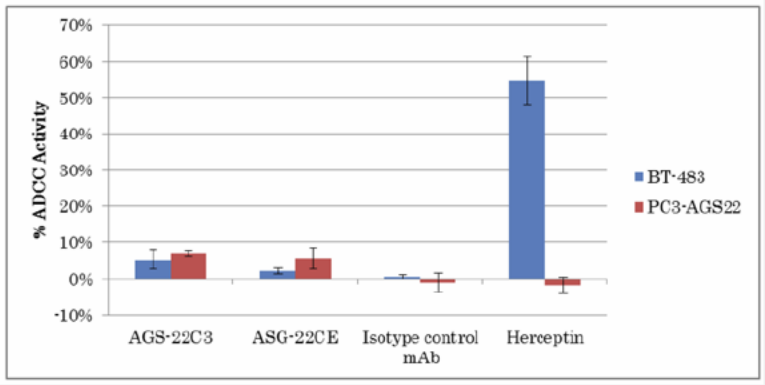
Methods and results

The objective of these studies was to evaluate the ability of AGS-22C3 (mAb) and ASG-22CE (ADC) to mediate antibody dependent cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). AGS-22C3 and ASG-22CE concentrations were 14.36 mg/mL and 10.5 mg/mL, respectively. BT-483 (breast cancer cells) and PC3-AGS22 cell lines (prostate cancer cells) expressing Nectin-4 were used in the presence of effector cells and normal human PBMCs. For the ADCC, the activity was determined using LDH release assay and CytoTox 96® Non-Radioactive Cytotoxicity Assay (Promega). For the CDC, the activity was determined by flow cytometry.

Neither AGS-22C3 nor ASG-22CE promoted ADCC and CDC activity when tested against BT-483 or PC3-AGS22 cell lines while the positive control Herceptin reported to have ADCC activity (55%). Furthermore, the positive control rituximab showed no CDC activity using BT-483 target cells while CDC activity (40-71%) was reported using the B-cell lymphoma cell line Raji.

Figure 4: ADCC and CDC activity of AGS-22C3 and ASG-22CE

Figure 1. Representative Graph of ADCC Activity of AGS-22C3 and ASG-22CE using BT-483 and PCT-AGS22 Target Cells



(Excerpted from Applicant's report)

Figure 1. CDC Activity of AGS-22C3 and ASG-22CE using BT-483 Target Cells

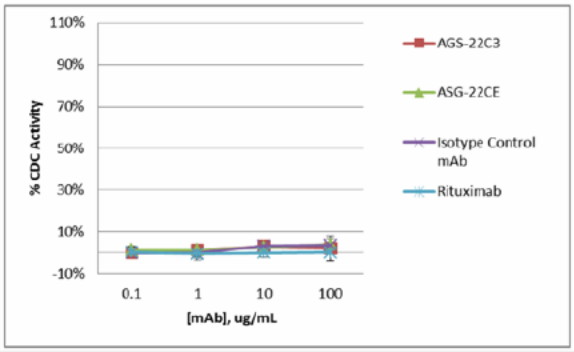


Figure 2. CDC Activity of AGS-22C3 and ASG-22CE using PC3-AGS22 Target Cells

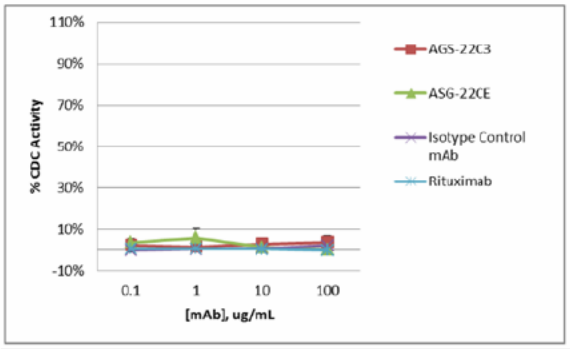
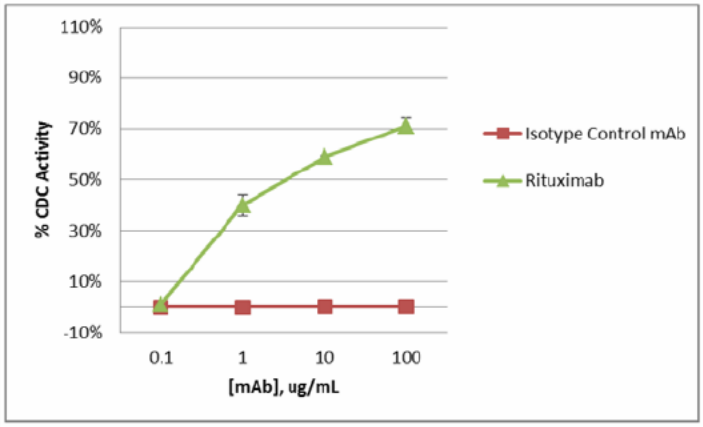


Figure 3. Positive Control CDC Activity of Rituximab using Raji Target cells



(Excerpted from Applicant's report)

- **Study title: Antibody-dependent cellular phagocytosis (ADCP) of AGS-22C3 and AGS-22C3E (Study # TRN-5259)**

Methods and results

The objective of the study was to evaluate the ADCP activity of AGS-22C3E and AGS-22C3 in PC-3-Nectin-4^{+} and MDA-MB-468 breast carcinoma cells, which express Nectin-4. The levels of ADCP effector function activity of macrophages was opsonized with AGS-22C3E and AGS-22C3.

The total antibody-dependent cellular phagocytosis (ADCP) ranged between 40% and 70% for the AGS-22C3 or AGS-22C3E compared to <30% ADCP activity in the no drug control group. AGS-22C3E and AGS-22C3 mediated ADCP activity at concentrations ≥200 ng/ml.

- **Study title: In vivo, multiple studies in a human bladder cancer xenograft model in mice were reported (Study # RD10-009 & ES15-015).**

Methods and results

AGS-22M6E administration resulted in tumor growth inhibition relative to the unconjugated antibody and the control (5% dextrose).

Table 11: Xenograft tumor studies in mice

Study #	Tumor Model	Species	Route (vehicle/ formulation) & frequency	Active/ effective dose(s) (mg/kg)	Tumor inhibition (%)[1]	*Antitumoral response*
Study # RD10-009						
AGS-22M6E (ADC)	AG-B1 (human bladder)	SCID Mice	IV; 5% dextrose; Every 4 days	0.8 mg/kg	75.7	Tumor growth inhibition
AGS-22M6 (Unconjugated antibody)					1.4	
Study # ES15-015						
ASG-22CE (ADC)	AG-B8 (human bladder)	SCID Mice	IV; 5% dextrose; BIW x 3 doses	0.5 mg/kg	102	Tumor growth inhibition
5% dextrose					60.2	

[1]*relative to the control group (5% dextrose)*

Data from peer-reviewed publications

- In a peer-reviewed publication authored by Seattle Genetics [5], the authors reported that following internalization of the ADC complex, MMAE attached to the mAbs by a cathepsin B-cleavable peptide linker released via proteolytic cleavage.
- In a peer-reviewed publication authored by Seattle Genetics [6], the authors stated that intracellular release of MMAE into the cytosol induced growth arrest in G2/M phase followed by apoptotic cell death.

Secondary Pharmacology

Data:
No secondary pharmacology studies were performed.

The Applicant's Position:
No secondary pharmacodynamic studies of the ADCs were conducted; however, the hypothetical secondary effects of enfortumab vedotin potentially interacting with the normal function of Nectin-4 as a cell adhesion molecule in adult and developing tissues, angiogenesis, vaccination, and in mammary and placental tissues was evaluated across the literature and nonclinical studies with the ADC, small molecule, and unconjugated antibody. Based upon a comprehensive review of nonclinical studies and clinical data, the lack of preclinical findings associated with these processes and/or the known toxicities of MMAE on these tissues, and due to a lack of any observed effects with the unconjugated antibody, these hypothetical secondary effects were considered to be not relevant for clinical dosing.

Consistent with this analysis, toxicities observed in tissues identified by tissue cross reactivity studies as Nectin-4 expressing, such as the skin, were considered related to the target-mediated uptake of monomethyl auristatin E (MMAE) and not an effect of the anti-Nectin-4 antibody.

The FDA's Assessment:
No secondary pharmacology studies were performed or submitted by the Applicant. No specific study reports or peer reviewed scientific publications were cited under the above section (secondary pharmacology); as such, the Applicant's hypothetical position regarding

[5] *Doronina SO, et al. Development of potent monoclonal antibody auristatin conjugates for cancer therapy. Nat Biotechnol. 2003;21:778-84.*

[6] *Francisco JA, et al. cAC10-vcMMAE, an anti-CD30-monomethyl auristatin E conjugate with potent and selective antitumor activity. Blood. 2003;102:1458-65.*

secondary effects could not be substantiated by this reviewer.

Safety Pharmacology

Data:
MMAE was assessed for cardiovascular safety in an in vitro human ether-à-go-go (hERG) channel assay. The antibody portion of the ADC, being too large to cross plasma membranes and unable to access and block the promiscuous inner pore of the hERG channel (5), was not evaluated in this in vitro assay. Electrocardiogram (ECG), heart rate, blood pressure, respiratory and central nervous system (CNS) safety pharmacology parameters were evaluated as part of the general toxicology studies performed with the ADC.

MMAE, at concentrations greater than 19,000-fold higher than the clinically observed C_{max} had limited (less than 50%) inhibition of potassium conductance via hERG channels, and at 10 µmol/L there was no significant inhibition of hERG channel activity. No effect was observed on the QTc using the Fridericia's QT correction formula (QTcF) and RR-interval in cynomolgus monkeys at concentrations of AGS-22M6E up to 5.6-fold the clinically observed C_{max}.

The Applicant's Position:
No effect was observed on ECG, heart rate, blood pressure, respiratory or CNS safety pharmacology parameters evaluated as part of the general toxicology studies performed in cynomolgus monkeys with the ADC.

The FDA's Assessment:
The FDA agrees with the Applicant's safety pharmacology conclusions.

5.4. ADME/PK

Data:
Data are summarized in Table 12.

Table 12: ADME/PK Study Summary

Type of Study	Major Findings
Absorption	
Not applicable	
Distribution	
XS-0025 Plasma Protein Binding Assay of MMAE by Ultracentrifugation 96D-1201 Tissue Distribution via Quantitative Whole-Body Autoradiography in Male Long-Evans Rats Following a Single Intravenous Bolus Administration of [^{3}H]MMAE	MMAE was not highly bound to plasma proteins in animals or humans but was species-dependent with higher levels of binding in human and rat plasma proteins compared to mouse and cynomolgus monkey. ^{3}H-MMAE-derived radioactivity was well distributed in Long-Evans rats and elimination of radioactivity from most tissues was observed at 96-hour post dose.
Metabolism	
XT084006 Reaction Phenotyping: Identification of human CYP enzymes involved in the in vitro metabolism of [^{3}H]-MMAE XT084007 Metabolite characterization of [^{3}H]-MMAE in rat, monkey, and human hepatocytes	The metabolism of MMAE was similar in rat, cynomolgus monkey and human hepatocytes with the same metabolites formed. An in vitro study with a panel of recombinant human CYP enzymes revealed that MMAE was primarily metabolized by CYP3A4.
Excretion	
420501 Excretion, Mass Balance and Pharmacokinetics of Radioactivity in Sprague-Dawley Rats Following a Single Intravenous Bolus Dose of cAC10-vc-[^{3}H]-MMAE or [^{3}H]-MMAE	A mass balance study was performed in rats following a single intravenous dose of ^{3}H-MMAE. The major route of excretion in rats was via feces, with urinary excretion accounting for <15% of the dose. Unchanged MMAE was the predominant species excreted in both urine and feces.
Pharmacokinetics	
20005664 A 4-Week Toxicity Study of AGS-2M6E and AGS-22M6 Administered by Intravenous Infusion to Cynomolgus Monkeys, with a 6-Week Recovery Period 20021751 A 4-Week Study of AGS-22M6E and Enfortumab Vedotin by Intravenous Infusion Administration in Cynomolgus Monkeys with a 6-Week Recovery Period	Exposure to AGS-22M6E, defined by AUC and C_{max} for ADC and TAb, was approximately dose-proportional in cynomolgus monkeys from 1 mg/kg to 6 mg/kg. There were no sex differences in the toxicokinetics of the ADC and unconjugated antibody. In cynomolgus monkeys, systemic exposure to TAb as defined by AUC was greater in comparison to ADC due to consistently higher serum TAb concentrations, especially at the later time points. The median $t_{1/2}$ of ADC was 0.700 to 1.72 days, while those of TAb were 1.02 to 2.75 days in cynomolgus monkeys. No substantial systemic accumulation in ADC, TAb and MMAE was found with the once per week dosing schedule for AGS-22M6E but the presence of ATA tended to decrease the overall AUC following repeat dose

Type of Study	Major Findings
	administration. MMAE exposures following the administration of AGS-22M6E were approximately dose-proportional in cynomolgus monkeys. The toxicokinetics of MMAE following administration of AGS-22M6E appeared to be formation rate-limited; in contrast, that of MMAE following intravenous administration of MMAE alone exhibited higher clearance (CL) and a larger volume of distribution at steady state compared to MMAE conjugated to ADC. In addition, AGS-22M6E was found to be equivalent to enfortumab vedotin in terms of exposure, clearance, and immunogenicity.
Pharmacokinetic Drug Interactions	
No PK studies were performed. TK studies are described below.	
TK Data from General Toxicology Studies	
XT133043 In vitro evaluation of MMAE as an inducer of cytochrome P450 expression in cultured human hepatocytes XT085021 In vitro evaluation of MMAE as an inhibitor of human cytochrome P450 enzymes RPT-01709 Caco-2 Permeability and Efflux Transporter Interactions of MMAE 15-3234 In vitro interaction studies of MMAE with human BCRP, BSEP and MRP2 efflux (ABC) transporters, and with human OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2 uptake transporters	MMAE was found to be a mechanism-based CYP3A4/5 inhibitor but not an inducer of CYP1A2, 2B6, or 3A4/5. MMAE was a substrate of P-glycoprotein (P-gp) but not a substrate of breast cancer resistance protein (BCRP), multidrug resistance-associated protein 2 (MRP2), organic anion transporting polypeptide 1B1 or 1B3 (OATP1B1 or OATP1B3), organic cation transporter 2 (OCT2), or organic anion transporter 1 or 3 (OAT1 or OAT3). MMAE was not an inhibitor of the bile salt export pump (BSEP), P-gp, BCRP, MRP2, OCT1, OCT2, OAT1, OAT3, OATP1B1, or OATP1B3 at clinically relevant concentrations.
TK Data from Reproductive Toxicology Studies	Toxicity was demonstrated in a preliminary embryo-fetal toxicity study and therefore formal embryo-fetal toxicity studies with full toxicokinetics were not performed.
TK Data from Carcinogenicity Studies	Not applicable

The Applicant's Position:

The binding affinity of AGS-22M6E to rat, cynomolgus monkey, and human Nectin-4 were comparable indicating that both rats and cynomolgus monkeys were pharmacologically relevant species for safety testing of enfortumab vedotin. AUC exposure to total antibody (TAb) was greater in comparison to ADC due to deconjugation and clearance of higher drug loaded species. The systematic exposure to AGS-22M6E in cynomolgus monkeys was ~3-fold the human systemic exposure at the recommended clinical dose. In rats, at the maximum tolerated dose (MTD), the systematic exposure was also ~2-fold the human systemic exposure at the recommended clinical dose. The results from these Good Laboratory Practice (GLP) nonclinical studies provide relevant evaluations of clinical safety and dose limiting toxicities. The C_{max} of MMAE following AGS-22M6E administration was ~0.04% of peak ADC concentration in cynomolgus monkeys based on molar ratios. Circulating MMAE was formation-limited with a delayed t_{max} compared with the ADC. Pharmacokinetic profiles for ADC and MMAE were similar to those observed in humans. MMAE is primarily excreted unchanged through the feces. MMAE was identified as a substrate of CYP3A4 in vitro, and co-administration of drugs that strongly inhibit CYP3A4 may result in increased exposure to MMAE. MMAE is a substrate of P-gp but not an inhibitor at concentrations $\leq$5 μM.

The FDA's Assessment:

The FDA agrees with the Applicant's ADME and PK study summary results. Additional study results are presented in the table below.

Study	Major Findings
PK (repeat dose toxicology studies)	The AGS-22M6E (ADC) systemic exposure (AUC) at the MTD on Day 1 in the rat and monkey were higher than the human systemic exposure at the recommended clinical dose of 1.25 mg/kg (914.45 μg.hr/mL). o In the 4-week monkey study (# 20005664), AGS-22M6E systemic exposure at 3 mg/kg (MTD/HNSTD) was 2450 μg.hr/mL (Day 1) and 903 μg.hr/mL (Day 22). o In the 4-week rat study (# 20005662), AGS-22M6E systemic exposure at the MTD (5 mg/kg) on Day 1 was 1640 μg.hr/mL (AUC on Day 22 was not reported).
Distribution	
Study # 96D-1201: Tissue Distribution via Quantitative Whole-Body Autoradiography	• Plasma concentrations of [^{3}H]MMAE were quantifiable through 24 hours post dose. C_{max} was reported at 0.17 hours and by 96 hours the concentrations were below the quantitation limit (BQL).

in Male Long-Evans Rats Following a Single Intravenous Bolus Administration of [^{3}H]MMAE	• [^{3}H]MMAE radioactivity was reported in most tissues of the rats at concentrations that were higher than in the blood from 0.17 hours to 24 hours post dose. • The following tissues showed the lowest concentrations of [^{3}H]MMAE: brain, spinal cord, eye lens. • The highest concentrations of [^{3}H]MMAE were reported in the bile (contents of the alimentary canal) and urinary bladder, suggesting that both were routes of elimination of [^{3}H]MMAE. • Elimination of [^{3}H]MMAE from all rat tissues was reported at 96 hours post dose (BQL), except for the eye uveal tract, 672 hours post dose, indicating, that [^{3}H]MMAE had an association with melanin. Eye lens levels were BQL by 0.17 hours.
Excretion	
Study # 420501: Excretion, Mass Balance and Pharmacokinetics of Radioactivity in Sprague-Dawley Rats Following a Single Intravenous Bolus Dose of cAC10-vc-[^{3}H]-MMAE or [^{3}H]-MMAE	• In feces, in addition to the major ^{3}H-MMAE peak, a metabolite of the parent compound (M6=C4) was characterized. The Applicant stated that MS/MS analysis showed that the M6 component appeared to be due to O-demethylation of the parent drug (MMAE) on the dolaproline residue. • C4 was also found in human feces. • No sex significant differences were reported in mean total recoveries of radioactivity. • The half-life of the ADC (cAC10-vc-^{3}H-MMAE) was between 8.5 to 10.7 days, and for the unconjugated small molecule ^{3}H-MMAE was 1 to 2.3 days. • ^{3}H-MMAE was cleared from the circulation and excreted faster than the ADC.

Table 13: Summary of proposed cAC10-vc-[^{3}H]-MMAE and [^{3}H]-MMAE metabolites in male and female rat feces (12-24 hours)

Table 2 **Summary of Proposed cAC10-vc-[^{3}H]-MMAE and [^{3}H]-MMAE Metabolites in Male and Female Rat Feces (12-24 Hours), Analyzed by LC-MS/MS**

Metabolite	m/z of $[M+H]^+$	m/z of Product Ions	Relative Retention Time*	Biotransformation
[^{3}H]-MMAE	718	686, 605, 506, 321, 152, 134	1.0	None: unchanged MMAE
M6	704	672, 591, 492, 307, 152, 134	0.94	Dolaproline O-demethylation

Note: *, Determined by LC-MS/MS

M6=C4

(Excerpted from Applicant's report)

Metabolism

Study #: XT084007: Metabolite characterization of [^{3}H]-MMAE in rat, monkey, and human hepatocytes

- Loss of substrate: The 240-minute incubations with hepatocytes from rat, monkey and human resulted in 32, 18 and 31% loss of [^{3}H]-MMAE, respectively.

- Twelve metabolites (C1 to C12) were detected in incubations of 10 µM [^{3}H]-MMAE with hepatocytes sample from rat, monkey and human. Samples were analyzed by mass spectrometry. Metabolites were formed by hydroxylation, demethylation, dehydrogenation or hydrolysis.

- All metabolites reported in the human hepatocytes were also detected in the rat and monkey.

Table 14: Metabolite profile and characterization

Table 6: Metabolite profile and characterization

XT metabolite assignment	*m/z*	Retention time (min)	Change in mass (amu) from MMAE	Proposed transformation from MMAE	Rat	Monkey	Human
C1	734	10.7	+16	Hydroxylation	+	+	ND
C2	734	11.0	+16	Hydroxylation	ND	+	ND
C3	734	11.2	+16	Hydroxylation	+	+	+
C4	704	11.3	−14	*O*-Demethylation	+	+	+
C5	605	11.7	−113	Amide hydrolysis	+	+	+
C6	734	12.0	+16	Hydroxylation	+	+	+
C7	704	12.3	−14	*N*-Demethylation	+	+	+
C8	716	14.2	−2	Oxidation of alcohol to form a ketone	+	+	+
C9	734	14.8	+16	Hydroxylation	+	+	+
C10	718	17.9	+0	*N*-demethylation + hydroxylation to form a nitroso compound	+	+	+
C11	734	18.9	+16	Hydroxylation	ND	+	ND
C12	716	19.4	−2	Oxidation of alcohol to form a carbonyl (following formation of the nitroso compound)	ND	+	+
Parent	718	12.6	+0	-	+	+	+

\+ Peak detected
ND Not detected

(Excerpted from Applicant's report)

Other Data

Study # XT133043: In vitro evaluation of MMAE as an inducer of cytochrome P450 expression in cultured human hepatocytes	The study was designed to assess the potential of MMAE for CYP (CYP1A2, CYP2B6, CYP3A4/5) induction in cultured human hepatocytes. MMAE treatment of cultured human hepatocytes up to 10 nM did not result in an increase in CYP activity, while concentrations of 100 and 1000 nM resulted in decreases in CYP1A2, 2B6 and 3A4/5 metabolic activity, mRNA levels or western immunoblot protein levels. In conclusion, MMAE was not an inducer of CYP1A2, CYP2B6, CYP3A4/5.

Study title: In vitro interaction studies of MMAE with human BCRP, BSEP and MRP2 efflux (ABC) transporters, and with human OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2 uptake transporters (Study #15-3234):

The study was performed to characterize the interaction of MMAE with the human efflux transporters and the human uptake transporters.

Vesicular transport assay was performed with inside-out membrane vesicles prepared from cells overexpressing human ABC transporters BCRP, BSEP, and MRP2. Uptake experiments using CHO or HEK293 cells were used. These cells expressed the respective human uptake transporters OATP1B1, OATP1B3, OAT1, OAT3, OCT1, and OCT2.

The Study director concluded that "MMAE at the highest applied concentration of 5 µM (6.58 µg/mL) interacted with OCT1 (29%) and OCT2 (23%), yet did not inhibit (defined as inhibition <20%) BCRP, BSEP, MRP2, OAT1, OAT3, OATP1B1 and OATP3B." A concentration of 5 µM (6.58 µg/mL) is higher than the MMAE C_{max} (3.9 µg/mL) at the enfortumab vedotin clinical dose of 1.25 mg/kg (Clinical study # EV-201).

Table 15: Effect of MMAE on the OCT1 and OCT2-mediated transport of metformin measured

OCT1-mediated transport of metformin				
Compound	**Nominal Concentration (µmol/L)**	**Transporter specific accumulation (cpm)**	**Relative transporter specific accumulation (% of control)**	**Relative inhibition (%)**
MMAE	5.00	109.00 (14.62)	71.24 (9.80)	29
	1.00	139.33 (7.30)	91.07 (5.53)	9
	0.20	150.67 (12.36)	98.47 (8.62)	2
	0.04	161.33 (14.74)	105.45 (10.16)	-5
	0.008	164.33 (7.70)	107.41 (6.02)	-7
DMSO	1 (%, v/v)	153.00 (4.69)	100.00 (4.34)	0
OCT2-mediated transport of metformin				
Compound	**Nominal Concentration (µmol/L)**	**Transporter specific accumulation (cpm)**	**Relative transporter specific accumulation (% of control)**	**Relative inhibition (%)**
MMAE	5.00	231.33 (12.06)	76.52 (5.10)	23
	1.00	269.67 (9.13)	89.20 (4.78)	11
	0.20	309.67 (17.94)	102.43 (7.30)	-2
	0.04	280.00 (3.56)	92.61 (4.02)	7
	0.008	318.33 (13.03)	105.29 (6.14)	-5
DMSO	1 (%, v/v)	302.33 (12.54)	100.00 (5.87)	0

(Excerpted from Applicant's report)

Study title: In vitro evaluation of MMAE as an inhibitor of human cytochrome P450 enzymes (Study # XT085021).

The study was designed to evaluate the ability of MMAE to inhibit the major CYP enzymes in human liver microsomes. The target concentrations of MMAE ranged between 0.1 to 100 µM (0.131 µg/mL to 131.6 µg/mL).

- MMAE resulted in concentration-dependent inhibition of CYP3A4/5.
- There was no reported inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP2D6.

Table 16: In vitro evaluation of MMAE as an inhibitor of human CYP enzymes

Table 6: Summary of results: *In vitro* evaluation of MMAE as an inhibitor of human CYP enzymes

		Direct inhibition		Time-dependent inhibition		
		Zero-minute preincubation		30-minute preincubation		Potential for time-dependent inhibition [c]
Enzyme	**CYP reaction**	**IC_{50} (µM) [a]**	**Maximum inhibition at 100 µM (%) [b]**	**IC_{50} (µM) [a]**	**Maximum inhibition at 100 µM (%) [b]**	
CYP1A2	Phenacetin *O*-deethylation	>100	17	>100	19	Little or no
CYP2B6	Bupropion hydroxylation	>100	2.6	>100	NA	Little or no
CYP2C8	Amodiaquine *N*-dealkylation	>100	NA	>100	NA	Little or no
CYP2C9	Diclofenac 4´-hydroxylation	>100	NA	>100	2	Little or no
CYP2C19	*S*-Mephenytoin 4´-hydroxylation	>100	17	>100	18	Little or no
CYP2D6	Dextromethorphan *O*-demethylation	>100	10	>100	10	Little or no
CYP3A4/5	Testosterone 6β-hydroxylation	>100	27	0.6	92	Yes[d, e, f]
CYP3A4/5	Midazolam 1´-hydroxylation	10	89	0.4	97	Yes

(Excerpted from Applicant's report)

5.5. Toxicology

5.5.1. General Toxicology

Data:

A GLP 3-Month Intravenous Toxicity Study of Enfortumab Vedotin in Sprague-Dawley Rats / 20117437:

Key Study Findings

- No enfortumab vedotin-related mortality, changes in body weight (absolute and gains) changes, food consumption, ophthalmology, coagulation, or urinalysis parameters were observed
- Identified target organs of toxicity included the testis, epididymis, skin and injection site, mammary gland, Harderian gland, and eye (cornea)
- Nonadverse changes in hematology (decreased erythrocyte mass) and clinical chemistry (elevated liver enzymes) were observed

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 0.5, 2, or 5 mg/kg enfortumab vedotin for 3 months (q1w x 13 doses)
Route of administration:	IV
Formulation/Vehicle:	5% (w/v) sterile dextrose solution (prepared from powder in sterile water for injection, USP)
Species/Strain:	Rat/Sprague-Dawley
Number/Sex/Group:	10
Age:	10 to 12 weeks
Satellite groups/ unique design:	9/sex/group (TK satellite animals)
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major Findings
Mortality	No mortality observed
Clinical Signs	Skin abrasions (5 mg/kg)
Food Consumption	No drug-related changes were observed
Body Weights	No drug-related changes in body weight or body weight gains were observed
Ophthalmoscopy	No drug-related changes were observed
Hematology	

Hematology, Day 92 (Sex: No. Evaluated)	M:10	F:9	M:10	F:10	M:10	F:10	M:9	F:10
Red blood cell count (10^6/μL)	8.515	8.204	–	7.914	–	7.748*	6.759*	7.342*
Hemoglobin concentration (g/dL)	14.83	15.12	–	14.62*	–	14.40*	13.24*	13.74*
Hematocrit (%)	44.77	44.33	–	42.57*	–	42.16*	40.08*	40.30*
Reticulocyte count (10^9/L)	174.95	147.16	–	–	–	–	297.74*	186.50*
Mean Corpuscular Volume (fL)	52.59	–	–	–	–	–	61.13	–
Mean Corpuscular Hemoglobin (pg)	17.40	–	–	–	–	–	20.10*	–
Red Blood Cell Distribution Width (%)	14.11	12.40	–	–	–	–	17.19*	13.61*
Platelet Count (10^3/μL)	846.3	813.0	–	–	965.9	901.5	1153.1*	1033.4*

Clinical Chemistry

Chemistry, Day 92 (Sex: No. Evaluated) †††	M:10	F:9	M:10	F:10	M:10	F:10	M:10	F:10
Alanine Aminotransferase (U/L)	43.6	24.6	–	–	–	–	79.3*	54.5
Aspartate Aminotransferase (U/L)	125.5	99.3	–	–	–	–	206.7*	197.5
Alkaline Phosphatase (U/L)	75.3	29.1	–	–	–	–	89.6	37.4
Total Bilirubin (mg/dL)	0.15	–	–	–	–	–	0.26*	–
Albumin (g/dL)	–	3.60	–	–	–	–	–	3.41
Globulin (g/dL)	2.82	3.00	–	–	–	–	3.17*	3.30*
Albumin/Globulin Ratio	1.04	1.20	–	–	–	–	0.90*	1.04*
Cholesterol (mg/dL)	62.2	80.1	–	–	–	98.9	94.9*	122.7*

Urinalysis	No drug-related changes were observed
Gross Pathology	Small and/or soft testes at ≥ 2 mg/kg
Organ Weights	Decreased testis weights in males (≥ 2 mg/kg) and adrenal gland weights in females (≥ 2 mg/kg) with increase liver weights in females at 5 mg/kg.
Histopathology	Degeneration of the testis, and hypospermia in the epididymis, at ≥ 2 mg/kg in males. Skin (serocellular crust, erosion/ulcer, inflammation, and acanthosis) at 5 mg/kg. Mammary gland atrophy at 5 mg/kg in females and findings of mitotic figures or single cell

	necrosis likely related to the presence of MMAE observed in skin, injection site, Harderian gland, eye (cornea), mammary gland, testis, and epididymis.
Other evaluations	-

-: No noteworthy findings
*ANOVA with Dunnett's/Dunn's P ≤ 0.05
†††Gamma glutamyltransferase was elevated in 1 male rat treated with 5 mg/kg/dose

A 4-Week Toxicity Study of AGS-22M6E and AGS-22M6 Administered by Intravenous Infusion to Cynomolgus Monkeys, with a 6-Week Recovery Period / 20005664:

Key Study Findings

- No test article-related changes observed in urinalysis, prothrombin time, activated partial thromboplastin time (APTT), ECG, blood pressure, and heart rate, and no ocular effects.
- ADC tissue effects were limited to skin and injection site observations at doses equal to or greater than 1 mg/kg and to hematologic findings of decreased red cell parameters and neutrophils and lymphoid tissue lesions. All findings demonstrated reversibility, and the no observed adverse effect level (NOAEL) and MTD was determined to be 3 mg/kg.
- Enfortumab vedotin and AGS-22M6E comparability was confirmed in a subsequent bridging toxicology study in monkeys (20021751), and comparable PK, immunogenicity, and toxicity profiles were observed.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 1, 3 and 6 mg/kg AGS-22M6E, 6 mg/kg AGS-22M6, and 0.1093/0.0545 mg/kg MMAE (q1w x 4 doses)
Route of administration:	IV
Formulation/Vehicle:	0.9% sodium chloride, USP
Species/Strain:	Monkey/Cynomolgus
Number/Sex/Group:	5
Age:	2.5 to 5 years
Satellite groups/ unique design:	2/sex/group designated for recovery
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major Findings

<table>
<tr><td>Mortality</td><td>Mortality observed at 6 mg/kg.</td></tr>
<tr><td>Clinical Signs</td><td>Abrasions, dry, and/or reddened skin. Watery feces and lethargy observed at non-tolerated doses.</td></tr>
<tr><td>Body Weights</td><td>No ADC-related changes were observed</td></tr>
<tr><td>Food Evaluation</td><td>No ADC-related changes were observed</td></tr>
<tr><td>Ophthalmology</td><td>No drug-related changes were observed</td></tr>
<tr><td>Veterinary physical examinations (RR, HR, BT)</td><td>No drug-related changes were observed</td></tr>
<tr><td>Hematology</td><td>Exemplary data are presented as a fold change versus respective predose values. Other changes in hematology included reversible decreases in hematocrit and hemoglobin at doses greater than and equal to 3 mg/kg of AGS-22M6E, with reversible lymphocyte and monocyte decreases at doses 6 mg/kg/week and 0.1093/0.0545/mg/kg/week of MMAE.
<table>
<tr><th>Dose Level (mg/kg/week)</th><th colspan="2">0</th><th colspan="2">1</th><th colspan="2">3</th><th colspan="2">6</th><th colspan="2">6 (AGS-22M6)</th><th colspan="2">0.1093/ 0.0545 MMAE</th></tr>
<tr><td>Hematology, Day 8 (No. of animals)§</td><td>M:5</td><td>F: 5</td><td>M: 5</td><td>F: 5</td><td>M:5</td><td>F: 5</td><td>M: 5</td><td>F: 5</td><td>M: 5</td><td>F: 5</td><td>M: 5</td><td>F:5</td></tr>
<tr><td>Reticulocytes</td><td>2.34</td><td>2.48</td><td>-</td><td>-</td><td>1.72</td><td>0.91*</td><td>0.42*</td><td>0.87*</td><td>-</td><td>-</td><td>0.39*</td><td>0.28*</td></tr>
<tr><td>RBC</td><td>0.94</td><td>0.91</td><td>-</td><td>-</td><td>0.90</td><td>0.88</td><td>0.84</td><td>0.87</td><td>-</td><td>-</td><td>0.75*</td><td>0.80</td></tr>
<tr><td>Neutrophils</td><td>-</td><td>-</td><td>-</td><td>-</td><td>1.32</td><td>0.78</td><td>0.21</td><td>0.61</td><td>-</td><td>-</td><td>0.07*</td><td>0.01*</td></tr>
<tr><td>Eosinophils</td><td>-</td><td>-</td><td>-</td><td>-</td><td>1.76</td><td>0.82</td><td>0.57</td><td>0.68</td><td>-</td><td>-</td><td>0.06*</td><td>0.02*</td></tr>
</table>
* Denotes values that are statistically (P ≤ 0.05) different from concurrent controls.
§The data are presented as a fold change versus respective predose.
-: no noteworthy findings</td></tr>
<tr><td>Clinical Chemistry</td><td>No ADC-related changes were observed at tolerated dose levels.</td></tr>
<tr><td>Urinalysis</td><td>No drug-related changes were observed</td></tr>
<tr><td>Gross Pathology</td><td>No drug-related changes were observed</td></tr>
<tr><td>Organ Weights</td><td>No drug-related changes were observed</td></tr>
<tr><td>Histopathology</td><td>Findings with the ADC consisted of Injection site inflammation and thrombus at ≥ 1 mg/kg, Skin inflammation (subcutaneous and dermis), hyperplasia, and hyperkeratosis at 6 mg/kg, and lymph node bilateral hyperplasia, mesenteric macrophage infiltrate at ≥ 3 mg/kg.</td></tr>
</table>

The Applicant's Position:

The toxicology program evaluated the ADC in a series of GLP-compliant repeat dose studies in the cynomolgus monkey and rat as they were identified as relevant nonclinical test species based on comparable antigen binding affinities. The toxicities observed in animals were consistent with target-mediated uptake of enfortumab vedotin as well as some target-independent effects of MMAE. Target-mediated skin toxicity correlated with Nectin-4 expression. Bone marrow hypocellularity was the primary target-independent toxicity observed and was observed with both the ADC and MMAE. The target organs of skin, bone marrow, eye (corneal epithelium), and intestine correlated with clinically observed toxicities, and were reversible following cessation of treatment. No toxicities were observed with the unconjugated

antibody, suggesting no impact from antigen binding alone.

The FDA's Assessment:

In general, the FDA agrees with the study results presented by the Applicant. Additional study results are presented below for clarity/completeness.

A GLP 3-Month Intravenous Toxicity Study of Enfortumab Vedotin in Sprague-Dawley Rats / 20117437:

Methods: In this study, rats were intravenously administered enfortumab vedotin (0.5, 2, or 5 mg/kg) once weekly for 13 weeks. Recovery was not evaluated.

- At 5 mg/kg, decreases in body weight gains were reported in males (-18%).
- At 5 mg/kg, decreases in PT (-8%) and PTT (-19%) were reported in males.
- At 5 mg/kg, scabs were reported on the dorsal skin of the rats.
- At doses ≥2 mg/kg, decreases in testes, epididymis, adrenal gland and increase in liver weights were reported.

Table 17: A 3-month rat toxicology study - summary organ weight data-terminal euthanasia (day 92)

Summary Organ Weight Data – Terminal Euthanasia (Day 92)

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (mg/kg/dose)	**0**	**0.5**	**2**	**5**	**0**	**0.5**	**2**	**5**
No. animals examined	**10**	**10**	**10**	**10**	**9**	**10**	**10**	**10**
Testis - No. weighed	10	10	10	10	NA	NA	NA	NA
Absolute value (g)[a]	3.60	-2	**-28**	**-51**	NA	NA	NA	NA
% of body weight	0.65	-2	**-28**	**-50**	NA	NA	NA	NA
% of brain weight	160.98	0	**-28**	**-50**	NA	NA	NA	NA
Epididymis - No. weighed	10	10	10	10	NA	NA	NA	NA
Absolute value (g)	1.57	-5	-9	**-20**	NA	NA	NA	NA
% of body weight	0.28	-5	-9	-16	NA	NA	NA	NA
% of brain weight	70.12	-3	-8	-18	NA	NA	NA	NA
Adrenal Gland - No. weighed	10	10	10	10	9	10	10	10
Absolute value (g)	0.05	+2	+3	-3	0.07	-16	**-26**	**-18**
% of body weight	0.01	+3	+5	+4	0.02	-16	**-27**	-17
% of brain weight	2.40	+4	+3	0	3.53	-14	**-25**	-16
Liver - No. weighed	10	10	10	10	9	10	10	10
Absolute value (g)	12.23	+2	+3	+1	6.99	-4	+2	+10
% of body weight	2.17	+4	+5	+7	2.37	-3	+2	**+12**
% of brain weight	545.60	+4	+4	+3	341.37	-1	+4	**+14**

NA = not applicable.

(Excerpted from Applicant's report)

- Histopathology:
  - At doses ≥2mg/kg (AUC 784 µg.hr/mL), testes, epididymis and mammary gland (males and females) toxicity were reported. Exposure at 2 mg/kg, was 0.86-fold the AUC of 914.4 µg*hr/mL in humans at the clinical recommended dose of 1.25 mg/kg.

- At doses ≥0.5 mg/kg (AUC 175 µg.hr/mL), eye and injection site toxicity were reported.
- Harderian gland toxicity was reported; however, this organ is not present in the human, and clinical relevance of this toxicity is uncertain.

Table 18: A 3-month rat toxicology study – histopathology findings

	No. of animals affected							
Sex	**Males**				**Females**			
Dose (mg/kg/dose)	**0**	**0.5**	**2**	**5**	**0**	**0.5**	**2**	**5**
No. Examined	10	10	10	10	10	10	10	10
Treatment-related Findings:								
EPIDIDYMIS								
Sperm granuloma					NA	NA	NA	NA
– *Minimal*	0	1	0	2				
– *Mild*	0	0	0	0				
Cell debris, luminal					NA	NA	NA	NA
– *Minimal*	1	1	0	1				
– *Mild*	0	0	0	5				
– *Moderate*	0	0	4	2				
– *Marked*	0	0	1	0				
Reduced sperm, luminal					NA	NA	NA	NA
– *Mild*	1	1	2	1				
– Moderate	0	0	2	3				
– Marked	0	0	1	4				
Single cell necrosis, epithelial					NA	NA	NA	NA
– Minimal	0	0	0	2				

	No. of animals affected							
Sex	**Males**				**Females**			
Dose (mg/kg/dose)	**0**	**0.5**	**2**	**5**	**0**	**0.5**	**2**	**5**
EYE								
Mitotic figures, abnormal, cornea – *Minimal*	0	3	4	1	0	0	0	2
TESTIS								
Degeneration/atrophy, seminiferous tubule – *Minimal* – *Moderate* – *Marked*	0 1 0	0 1 0	2 1 3	2 0 7	NA	NA	NA	NA
Mitotic figures, abnormal, interstitial – *Minimal*	0	0	2	6	NA	NA	NA	NA
SITE, ADMINISTRATION IV TAIL								
Mitotic figures, abnormal, epidermal, adnexa – *Minimal*	0	4	8	5	0	7	5	7
Single cell necrosis, epidermal, adnexa – *Minimal*	0	2	5	3	0	3	2	2
Necrosis – *Moderate*	0	0	0	0	0	0	1	0
GLAND, HARDERIAN								
Mitotic figures, abnormal, epidermal, – *Minimal*	0	0	0	1	0	0	0	1
Single cell necrosis, epithelial – *Minimal*	0	0	0	1	0	0	0	1
LIVER								
Fibrosis, centrilobular – *Mild*	0	0	0	0	0	0	0	1
Extramedullary hematopoiesis – *Minimal*	0	0	0	0	0	0	0	1
Anisokarryosis, hepatocellular – *Minimal*	0	0	0	0	0	0	0	1

	No. of animals affected							
Sex	**Males**				**Females**			
Dose (mg/kg/dose)	**0**	**0.5**	**2**	**5**	**0**	**0.5**	**2**	**5**
Inflamation, mixed cell, portal – *Minimal*	0	0	1	0	0	0	1	0
BONE MARROW								
Increased cellularity, erythroid – *Mild*	0	0	0	1	0	0	0	0
MAMMARY GLAND								
Atrophy – *Moderate* – *Marked*	0 0	0 0	0 0	1 1	0 0	0 0	0 0	0 0
Mitotic figures, abnormal – *Minimal*	0	0	0	1	0	0	1	2
Single cell necrosis – *Minimal*	0	0	0	0	0	0	0	2

NA= Not Applicable

Toxicokinetics

Enfortumab Vedotin (ADC) and MMAE (free drug)

- Exposure (AUC_{0-24} and C_{max}) increased in approximately dose-proportional manner between 0.5 and 5 mg/kg/dose.
- No accumulation was reported after repeat dosing.
- No significant gender differences in systemic exposure were reported.
- Decreases in plasma exposure levels on day 85 were reported due to the presence of ADAs.

Table 19: A 3-month rat toxicology study – enfortumab vedotin toxicokinetic parameters

Table 2.3: Summary (± SE) Enfortumab Vedotin Toxicokinetic Parameters in Sex Combined Sprague-Dawley Rat Serum Following 0.5, 2 and 5 mg/kg/dose Once Weekly IV Bolus Administration of Enfortumab Vedotin on Days 1 and 85

Analyte	Gender	Day	Dose (mg/kg/dose)	T_{max} (hr)	T_{last} (hr)	C_{max} (ng/mL) ± SE	$AUC_{(0-t)}$ (hr*ng/mL) ± SE	$AUC_{(0-t)}/D$ (hr*ng/mL/ (mg/kg))	$AUC_{(0-inf)}$ (hr*ng/mL)	$T_{1/2}$ (hr)	R_{Cmax}	R_{AUC}	CL (mL/hr/kg)	Vd (mL/kg)
Enfortumab Vedotin	Sex Combined	1	0.5	0.08	96	15900 ± 578	168000 ± 20600	337000	175000	19.4	NA	NA	2.86	80.2
			2	1	96	40400 ± 1860	766000 ± 33300	383000	784000	19.0	NA	NA	2.55	70.0
			5	0.08	96	125000 ± 7090	2300000 ± 94300	459000	2430000	24.4	NA	NA	2.06	72.6
		85	2	6	6	25800 ± 7970	NR1	NR1	NC	NC	0.640	NC	NR1	NC
			5	0.08	96	59100 ± 25600	831000 ± 270000	166000	865000	19.2	0.472	0.362	5.53	153

R_{Cmax} = Day 85 C_{max} / Day 1 C_{max}; R_{AUC} = Day 85 $AUC_{(0-t)}$ / Day 1 $AUC_{(0-t)}$;
NA = Not applicable; ID = Insufficient data; SE = Standard error;
NC = Not calculable;
NR1 = Not reported because less than 3 consecutives quantifiable concentration postdose;
NR2 = Not reported because Rsq was less than 0.800 and/or the extrapolation of AUC to infinity was greater than 20%.

(Excerpted from Applicant's report)

Table 20: A 3-month rat toxicology study – MMAE (free drug) toxicokinetic parameters

Table 2.6: Summary (± SE) MMAE Toxicokinetic Parameters in Sex Combined Sprague-Dawley Rat Serum Following 0.5, 2 and 5 mg/kg/dose Once Weekly IV Bolus Administration of Enfortumab Vedotin on Days 1 and 85

Analyte	Gender	Day	Dose (mg/kg/dose)	T_{max} (hr)	T_{last} (hr)	C_{max} (pg/mL) ± SE	$AUC_{(0-t)}$ (hr*pg/mL) ± SE	$AUC_{(0-t)}/D$ (hr*pg/mL/ (mg/kg))	$AUC_{(0-inf)}$ (hr*pg/mL)	$T_{1/2}$ (hr)	R_{Cmax}	R_{ATC}
MMAE	Sex Combined	1	0.5	24	48	29.4 ± 2.13	1140 ± 50.3	2270	NC	NC	NA	NA
			2	24	96	104 ± 7.98	6330 ± 406	3170	NC	NC	NA	NA
			5	24	96	303 ± 20.8	16600 ± 604	3330	NC	NC	NA	NA
		85	0.5	6	6	47.8 ± 21.5	NR1	NR1	NC	NC	1.63	NC
			2	1	96	242 ± 65.1	4830 ± 754	2420	4950	18.4	2.32	0.763
			5	1	96	951 ± 355	22400 ± 5060	4480	23400	20.1	3.14	1.35

R_{Cmax} = Day 85 C_{max} / Day 1 C_{max}; R_{AUC} = Day 85 $AUC_{(0-t)}$ / Day 1 $AUC_{(0-t)}$;
NA = Not applicable; ID = Insufficient data; SE = Standard error;
NC = Not calculable;
NR1 = Not reported because less than 3 consecutives quantifiable concentration postdose.

(Excerpted from Applicant's report)

ADAs

- ADAs were reported on Day 99 in 17 out of 18 rats at 0.5 mg/kg.
- ADAs were reported on Day 99 in 14 out of 18 rats at 2 mg/kg.
- ADAs were reported on Day 99 in 13 out of 17 rats at 5 mg/kg.
- Decreases in systemic exposure levels were reported on day 85 due to the presence of ADAs.

Table 21: A 3-month rat toxicology study – ADAs on day 85

List of ATA Negative and Confirmed Positive Samples on Day 85 at 336 Hours Postdose (Day 99)

Group No.	Test Material	Dose Level (mg/kg/dose)	ATA Negative		ATA Confirmed Positive	
			Males	Females	Males	Females
5	Enfortumab Vedotin	0.5	-	5507	5001 to 5009	5501 to 5506, 5508, 5509
6	Enfortumab Vedotin	2	6002, 6003, 6009	6501	6001, 6004 to 6008	6502 to 6509
7[a]	Enfortumab Vedotin	5	7002	7505, 7506, 7507	7001, 7003, 7005 to 7009	7501 to 7504, 7508, 7509

(Excerpted from Applicant's report)

The following findings were reported in the 13-week repeat dose toxicology study in rats but were not reported in the 4-week study in rats (Study # 20005662):

- Microscopic findings in the eye, which included increased abnormal mitotic figures in the cornea
- Microscopic findings in the harderian gland, which included abnormal epidermal mitotic figures; single cell epithelial necrosis.
- Microscopic findings in the mammary gland, which included atrophy, single cell necrosis and abnormal mitotic figures reported in male and females.
- Decreases in PT (-8%) and PTT (-19%) in males at 5 mg/kg.

A 4-Week Toxicity Study of AGS-22M6E and AGS-22M6 Administered by Intravenous Infusion to Cynomolgus Monkeys, with a 6-Week Recovery Period / 20005664:

The 4-week monkey toxicology study was reviewed by the FDA under IND # (b) (4), the original IND submitted with AGS-22M6E. In general, we agree with the results presented by the applicant. The following are additional study findings as presented in the original IND.

Methods: In this study, monkeys were intravenously administered AGS-22M6E (1, 3 and 6 mg/kg), AGS-22M6 (6 mg/kg), and MMAE (dose was reduced from 0.1093 to 0.0545 mg/kg) once weekly for 4 weeks.

Key Study Findings

- Mortalities (moribund sacrificed or found dead) were reported in 30% of the monkeys administered the ADC (AGS-22M6E) at 6 mg/kg (6.7-fold higher than the human exposure [6150 µg.hr/mL vs 914.4 µg.hr/mL in human] at the clinical recommended dose of 1.25 mg/kg) and in 25% of the monkeys administered MMAE at 0.193/0.0545 mg/kg. Deaths were reported as early as study day 11. Severe clinical observations were reported prior to death that included decreased activity, lethargy, low food consumption, dry skin and reddened skin. Cause of death was attributed to skin lesions, lethargy, bone marrow toxicity, and mild liver toxicity.
- Dosing for all animals at the 6 mg/kg dose was ceased after the administration of the second dose (Day 8) due to the severe signs of toxicity reported.
- In one female dead monkey, a dose of 6 mg/kg AGS-226ME resulted in histopathological findings in the heart consisting of epicardial fibrosis and thrombus; however, there was no evidence of changes in ECG parameters, heart rate, or blood pressure, or findings in other test-article treated animals.
- Skin was a major target organ with abrasions, necrotic lesions, scale, and rash Surviving high dose animals did not show full recovery of skin toxicity by the end of the recovery period
- The lacrimal gland is a potential target organ with histopathologic findings of lymphocyte infiltration accompanied by observations of ptosis, eye discharge, and periorbital swelling; no significant ophthalmology findings
- One monkey administered MMAE exhibited axonal degeneration of the sciatic nerve.
- Additional target organs of toxicities included injection site, bone marrow, liver and GI. Bone marrow and liver toxicity appear to be related to MMAE
- No adverse effects were reported following AGS-22M6 (unconjugated antibody) administration.

Table 22: A 4-week monkey toxicology study – histopathology findings

Microscopic Findings (Early Death)	Sex / Dose (mg/kg) / N	Males 6 2	Males MMAE 1	Females 6 1	Females MMAE 1
Adrenal	Mineralization, Mild				1
Bone Marrow	Hypocellular, Myeloid, Mod			1	
Duodenum	Brunner's Gland Dilation, Mild				1
Heart	Epicardial Fibrosis			1	
	Thrombus			1	
Ileum	Lymphatic Dilation, Min				1
Jejunum	Lymphatic Dilation, Mod			1	
Cecum	Hemorrhage, Mod		1		
	Coagulative Necrosis, Marked		1		
Colon	Hemorrhage, Marked		1		
	Coagulative Necrosis, Marked		1		
Skin, Other	Ulcer				
	Mild	1			
	Mod	2		1	1
	Marked				1
	Ulcer, Multifocal, Marked			1	
	Mono Infilt, Dermis				
	Mild	2			
	Mod	1			1
	Subcu Congestion, Mod	1			
	Epidermal Hyperplasia				
	Mild	2			1
	Mod	1			
	Hyperkeratosis, Mild	1			
	Subcu Hemorrhage, Mild	1			
	Mixed Inflamm, Dermis, Mod			1	1
	Mixed Inflamm, Subcu,				
	Mild			1	
	Mod	1		1	
	Multifocal Erosion, Mod				1
	Epiderm Necrosis w/Inflamm, Mod				1

Microscopic Findings	Sex	Males						Females					
	Dose (mg/kg)	0	1	3	6	Ab 6	MMAE	0	1	3	6	Ab 6	MMAE
	N Main (Recovery)	3 (2)	3 (2)	3 (2)	1 (2)	3 (2)	2 (2)	3 (2)	3 (2)	3 (2)	2 (2)	3 (2)	2 (2)
Adrenal	Hemorrhage, Cap., Mild			1									
	Hemorrhage, Medulla, Min			1									
	Mineralization												
	Mild					1		(1)					
	Mod			1									
Bone Marrow	Hypercellular, Myelo, Mod.										1		
	Hyperplasia, Mild												1
Lacrimal Gland	Lymph Infilt.												
	Min		2	1		1		1		1	(1)	1 (2)	1
	Mild			1				1	2 (1)	2 (1)	1 (1)		
	Mod										1		
Ileum	Lymphatic Dilation												
	Min		1			2			2			1	
	Mild				1 (1)				(1)	2			
Liver	Fatty Focus						1						
	Purulent Granuloma, Mod				1								
	Hepat. Vacuolation, Mild												1

Microscopic Findings	Sex	Males						Females					
	Dose (mg/kg)	0	1	3	6	Ab 6	MMAE	0	1	3	6	Ab 6	MMAE
	N Main (Recovery)	3 (2)	3 (2)	3 (2)	1 (2)	3 (2)	2 (2)	3 (2)	3 (2)	3 (2)	2 (2)	3 (2)	2 (2)
Skin, Other	Mono Inflam, Dermis, Mild				1	1					2		
	Epidermal Hyperplasia												
	Mild					1					1		
	Mod				1								
	Hyperkeratosis												
	Min										1		
	Mild				1						1		
	Mono Inflam, Subcu, Mild										1		
Sciatic Nerve	Axonal Degen, Mod						1						
	Mono Infilt, Mild						1						

- Organ weight changes were reported:

Table 23: A 4-week monkey toxicology study – organ weight changes relative to body weight (% change from control)

	AGS-22M6E (ADC)						AGS-22M		MMAE	
Parameters	1 mg/kg		3 mg/kg		6 mg/kg		6 mg/kg		0.193/0.0545 mg/kg	
Sex	M	F	M	F	M	F	M	F	M	F
Thymus	--	--	--	--	NA	NA	--	--	-59	-60
Spleen	13	36	46	45	NA	NA	38	42	7	55
Adrenal	--	--	24	--	NA	NA	24	6	41	13
Testes	--	--	--	--	NA	NA	--	--	-26	--
Prostate	137	--	35	--	NA	NA	--	--	29	--
Lung	--	--	--	--	NA	NA	--	11	--	23
Ovaries	--	--	--	-36	NA	NA	--	19	--	--

NA= organ weights were not available

Toxicokinetics

- Exposure to the naked antibody and the ADC were dose dependent.
- Exposure to naked antibody was higher than to ADC.

- There was a significant decrease in overall exposure for both ADC and total antibody at the late time-point (Day 22) compared to Day 1.
- The half-life for total antibody (2.75 days) was approximately 1 day longer than for ADC (1.72 days).
- MMAE exposure from ADC was dose dependent with no evidence of accumulation.

Table 24: A 4-week monkey toxicology study – AGS-22M6E and AGS 22M6 toxicokinetic parameters

ADC=intact antibody vs. T ab (conjugated+ unconjugated)

Analyte		ADC						Total Ab					
Group		2		3		4		2		3		4	
AGS-22M6E_Dose (mg/kg)		1		3		6		1		3		6	
Dosing Day		1	22[a]	1	22[a]	1	8[a]	1	22[a]	1	22[a]	1	8[a]
AUC(0-∞) (ug-h/mL)	Mean	650	487	2530	909	5380	6080	1240	1220	5220	1660	12200	10500
	Std Dev	77.1	282	347	743	621	ND[b]	162	865	764	1280	1950	2760
	N	10	5	10	6	10	2	6	5	10	6	9	3
	Median	645	530	2450	682	5470	6080	1210	1210	5170	1320	12800	11900
AUC(0-168h) (ug-h/mL)	Mean	634	471	2450	903	5080	6150	1120	1070	4530	1610	10200	9210
	Std Dev	73.1	264	319	732	573	858	122	689	625	1220	2100	2760
	N	10	5	10	6	10	7	6	5	10	6	9	3
	Median	631	517	2370	681	5170	6180	1100	1090	4450	1310	9780	10400
AUClast (ug-h/mL)	Mean	631	466	2430	856	5050	6310	1110	1060	4470	1850	10400	11900
	Std Dev	72.5	266	315	689	567	850	104	687	611	1290	2360	3160
	N	10	5	10	7	10	7	10	5	10	7	10	7
	Median	628	517	2360	560	5120	6350	1110	1090	4400	1600	9610	12100
Tlast (h)	Mean	162	124	161	135	161	274	162	138	161	157	161	327
	Std Dev	0.975	59.0	0.971	74.4	0.990	38.3	0.975	42.5	0.971	97.6	0.990	80.9
	N	10	5	10	7	10	7	10	5	10	7	10	7
	Median	162	166	162	167	162	262	162	166	162	167	162	328
Cmax (ug/mL)	Mean	24.6	21.2	76.6	63.7	151	137	30.3	29.6	94.4	106	200	162
	Std Dev	2.05	5.17	7.65	16.9	16.8	24.1	3.45	7.53	12.8	59.6	33.8	21.5
	N	10	5	10	7	10	7	10	5	10	7	10	7
	Median	24.7	21.8	75.8	59.4	153	127	29.6	34.3	96.4	84.0	202	160
$t_{1/2}$ λz (day)	Mean	1.37	1.20	1.43	0.700	1.72	1.53	2.14	1.66	2.46	1.02	2.75	1.82
	Std Dev	0.0936	0.604	0.132	0.419	0.177	ND	0.173	1.08	0.332	0.649	0.888	0.596
	N	10	5	10	6	10	2	6	5	10	6	9	3
	Median	1.37	1.41	1.45	0.74	1.72	1.53	2.10	1.93	2.37	1.07	2.94	1.97

(Excerpted from Applicant's report)

Table 25: A 4-week monkey toxicology study – MMAE from ADC toxicokinetic parameters

Table 4: MMAE from ADC

Group		2		3		4	
AGS-22M6E Dose		1 mg/kg/dose		3 mg/kg/dose		6 mg/kg/dose	
Day		1	22	1	22	1	8
AUC(0-∞) (pg-h/mL)	Mean	4640	4930	15300	16600	32500	26500
	Std Dev	773	1230	1690	2320	5730	ND[a]
	N	8	7	4	8	5	1
	Median	4660	5420	15900	16700	34000	26500
AUC(0-168h) (pg-h/mL)	Mean	3710	4040	11700	15000	24400	24500
	Std Dev	690	917	1040	2000	2990	2290
	N	8	7	4	8	4	7
	Median	3730	4390	12000	15000	24800	24200
AUClast (pg-h/mL)	Mean	3400	3370	12000	14100	23200	28900
	Std Dev	790	1400	1400	3150	2600	2680
	N	10	10	10	10	10	7
	Median	3550	3850	11800	14300	23900	28800
Tlast (h)	Mean	145	129	161	164	161	262
	Std Dev	21.2	52.5	0.971	39.9	0.99	31.7
	N	10	10	10	10	10	7
	Median	160	166	162	167	162	262
Cmax (pg/mL)	Mean	34.3	42.9	105	226	202	215
	Std Dev	5.96	6.69	12.2	142	34.2	40.0
	N	10	10	10	10	10	7
	Median	36.0	42.5	104	177	192	211
Tmax (h)	Mean	ND	ND	ND	ND	ND	ND
	Std Dev	ND	ND	ND	ND	ND	ND
	N	10	10	10	10	10	7
	Median	48	18.5	48	18	60	0.5
$t_{1/2}\lambda z$ (day)	Mean	2.58	2.32	2.92	1.87	3.08	2.52
	Std Dev	0.248	0.64	0.173	0.573	0.554	ND
	N	8	7	4	8	5	1
	Median	2.66	2.70	2.88	2.08	3.08	2.52

TK parameters are reported to 3 significant figures except for Tmax and Tlast
[a] ND = Not determined

(Excerpted from Applicant's report)

Toxicokinetics following MMAE administration

- MMAE was found at low serum levels (pg.h/mL) in the circulation following AGS-22M6E administration compare to µg.h/mL for the AGS-22M6E.
- The AUC on day 22 for the MMAE group (75200 pg.h/mL for males or 55900 pg.h/mL for females) was 2 to 3-fold higher than the AUC reported for the MMAE following AGS-22M6E administration (24500 pg.h/mL).
- MMAE administration resulted in $T_{1/2}$ of 22.7 hours (0.95 days), while the $T_{1/2}$ for the MMAE following AGS-22M6E administration was 3.1 days.

Table 26: A 4-week monkey toxicology study – MMAE toxicokinetic parameters

Table 24 Descriptive Statistics of MMAE TK Parameters from Male and Female Monkeys in Dose Group 6

MMAE Dose (mg/kg)		0.1093		0.0545	
Study Day		1		22	
Sex		Female	Male	Female	Male
$AUC_{(0-\infty)}$ (pg-h/mL)	Mean	152000	155000	75000	55700
	Std Dev	21900	27000	7420	15400
	N	5	5	4	4
	Median	152000	149000	75800	57600
$AUC_{(0-168h)}$ (pg-h/mL)	Mean	151000	154000	75200	55900
	Std Dev	21100	27300	7340	15400
	N	5	5	4	4
	Median	151000	149000	76000	57900
AUC_{last} (pg-h/mL)	Mean	150000	154000	74700	55300
	Std Dev	21000	27300	7520	15400
	N	5	5	4	4
	Median	151000	149000	75600	56900
T_{last} (h)	Mean	159	159	71	83
	Std Dev	0.0874	0.0724	27.2	23.5
	N	5	5	4	4
	Median	159	159	71	95
C_{max} (pg/mL)	Mean	303000	270000	431000	213000
	Std Dev	104000	76800	192000	135000
	N	5	5	4	4
	Median	338000	273000	485000	199000

(Excerpted from Applicant's report)

ADAs following AGS-22M6E and AGS-22M6 administration

- ADAs were reported in 50%, 40 % and 43% of the monkeys administered AGS-22M6E at 1, 3 and 6 mg/kg, respectively. Only 10% of the monkeys administered the naked antibody reported to have ADAs.

Table 27: A 4-week monkey toxicology study – summary of ADAs following AGS-22M6E and AGS-22M6 administration

Table 25 Summary Table on Incidence of Seroconversion

Group	Test Material	Dose Level	Dose Schedule	Seroconversion – #POS of total number (%POS)[a]		
				Female Monkeys	Male Monkeys	pooled M&F
1	Vehicle	0 mg/kg/dose	QW x4[b]	0 of 5 (0%)	0 of 5 (0%)	0 of 10 (0%)
2	AGS-22M6E	1 mg/kg/dose	QW x4	2 of 5 (40%)	3 of 5 (60%)	5 of 10 (50%)
3	AGS-22M6E	3 mg/kg/dose	QW x4	2 of 5 (40%)	2 of 5 (40%)	4 of 10 (40%)
4	AGS-22M6E	6 mg/kg/dose	QW x2[c]	2 of 4 (50%)	1 of 3 (33.3%)	3 of 7 (43%)
5	AGS-22M6	6 mg/kg/dose	QW x4	1 of 5 (20%)	0 of 5 (0%)	1 of 10 (10%)

[a] Number of positive animals out of a total number of animals in the group (percent of animals with positive ATA results)
[b] QW x4 = Once-a-week for 4 weeks
[c] QW x2 = Once-a-week for 2 weeks

(Excerpted from Applicant's report)

General toxicology; additional studies

Data:
N/A

The Applicant's Position:
N/A

The FDA's Assessment:

- **Study title: A 4-Week Toxicity Study of AGS-22M6E and AGS-22M6 Administered by Intravenous Injection to Sprague-Dawley Rats, with a 6- Week Recovery Period (Study # 20005662)**

Study # 20005662 was reviewed by the FDA under IND # (b) (4) for ASG-22CE. The following is a summary of the findings as presented in the original IND.

Methods: In this study, rats were administered intravenously AGS-22M6E (conjugate) at 2, 5 and 10 mg/kg or AGS-22M6 (Ab only) at 10 mg/kg once weekly for 4 weeks.

Key Study Findings

- One male rat dosed with 10 mg/kg AGS-22M6E (conjugate) died on Day 27 with toxicity to the bone marrow (hypocellularity), liver (elevated AST, ALT, GGT), and histopathology findings of degeneration and hypospermia in the male reproductive organs.
- The remaining surviving animals showed skin and liver toxicity. Findings showed partial or full recovery.
- Myelosuppression was evident in histopathology signs of bone marrow hypocellularity and reductions in RBC, Hb, Hct.
- The toxicity in this study was largely observed in the 10 mg/kg AGS-22M6E group, and was not mimicked in the animals who received 10 mg/kg of AGS-22M6 (Ab alone).
- In rats administered 5 and 10 mg/kg AGS-22M6E, testes weights were 33% and 45% lower than controls, respectively. Testes in animals receiving 10 mg/kg of the AGS-22M6 (Ab alone) were similar to controls.
- At doses ≥2mg/kg, dose-dependent AGS-22M6E related microscopic findings were reported in the epididymis, prostate, seminal vesicle, and testes at the end of the dosing period (Day 29).

Table 28: A 4-week rat toxicity study – histopathology findings terminal necropsy

Removal Reason: TERMINAL NECROPSY	0 mg/kg/d	2.0 mg/kg/d	5 mg/kg/d	10 mg/kg/d	10 mg/kg/d
Number of Animals on Study :	10	10	10	9	10
Number of Animals Completed:	(10)	(10)	(10)	(9)	(10)
COLON:					
EPIDIDYMIS;					
Examined	(10)	(10)	(10)	(9)	(10)
Within Normal Limits	10	4	2	0	9
Granuloma Sperm; unilateral	(0)	(0)	(1)	(1)	(1)
mild	0	0	1	1	1
Granuloma Sperm; bilateral	(0)	(0)	(1)	(0)	(0)
mild	0	0	1	0	0
Hypospermia/Abnormal Spermatids; Duct; Lumen; bilateral	(0)	(6)	(8)	(9)	(0)
minimal	0	3	2	1	0
mild	0	3	5	2	0
moderate	0	0	0	5	0
marked	0	0	1	1	0
PROSTATE;					
Examined	(9)	(10)	(10)	(9)	(10)
Within Normal Limits	7	3	10	6	6
Not Examined: NOT FOUND AT TRIMMING	1	0	0	0	0
Infiltrate, Mononuclear Cell	(2)	(7)	(0)	(2)	(4)
minimal	0	3	0	1	3
mild	2	4	0	1	1
Hypoplasia; Glandular	(0)	(0)	(0)	(1)	(0)
moderate	0	0	0	1	0
SEMINAL VESICLE;					
Examined	(10)	(10)	(10)	(9)	(10)
Within Normal Limits	10	10	10	7	10
Hypoplasia; Glandular; bilateral	(0)	(0)	(0)	(2)	(0)
mild	0	0	0	1	0
moderate	0	0	0	1	0

TESTIS;					
Examined	(10)	(10)	(10)	(9)	(10)
Within Normal Limits	10	8	3	0	10
Degeneration; Tubular epithelium; bilateral	(0)	(2)	(7)	(9)	(0)
minimal	0	2	5	2	0
mild	0	0	1	5	0
moderate	0	0	0	2	0
marked	0	0	1	0	0

(Excerpted from Applicant's report)

- At the end of the recovery period (Day 64), AGS-22M6E related microscopic findings were reported in the testes and epididymides. Testicular tubular epithelial degeneration and the related epididymal finding of hypospermia/abnormal spermatids were more prominent on Day 64 in the males that received AGS-22M6E than on Day 29.

Table 29: A 4-week rat toxicity study – histopathology findings recovery necropsy

Removal Reason: RECOVERY NECROPSY	0 mg/kg/d	2.0 mg/kg/d	5 mg/kg/d	10 mg/kg/d	10 mg/kg/d
Number of Animals on Study :	5	5	5	5	5
Number of Animals Completed:	(5)	(5)	(5)	(5)	(5)
EPIDIDYMIS;					
Examined	(5)	(5)	(5)	(5)	(5)
Within Normal Limits	5	0	0	0	4
Hypospermia/Abnormal Spermatids; Duct; Lumen; unilateral	(0)	(0)	(0)	(0)	(1)
marked	0	0	0	0	1
Hypospermia/Abnormal Spermatids; Duct; Lumen; bilateral	(0)	(5)	(5)	(5)	(0)
mild	0	2	0	0	0
moderate	0	2	0	0	0
marked	0	1	5	5	0
TESTIS;					
Examined	(5)	(5)	(5)	(5)	(5)
Within Normal Limits	5	0	0	0	4
Degeneration; Tubular epithelium; unilateral	(0)	(0)	(0)	(0)	(1)
marked	0	0	0	0	1
Degeneration; Tubular epithelium; bilateral	(0)	(5)	(5)	(5)	(0)
mild	0	3	0	0	0
moderate	0	2	0	0	0
marked	0	0	5	5	0
Mineralization; Seminiferous tubule; bilateral	(0)	(0)	(0)	(2)	(0)
minimal	0	0	0	1	0
mild	0	0	0	1	0

(Excerpted from Applicant's report)

Toxicokinetics

Table 30: A 4-week rat toxicity study – ADC and TAb toxicokinetic parameters

Table 8 ADC and TAb Serum TK Parameters for Study Days 1 and 22

Study Group		7		8		9	
AGS-22M6E Dose		2.0 mg/kg/dose		5.0 mg/kg/dose		10 mg/kg/dose	
Study Day		1	22	1	22	1	22
TK Parameter[a]		Antibody –drug Conjugate (ADC)					
AUCinf	(ug-h/mL)	1160	NR[c]	1650	NR	6120	NR
AUClast[b]	(ug-h/mL)	1150	842	1630	1640	6030	3920
AUC168h	(ug-h/mL)	1150	862	1630	NR	6030	3920
Cmax	(ug/mL)	57.3	54.1	131	111	276	206
Tmax[d]	(h)	0.0167	0.0167	0.0167	0.0167	0.0167	0.0167
T1/2	(day)	0.994	NR	1.22	NR	1.32	NR
CL	(mL/h-kg)	1.73	NR	3.03	NR	1.63	NR
Vss	(mL/kg)	40.2	NR	95.7	NR	47.4	NR
TK Parameter		Total Antibody (TAb)					
AUCinf	(ug-h/mL)	2110	NR	NR	NR	11600	NR
AUClast[e]	(ug-h/mL)	2050	NR	2420	NR	10600	NR
AUC168h	(ug-h/mL)	2050	NR	2420	NR	10600	NR
Cmax	(ug/mL)	72.6	67.2	150	130	328	256
Tmax[d]	(h)	0.0167	0.0167	0.0167	0.0167	0.0167	0.0167
T1/2	(day)	1.40	NR	NR	NR	2.15	NR
CL	(mL/h-kg)	0.949	NR	NR	NR	0.862	NR
Vss	(mL/kg)	35.9	NR	NR	NR	51.6	NR

[a] TK parameters were derived using median concentration-time profiles and are reported to 3 significant figures except for Tmax
[b] AUClast for ADC = AUC(0-168h) for Day 1 and Day 22
[c] NR = No reportable result due to unacceptable TK curve fitting
[d] Tmax is taken directly from the concentration data and correspond to the time immediately after IV infusion (0.0167h)
[e] AUClast for TAb = AUC(0-168h) for Day 1 and AUC(0-336h) for Day 22

- ADAs were reported on Day 29 at doses ≥2mg/kg.
- Decreases in systemic exposure levels were reported on day 22 due to the presence of ADAs.

Table 31: A 4-week rat toxicology study – summary of ADAs following AGS-22M6E and AGS-22M6 administration

Table 13 Summary Table of Incidence of Seroconversion

Main Study Group Number	Dose (mg/kg/dose)	Test Material	Male Rats		Female Rats		Pooled (M & F)
			% POS (# POS of Total #)[a]	Titer range	% POS (# POS of Total #)	Titer range	% POS (# POS of Total #)
1	0	AGS-22M6E	0% (0 of 15)	NA	0% (0 of 15)	NA	0% (0 of 30)
2	2	AGS-22M6E	35.7% (5 of 14)[b]	250 - 6250	33.3% (5 of 15)[c]	50 - 6250	34.5% (10 of 29)[d]
3	5	AGS-22M6E	26.7% (4 of 15)	50 - 31250	13.3% (2 of 15)	50	20% (6 of 30)
4	10	AGS-22M6E	7.14% (1 of 14)	10	6.67% (1 of 15)[b]	1250	6.9% (2 of 29)
5	10	AGS-22M6	6.67% (1 of 15)	250	13.3% (2 of 15)	50 - 6250	10.0% (3 of 30)

[a] Percent of animals with positive ATA results (number of positive animals out of a total number of animals in the group or subgroup)
[b] one positive animal at Day 29
[c] two positive animals at Day 29
[d] three positive animals at Day 29

- **Study title: A 4-Week Study of AGS-22M6E and AGS-22C3E by Intravenous Infusion Administration in Cynomolgus Monkeys with a 6-Week Recovery Period (Study # 20021751)**

Study # 20021751 was reviewed by the FDA under IND # 116360 for ASG-22CE (Sponsor, Agensys, Inc.). The following is a summary of the findings as presented in the original IND.

Methods: Dose of 3 mg/kg was administered to monkeys by the intravenous infusion route (5 mg/mL), once weekly (days 1, 8, 15 and 22).

During the product development of the antibody portion of the ADC, the Applicant changed the cell line used for the antibody production (b) (4) (AGS-22M6) to CHO cells (AGS-22C3). The Applicant conducted a 4-week repeat-dose bridging toxicology study in cynomolgus monkeys of the ADCs *(AGS-22M6E and AGS-22C3E)*. Overall, the toxicity profiles of AGS-22M6E and AGS-22C3E (3 mg/kg via weekly intravenous infusion) were similar in incidence and severity. All animals survived to scheduled necropsy. Findings included, clinical observations (dry skin, reddened areas of skin); decreased erythrocyte mass (red blood cell, hemoglobin, and hematocrit count), reticulocytes, neutrophils, eosinophils; macroscopic findings (scales on the skin) and microscopic findings (bone marrow, injection site, and skin). No findings were reported at the end of the recovery period. Both ADCs showed comparable toxicokinetic profiles. ADAs did not affect the TK concentrations.

Table 32: A 4-week monkey study of AGS-22M6E and AGS-22C3E – toxicokinetic parameters

Table 2 Mean (±SD) Non Compartmental Toxicokinetic parameters in cynomolgus monkeys following a weekly IV Infusion of AGS-22M6E or AGS-22C3E at 3.0 mg/kg

A. ADC

Statistic	C_{max} (µg/mL)		$T_{1/2\lambda z}$ (day)	$AUC_{\tau(0-7)}$ (day*µg/mL)	CLss (mL/day/kg)
	First dose	Last dose	First dose	First dose	First dose
Group 2: AGS-22M6E					
N:	10	10	10	10	10
Mean:	77.9	48.9	1.70	108	27.8
SD	8.40	14.9	0.469	8.11	2.06
%CV:	10.8	30.6	27.6	7.50	7.39
Group 3: AGS-22C3E					
N:	10	10	10	10	10
Mean:	98.0	78.4	1.53	125	24.7
SD:	8.96	10.6	0.129	23.5	4.56
%CV:	9.14	13.6	8.40	18.7	18.5

N = number of animals; $T_{1/2\lambda z}$ = terminal half-life; C_{max} = maximum serum concentration; $AUC_{\tau(0-7)}$ = area under the concentration–time curve from Time = 0 to 7 days; CLss = clearance at steady state.

B. TAb

Statistic	C_{max} (µg/mL)		$T_{1/2\lambda z}$ (day)	$AUC_{\tau(0-7)}$ (day*µg/mL)	CLss (mL/day/kg)
	First dose	Last dose	First dose	First dose	First dose
Group 2: AGS-22M6E					
N:	10	10	10	10	10
Mean:	72.1	69.1	3.23	189	15.9
SD	10.8	15.9	1.63	15.0	1.30
%CV:	15.0	23.1	50.4	7.90	8.18
Group 3: AGS-22C3E					
N:	10	10	10	10	10
Mean:	129	92.5	2.09	209	14.7
SD:	37.0	25.0	0.217	34.3	2.42
%CV:	28.7	27.0	10.4	16.4	16.4

N = number of animals; $T_{1/2\lambda z}$ = terminal half-life; C_{max} = maximum serum concentration; $AUC_{\tau(0-7)}$ = area under the concentration–time curve from Time = 0 to 7 days; CLss = clearance at steady state.

C. MMAE

Statistic	C_{max} (ng/mL)		$T_{1/2\lambda z}$ (day)	$AUC_{\tau(0-7)}$ (day*ng/mL)	CLss (mL/day/kg)
	First dose	Last dose	First dose	First dose	First dose
Group 2: AGS-22M6E					
N:	10	10	10	10	10
Mean:	0.0808	0.267	4.31	0.408	7480000
SD	0.0130	0.351	1.20	0.0640	1170000
%CV:	16.1	132	27.8	15.6	15.6
Group 3: AGS-22C3E					
N:	10	10	10	10	10
Mean:	0.0936	0.149	3.54	0.466	6630000
SD:	0.0207	0.0322	1.62	0.0860	1220000
%CV:	22.1	21.7	45.8	18.5	18.5

N = number of animals; $T_{1/2\lambda z}$ = terminal half-life; C_{max} = maximum serum concentration; $AUC_{\tau(0-7)}$ = area under the concentration–time curve from Time = 0 to 7 days; CLss = clearance at steady state.

(Excerpted from Applicant's report)

- **Study title: Assessment of the Potential Tissue Cross Reactivity of AGS-22M6E with a Selected Panel of Human Tissues (Study # 8236219)**

The tissue cross reactivity study using human tissues was reviewed by the FDA under IND # (b) (4) for AGS-22M6E. The following are key study findings as presented in the original IND.

Results: Specific positive staining was reported in the eye, esophagus, placenta, skin, tonsil, and uterus/cervix, all in cells of epithelial origin.

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Data:

Bacterial Reverse Mutation Assay: AA66EH.503.BTL

Key Study Findings:

- MMAE, the small molecule cytotoxic agent of enfortumab vedotin, was negative in the bacterial reverse mutation assay.

GLP compliance: Yes

Test system: *Salmonella typhimurium* tester strains TA98, TA100, TA1535, TA1537 and *Escherichia coli* tester strain WP2 *uvr*A in the presence and absence of Aroclor-inducted rat liver S9 enzymes

The Applicant's Position:
MMAE, the small molecule cytotoxic agent of enfortumab vedotin, had no discernible mutagenic potential in this in vitro assay.

The FDA's Assessment:
The FDA agrees with the study results described above for SGD-001010 (MMAE). Additional study comments are presented below.

GLP-compliant study, with the following exceptions:

- The stability of the test article was not determined or provided in the final report.
- Analysis to determine the uniformity or concentration of the test article mixture and stability was not performed or provided in the final report.

In Vitro Assays in Mammalian Cells

Data:

L5178Y TK$^{+/-}$ Mouse Lymphoma Forward Mutation Assay with a Confirmatory Assay / 8204155:
Key Study Findings:

- MMAE, the small molecule cytotoxic agent of enfortumab vedotin, was negative in the mouse lymphoma forward mutation assay.

GLP compliance: Yes
Test system: Mouse lymphoma L5178Y TK$^{+/-}$ cell line; up to 100 ng/ml; +/-S9

The Applicant's Position:
MMAE, the small molecule cytotoxic agent of enfortumab vedotin, showed no discernible mutagenic potential in the mouse lymphoma forward mutation assay.

The FDA's Assessment:
The FDA agrees with the study results described above for SGD-1010 (MMAE). Additional study comments are presented below.

GLP-compliant study, with the following exceptions:

- Documentation that the test article was characterized under GLP or GMP conditions was not provided in the final report.
- Analysis to determine the uniformity or concentration of the test article mixture and stability was not performed or provided in the final report.

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Data:

***In Vivo* Rat Bone Marrow Micronucleus Assay / 8204151**:

Key Study Findings:

- Increase in micronucleated polychromatic erythrocytes at 0.1 and 0.2 mg/kg
- Induced micronuclei were predominantly centromere+ (aneugenic mode of action)

GLP compliance: Yes

Test system: Rat/Sprague Dawley; bone marrow micronuclei; single IV bolus injection 0.01, 0.1 or 0.2 mg/kg of MMAE

The Applicant's Position:

MMAE was aneugenic in the in vivo rat bone marrow micronucleus study, consistent with the pharmacological effect of MMAE on the mitotic apparatus (disruption of the microtubular network).

The FDA's Assessment:

The FDA agrees with the study results described above for SGD-001010 (MMAE). Additional study comments are presented below.

GLP compliant study, with the following exception:

- Documentation that the test article was characterized under GLP or GMP conditions was not provided in the final report.

Other Genetic Toxicity Studies

Data:

N/A

The Applicant's Position:

N/A

The FDA's Assessment:

N/A

5.5.3. Carcinogenicity

Data:

N/A

The Applicant's Position:
In accordance with International Council for Harmonisation (ICH) S9, carcinogenicity studies were not conducted for enfortumab vedotin as it is intended for treatment of metastatic UC.

The FDA's Assessment:
Carcinogenicity studies were not conducted or needed to support marketing of PADCEV in patients with advanced cancer.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Data:
N/A

The Applicant's Position:
N/A

The FDA's Assessment:
Fertility and early embryonic development studies were not conducted or needed to support marketing of PADCEV in patients with advanced cancer.

Embryo-Fetal Development

Data:

A Preliminary Embryo-Fetal Development Study of Enfortumab Vedotin by Intravenous Injection in Rats / 20119695

Key Study Findings:

- 2 mg/kg of enfortumab vedotin (approximately equal to the human C_{max}) resulted in increased post implantation loss and reduced numbers of viable fetuses. The surviving fetuses had an increased incidence of skeletal variations.
- 5 mg/kg of enfortumab vedotin (~3-fold the human C_{max}) resulted in complete litter loss.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	Day 6 and 13 of gestation (GD 6 and 13) at 0, 2 or 5 mg/kg/dose enfortumab vedotin
Route of administration:	IV
Formulation/Vehicle:	5% (w/v) sterile dextrose solution

Species/Strain:	Rat/Sprague-Dawley
Number/Sex/Group:	6 dams
Satellite groups:	Not applicable
Study design:	Treatment with 0, 2, or 5 mg/kg enfortumab vedotin on GD 6 and 13 by IV bolus with fetal examination by caesarian section on GD21
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	**Major findings**
Mortality	No maternal mortality. Fetal losses at 2 and 5 mg/kg
Clinical Signs	No drug-related changes were observed
Body Weights	Decreases at all dose levels, due at least in part, to litter losses
Necropsy findings	2 mg/kg: Decreased viable fetuses (early resorptions) with surviving fetuses featuring skeletal variations (mainly developmental delays), including asymmetric, fused, incompletely ossified, and misshapen sternebrae, misshapen cervical arch and unilateral ossification of the thoracic centra). 5 mg/kg: No live fetuses

The Applicant's Position:

Enfortumab vedotin and MMAE both demonstrated embryo-fetal toxicity in pregnant rats at exposures similar to those observed clinically. These toxicities are likely related to MMAE exposure of the fetus and not an effect of the anti-Nectin-4 antibody.

The FDA's Assessment:

The Applicant's assessment of the data was not complete. The Applicant did not summarize the embryo-fetal development (EFD) study in rats administered MMAE, the small molecule component of enfortumab vedotin, during organogenesis in the Assessment-Aid document (Study # 8204-397).

In regard to the summary data presented by the Applicant under study # 20119695, the FDA agrees with the Applicant's conclusion that enfortumab vedotin administration throughout organogenesis resulted in maternal toxicity, embryo-fetal lethality and skeletal anomalies. However, FDA disagrees with the Applicant's conclusion that no malformations were present following enfortumab vedotin administration. This reviewer concluded that enfortumab vedotin resulted in external, visceral and skeletal malformations (see table below).

In conclusion, intravenous administration of enfortumab vedotin or MMAE (the small molecule component of enfortumab vedotin) to pregnant rats during the period of organogenesis caused maternal toxicity (decrease in body weight) abortion and teratogenicity (embryo-fetal lethality and structural malformations and skeletal anomalies) at exposures approximately similar to the human exposures at the clinical recommended dose. The similarities in effects reported between enfortumab vedotin and MMAE suggest that enfortumab vedotin toxicity, at least in part, are due to MMAE toxicity.

Additional study findings/conclusions are presented below for clarity and completion:

Study title: A Preliminary Embryo-Fetal Development Study of Enfortumab Vedotin by Intravenous Injection in Rats (Study # 20119695)

Methods: In this GLP-compliant study, time-mated rats were intravenously administered enfortumab vedotin at 2 and 5 mg/kg on gestation days 6 and 13 (organogenesis period). A total of 6 pregnant rats were assigned to each group.

Results

- The study design was not sufficient to establish NOAEL, due to the small number of animals per group (6/group, not statistically powered to detect malformations).
- A dose responsive decrease (-9% and -30%, respectively) in maternal body weight was reported at 2 and 5 mg/kg, respectively.
- At 5 mg/kg, a decrease in food consumption was reported (up to 23%).
- Embryo-fetal lethality (decrease in number of live fetuses, increase in post implantation loss, early and late resorptions/fetal loss) was reported at doses ≥2 mg/kg. Total litter loss (100%) was reported at 5 mg/kg.

Table 33: A preliminary embryo-fetal study in rats administered enfortumab vedotin - cesarean section data (mean)

	Control	2 mg/kg	5 mg/kg
Number of resorptions	1	3.5	15.6
Early resorptions	1	3	15.6
Late resorption	0	0.5	0
Post implantation loss %	7.23	26.38	100

Number of live fetuses	12.3	9.2	0

- Decrease in fetal weight (-10%) was reported at 2 mg/kg.
- Malformations and skeletal anomalies were reported at 2 mg/kg:

Table 34: A preliminary embryo-fetal study in rats administered enfortumab vedotin - % litter incidence

	Control	2 mg/kg
Number of Litters	6	6
External malformations		
absent forepaw	0	16.7%
malrotated hindlimbs	0	16.7%
Gastroschisis	0	16.7%
Visceral malformations		
malpositioned internal organs (intestine, liver, pancreas, spleen, stomach)	0	16.7%
Skeletal malformations		
fused cervical arch	0	16.7%
Skeletal anomalies		
Sternebra, asymmetric-	0	50%
Sternebra, bipartite ossification-	0	16.7%
Sternebra, fused-	0	33.3%
Sternebra, incomplete ossification-	0	83.3%
Sternebra, misshapen-	16.7%	33.3%
Cervical arch, incomplete	0	16.7%

ossification		
Cervical arch, misshapen-	0	33.3%
Cervical centrum, unilateral ossification-	0	16.7%
Thoracic centrum, bipartite ossification	0	16.7%
Thoracic centrum, unilateral ossification-	0	50%

- Formulation stability analysis was not performed in compliance with GLP.
- Concentration (C_{max}) increased approximately in a dose proportional manner. AUC was not calculated.

Table 35: A preliminary embryo-fetal study in rats administered enfortumab vedotin – toxicokinetic parameters

Serum samples (GD 13, 10 min postdose)		
Dose	**2 mg/kg**	**5 mg/kg**
Mean C_{max} (µg/mL)	28.61	82.05

Conclusion: No maternal and developmental NOAEL was established. Enfortumab vedotin administration during organogenesis resulted in maternal toxicity, embryo-fetal lethality, decreased fetal weight, malformations (external, visceral and skeletal) and skeletal anomalies at doses ≥ 2 mg/kg (at exposures [C_{max}] approximately similar to the human exposure at the clinical recommended dose of 1.25 mg/kg). Total litter loss (100%) was reported at 5 mg/kg (at 3-fold higher than the exposure reported clinically).

Study Title: Intravenous Injection Study for Effects on Embryo-fetal Developmental and Toxicokinetics with SGN- 35 and SGD-1010 in Rats (Study # 8204-397)

Reviewer comment
The Applicant did not summarize this study in the Assessment-Aid document.
To characterize the toxicity of MMAE the small molecule component of enfortumab vedotin, the Applicant crossed referenced study # 8204-397 (owned by Seattle Genetics, Inc.).

Methods: In the GLP-compliant study, MMAE (SGD-1010) was administered intravenously to 35 time mated pregnant rats (25 main study and 9 for toxicokinetic evaluation) on gestation days 6 and 13 at a single dose level of 0.2 mg/kg (0.04 mg/mL).

Results

- All MMAE animals survived until scheduled sacrifice.
- Clinical observations included, pale (both ears), alopecia, red fluid in pan and pups in cage pan (indication of abortion).
- Decrease in maternal body weight was reported throughout the entire study period (-20%).
- One dam delivered early (i.e. abortion) and one dam had no viable fetuses.
- Embryo-fetal lethality was reported (reported as 'increases in early and late resorptions, post implantation loss and decrease in the number of live fetuses).

Table 36: Embryo-fetal study in rats administered MMAE - cesarean section data- mean

	Control	0.2 mg/kg
Number of Litters	25	25
Total number of resorptions	0.1	3.6
Early resorptions	0.1	3
Late resorption	0	0.6
Post implantation loss	1	27.4
Live fetuses	12.7	9.2

- Malformations (external, visceral and skeletal) were reported:

Table 37: Embryo-fetal study in rats administered MMAE -% litter incidence

	Control	0.2 mg/kg
Number of Litters	25	25
External malformations		
Protruding tongue	0	4.3%
Malrotated hindlimbs	0	8.7%
Gastroschisis	0	8.7%
Agnathia	0	4.3%

Visceral malformations		
situs inversus	0	4.5%
Skeletal malformations		
malformed mandible	0	4.3%
misaligned, fused and/or absent caudal vertebrae	0	4.3%
split sternebrae	0	4.3%
shortened fibula	0	4.3%

Toxicokinetics:

- MMAE serum concentrations were approximately 60% higher on GD 13 than on GD 6. MMAE was transferred across the placenta. SGD-1010 (MMAE) concentrations in amniotic fluid and fetal serum (mean 0.00983 ng/mL) on GD 18 were higher than those in maternal rat serum, indicating that SGD-1010 was transferred from maternal rat serum to fetus.
- The MMAE maternal and embryo-fetal toxicity were reported at approximately similar exposure level (AUC) reported at the clinical dose of 1.25 mg/kg (27.3 ng.day/mL).

Table 38: Embryo-fetal study in rats administered MMAE – maternal toxicokinetic parameters

Mean Toxicokinetic Parameters for SGD-1010 in Maternal Rat Serum Following Two Weekly Doses of SGD-1010

Dose Group	SGD-1010 Dose Level (mg/kg/dose)	N[a]	Gestational Day	C_{max} (ng/mL)	DN C_{max} (ng/mL)/(mg/kg/dose)	T_{max} (Day)	$AUC_{0\text{-last}}$ (ng·day/mL)	$AUC_{0\text{-1d}}$ (ng·day/mL)	DN $AUC_{0\text{-1d}}$ (ng·day/mL)/(mg/kg/dose)
12	0.2	9	6	29.7	148	0.00347	16.2	16.2	80.9
			13	50.2	251	0.00347	25.6	25.6	128

a Total number of animals. Blood from 3 animals/timepoint was collected.

(Excerpted from Applicant's report)

Table 39: Embryo-fetal study in rats administered MMAE -concentration in amniotic fluid and fetal serum

Ratio of SGD-1010 Concentration in Amniotic Fluid and Fetal Serum to Maternal Serum on GD 18

Dose Group	SGD-1010 Dose Level (mg/kg/dose)	Animal Number	Ratio Amniotic Fluid:Maternal Serum	Ratio Fetal Serum:Maternal Serum
12	0.2	B57515	NA	NA
		B57516	NA	0.0137:BLQ
		B57517	NA	0.0180:BLQ
		B57518	0.0151:BLQ	0.0141:BLQ
		B57519	0.0205:BLQ	NA
		B57520	NA	NA
		B57521	0.0192:BLQ	0.0132:BLQ
		B57522	NA	NA
		B57523	NA	NA

NA Not applicable, it was not possible to calculate ratios when the observed concentrations were below the lower limit of quantitation (BLQ).

Fetal serum values are ng/mL

(Excerpted from Applicant's report)

Conclusion: Administration of MMAE at 0.2 mg/kg during organogenesis resulted in maternal toxicity (decrease in body weight), abortion, embryo-fetal lethality and malformations (external, visceral and skeletal) at exposures [AUC] approximately similar to the reported human exposure at the clinical recommended dose. Toxicokinetic evaluation in dams revealed that MMAE was transferred across the placenta and that MMAE was present in fetus serum. As such, it is plausible that the observed teratogenicity was in part due to direct effects of MMAE on the embryo/fetus.

Prenatal and Postnatal Development

Data:

N/A

The Applicant's Position:

N/A

The FDA's Assessment:

Prenatal and postnatal development studies were not conducted or needed to support marketing of PADCEV in patients with advanced cancer.

5.5.5. Other Toxicology Studies

Data:

Testicular Toxicity Reversibility Study

A 4-Week Repeat Dose Intravenous Testicular Toxicity Study of Enfortumab Vedotin with a 24-Week Recovery Period in the Rat / 20135474

Key Study Findings:

- Enfortumab vedotin-related microscopic findings were noted in the testes spermatid/spermatocyte depletion and/or decreased vacuolation of the seminiferous tubules and epididymis (cell debris) on day 29 and on recovery days 64, 127 and 190 but had decreased incidence by the end of the recovery period indicating partial reversibility.
- Enfortumab vedotin-related decreased testis and epididymis weights were noted from day 29 through day 127 and resolved by the end of the recovery period on day 190.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0 or 2 mg/kg for 1 month (q1w x 4 doses)
Route of administration:	IV
Formulation/Vehicle:	5% (w/v) sterile dextrose solution
Species/Strain:	Rat/Sprague-Dawley
Number/Sex/Group:	20 males/group
Age:	10 to 11 weeks
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	No mortality observed
Clinical Signs	No drug-related changes were observed
Food Consumption	No drug-related changes were observed
Body Weights	No drug-related changes were observed
Gross Pathology	No drug-related changes were observed
Organ Weights	Decreased testis and epididymis weights were noted from day 29 through day 127 and resolved by the end of the recovery period on day 190.
Histopathology	Testes (spermatid/spermatocyte depletion and/or decreased vacuolation of the seminiferous tubules) and epididymis (cell debris) on day 29 and on

	recovery days 64, 127 and 190 but had decreased incidence by the end of the recovery period (Day 190).

Applicant's Position:
Testicular toxicity was observed in rats following repeat dosing of enfortumab vedotin at systemic exposures that were approximately equal to the human systemic exposure at the clinically recommended dose; the toxicity was shown to be partially reversible following a 24-week recovery period. There are no data on the effect of enfortumab vedotin on human fertility.

The FDA's Assessment:
The FDA disagrees that the effects on male reproductive organs was partially reversible following a 24-week recovery period. No reversibility of the testicular and epididymal findings was reported at the end of the recovery period.

In the 4-week rat study, at a dose of 2 mg/kg, the microscopic changes reported in the testes (spermatocyte depletion) and epididymis (cell debris) on day 29 were also reported by the end of the recovery period (day 190). A decrease in the incidence, but not severity, of the spermatocyte depletion in the testes was reported at the end of the recovery period (day 190). Additional testes findings were reported at the end of the recovery period that were not evident at the end of the dosing period (seminiferous tubule degeneration/atrophy, seminiferous tubule multinucleated giant cells), suggesting that continued exposure into the non-dosing period caused additional toxicity. No decreases in the incidence and severity of the findings reported in the epididymis were reported at the end of the recovery period.

Table 40: Testicular toxicity study in rats of enfortumab vedotin- histopathology findings (day 29)

20135474 - Intergroup Comparison of Histopathology Findings, Day 29

Removal Reason(s): TERMINAL EUTHANASIA	Male 0 mg/kg/day Group 1	Male 2 mg/kg/day Group 2
Number of Animals:	5	5
EPIDIDYMIS		
Examined	5	5
No Visible Lesions	5	4
Cellular debris	0	1
.... minimal	0	1
TESTIS		
Examined	5	5
No Visible Lesions	5	3
Depletion; germ cell; spermatocyte	0	2
.... mild	0	2

20135474 - Intergroup Comparison of Histopathology Findings, Day 190

Removal Reason(s): RECOVERY EUTHANASIA	Male 0 mg/kg/day Group 1	Male 2 mg/kg/day Group 2
Number of Animals:	5	5
EPIDIDYMIS		
Examined	5	5
No Visible Lesions	5	4
Cellular debris	0	1
.... mild	0	1
TESTIS		
Examined	5	5
No Visible Lesions	5	4
Depletion; germ cell; spermatocyte	0	1
.... mild	0	1
Degeneration/atrophy; seminiferous tubule	0	1
.... mild	0	1
Multinucleated giant cells; seminiferous tubule	0	1
.... mild	0	1

(Excerpted from Applicant's report)

The following studies were not summarized by the Applicant in the Assessment-Aid document:

<u>Phototoxicity Studies</u>

Study title: SGD-1006, SGD-1427 and SGD-1010 photo safety evaluation (Study # TRN-2926-A-NCR-EN)

The photo safety of SGD-1006 (vc-MMAE), SGD-1427 (NAC-vcMMAE) and SGD-1010 (MMAE) was assessed.

SGD-1006 and SGD-1427 did not show photo absorption in the range of 290-700 nm. A subsequent study conducted on SGD-1010 (MMAE) showed no photo absorption in the range of 290-700 nm. As such, MMAE and linker-MMAE are not considered phototoxic.

Study Title: Peripheral Glucose Uptake and Islet Viability and Insulin Secretion (Study # 18022-076622)

Objective of the study was to determine whether the negative control ADC (h00-1006[4]) or SGD-1010 (MMAE), impaired glucose uptake into peripheral tissue (human skeletal muscle) and to determine the toxicity (viability) and function (insulin secretion) of human islets after exposure to the test articles.

- Negative control: h00-1006[4] a humanized nonbinding immunoglobulin G1 control antibody conjugated with MMAE via the same protease-cleavable linker used in enfortumab vedotin (ADC)
- SGD-1010 (MMAE)
- Two glucose media were used: 1.4 mM (low glucose) or 11.2 mM (high glucose).
- Human skeletal muscle cells and human islets were obtained from two donors.

The following assays were used:

- A luminescent glucose uptake assay in human skeletal muscle cells
- Resazurin-based testing for islet viability in a microplate assay
- Propidium iodide for viability imaging, and an ELISA-based assay for determination of insulin content.

Results

- Neither the ADC nor MMAE inhibited glucose uptake by skeletal muscle cells at the concentrations ranging from 0.01 ng/mL to 30 ng/mL. Statistically significant increase in glucose uptake was reported at 100 ng/mL of MMAE. This effect was reported at concentration that was 26-fold higher than the C_{max} reported in human at the clinical recommended dose (C_{max} 3.9 ng/mL).

Table 41: Peripheral glucose uptake in skeletal muscle cells following exposure with MMAE

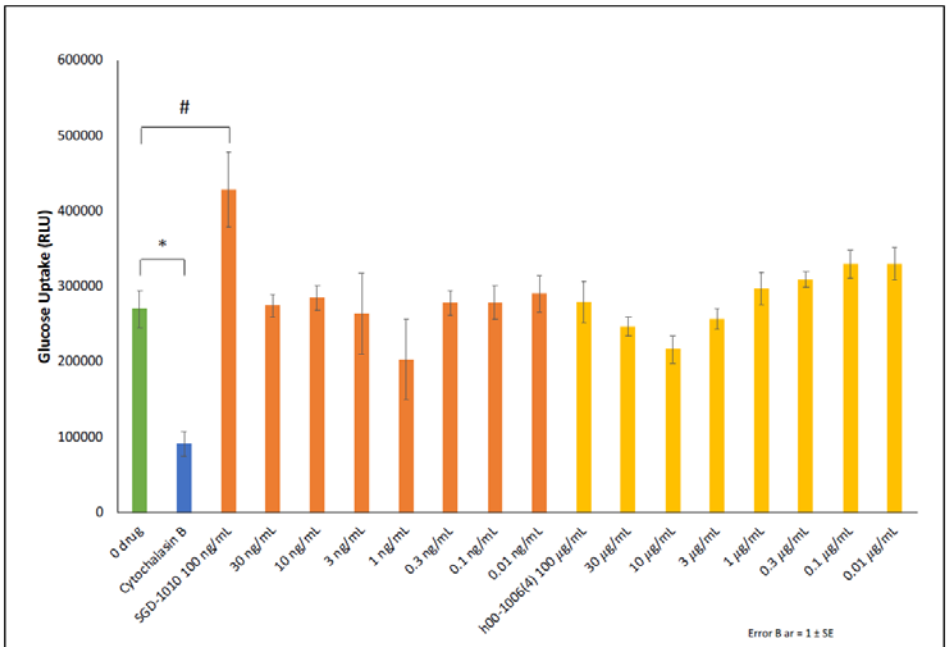


Figure 4.1.1: Glucose Uptake in Skeletal Muscle Cells. The glucose uptake (y-axis), represented in relative luminescent units (RLUs), is reported with the corresponding treatment group (x-axis). The Test Article, SGD-1010 is represented by orange bars and Test Article, h00-1006(4), is represented by yellow bars (n=4). The SGD-1010 at 100 ng/mL and Cytochalasin B had statistically significant differences in glucose uptake compared to the 0 Test Article (*, #, p<0.05).

(Excerpted from Applicant's report)

- At the high glucose condition, there was no change in human islet cell viability after 4 hour incubation, while with longer incubation (12 hours), concentration dependent loss of viability at MMAE concentrations ≥ 0.1 ng/mL (0.03-fold lower than the C_{max} reported in human at the clinical recommended dose) were reported. Viability decreased by approximately 30% between concentration 0 to 100 ng/mL. A decrease of <20% in human islet cell viability was reported at MMAE concentration similar to the C_{max} reported in patients at the clinical recommended dose.

  Exposure to the ADC (h00-1006[4]) at the low and high glucose media resulted in a decrease in islet cell viability. The decrease was reported following 12 hours incubation and was not concentration-dependent (at 0.01, 30 and 100 µg/mL).

Table 42: Islet viability following exposure with MMAE

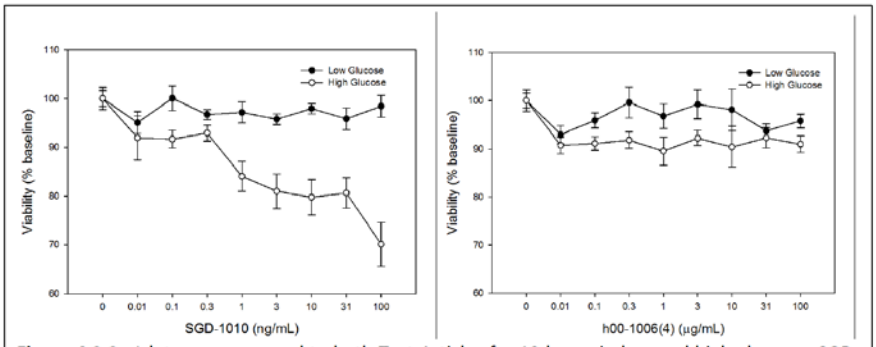


Figure 4.2.2: Islets were exposed to both Test Articles for 12 hours in low and high glucose. SGD-1010 (left graph) caused a decrease in cell viability when tested in high glucose, but not in low glucose. h00-1006(4) (right graph) caused a significant reduction that was not concentration-dependent in high glucose. At low glucose, select concentrations of h00-1006(4) were statistically less than baseline.

Islets were pre-incubated for 1 hour with low glucose CMRL media (1.4 mM) or high glucose CMRL media (11.2 mM)

(Excerpted from Applicant's report)

- The function of the islet cells was tested by measuring the amount of insulin secreted in response to low and high glucose for each test article after a 4 hour incubation. Following exposure with MMAE, insulin secretion decreased in non-concentration-dependent manner following incubation within high glucose media. The maximum decrease in insulin secretion at maximum concentration of MMAE (100 ng/mL) was 22% and 31% for Donor 1 and 2, respectively. This effect occurred at a concentration that was 26-fold higher than the C_{max} reported in human at the clinical recommended dose (C_{max} 3.9 ng/mL). No meaningful change was reported following exposure to the ADC.

Table 43: Insulin secretion following exposure with MMAE

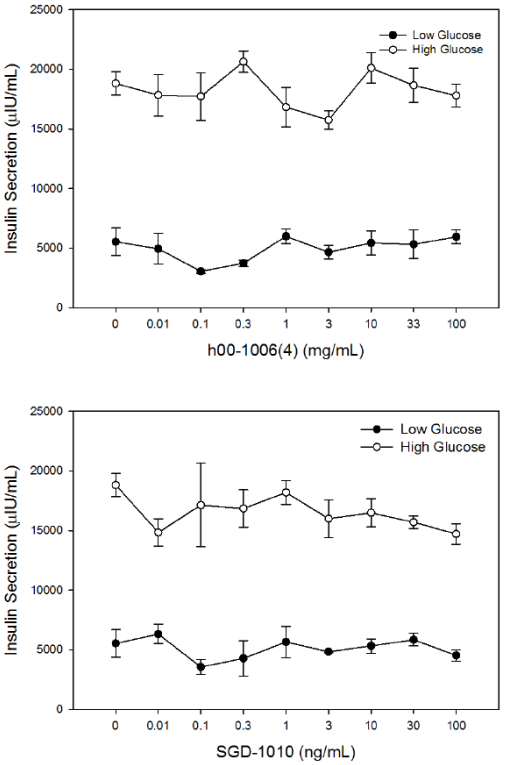


Figure 4.3.2: Islets from Donor 1 were exposed to both Test Articles at 8 concentrations in both low and high glucose. The upper graph demonstrates the response to h00-1006(4) in low (closed circles) and high (open circles) glucose. The lower graph illustrates the response to SGD-1010 in low and high glucose.

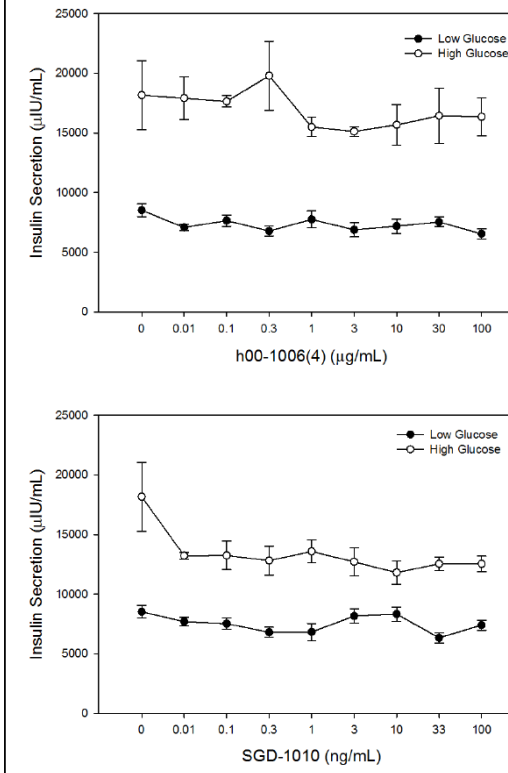


Figure 4.3.3: Islets from Donor 2 were exposed to both Test Articles at 8 concentrations in both low and high glucose. The upper graph demonstrates the response to h00-1006(4) in low (closed circles) and high (open circles) glucose. The lower graph illustrates the response to SGD-1010 in low and high glucose.

(Excerpted from Applicant's report)

In conclusion, there was significant increase in glucose uptake in human skeletal muscle cells following exposure to MMAE at 100 ng/mL (26-fold higher than the C_{max} reported in human at the clinical recommended dose). Loss in human islet viability was reported at concentrations ≥0.1 ng/mL following 12 hours incubation with MMAE (0.03-fold lower than the C_{max} reported in human at the clinical recommended dose). A decline in insulin secretion (not dose dependent) from human islets was reported following exposure to MMAE. Following ADC administration, a decline in islet cell viability was reported following 12 hours incubation, but was not concentration-dependent.

X	X
Eias Zahalka Primary Reviewer	Tiffany Ricks Supervisor

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

Enfortumab vedotin is an antibody-drug conjugate directed against Nectin-4, an adhesion protein located on the surface of cells. MMAE, a small molecule cytotoxin, is conjugated to the antibody via a protease-cleavable linker. The applicant is seeking approval of enfortumab vedotin (b) (4)

The proposed dosing regimen of enfortumab vedotin is 1.25 mg/kg (up to a maximum dose of 125 mg) given as an IV infusion over 30 minutes on Days 1, 8, and 15 of a 28-day cycle until disease progression or unacceptable toxicity.

The clinical pharmacology review focused on the dosing regimen (dose selection and dose cap), organ impairment, drug-drug interactions, population PK modeling, exposure-response analyses for efficacy and safety, and whether patient selection based on Nectin-4 baseline expression level was warranted.

RECOMMENDATIONS

The Office of Clinical Pharmacology has reviewed the information and data submitted in BLA 761137. This BLA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized in **Table 44** below.

Table 44. Key clinical pharmacology review issues

REVIEW ISSUE	RECOMMENDATIONS / COMMENTS
Pivotal and supportive evidence of effectiveness	The primary evidence of effectiveness comes from pivotal Study EV-201 (Cohort 1) in patients with previously treated locally advanced or metastatic urothelial cancer who have had a prior PD-1 or PD-L1 inhibitor and platinum-based therapy. An ORR of 44% was observed in 125 patients who received enfortumab vedotin at the proposed dosing regimen.
General dosing instructions	The proposed dosing regimen of 1.25 mg/kg IV (up to a maximum dose of 125 mg) given as an IV infusion over 30 minutes on Days 1, 8, 15 of a 28-day cycle is acceptable for approval.
Dosing in patient subgroups (intrinsic and	The following dosing recommendations should be followed:

extrinsic factors)	▪ Severe or moderate hepatic impairment: avoid use
Drug-drug interactions	No dose adjustments are recommended for drug-drug interactions. Closely monitor for signs of toxicity in patients taking concomitant strong CYP3A4 inhibitors, as potentially increased systemic exposure of MMAE may increase the incidence or severity of PADCEV toxicity.
Labeling	Overall, the proposed labeling recommendations are acceptable upon the applicant's agreement to the FDA revisions to the labeling. Clinical pharmacology labeling recommendations are detailed in Section 11.

Post-Marketing Requirement (PMR) or Commitment (PMC)
None.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:
Enfortumab vedotin exhibited linear dose-proportional PK at doses ranging from 0.5 to 1.25 mg/kg when administered as an intravenous infusion over ~30 minutes on days 1, 8, and 15 of a 28-day cycle in subjects with locally advanced or metastatic UC. Peak enfortumab vedotin concentrations were attained at the end of infusion. In contrast, plasma concentrations of free MMAE increased until ~2 days after enfortumab vedotin dosing. Minimal to no accumulation of enfortumab vedotin or free MMAE was observed.

Based on population PK analyses, estimates of enfortumab vedotin and free MMAE mean clearance were 0.104 L/h and 2.72 L/h, respectively. Terminal half-life was estimated to be ~3.35 days (80.5 h) for enfortumab vedotin and ~2.44 days (58.5 h) for MMAE. The elimination of MMAE appeared to be limited by its formation from enfortumab vedotin.

Population PK analyses were also used to estimate the total volume of distribution at steady state (sum of volume distribution of central and peripheral compartments) following an intravenous dose of 1.25 mg/kg enfortumab vedotin. The total volume of distribution at steady state was estimated to be 10.9 L for enfortumab vedotin and 218 L for MMAE.

A small fraction of the MMAE released from enfortumab vedotin is metabolized. In vitro data indicate that the metabolism of MMAE occurs primarily by CYP3A4. In vitro, the binding of MMAE to human plasma proteins ranged from 67.9% to 82.2%. MMAE is not likely to displace or to be displaced by highly protein-bound drugs. The excretion of MMAE occurs mainly in feces with a smaller proportion in urine. After a single dose of brentuximab vedotin, another ADC that contains MMAE, ~24% of the total MMAE administered was recovered in feces and urine

over a 1-week period (6), ~72% of which was recovered unchanged in the feces. A similar excretion profile of MMAE is expected after enfortumab vedotin administration.

The Applicant's Position:
Enfortumab vedotin exhibited linear PK in subjects who received enfortumab vedotin by intravenous administration. Population pharmacokinetic analysis indicated that distribution of enfortumab vedotin was limited to the central vascular compartment, with an elimination half-life of ~3.35 days (80.5 h) and minimal accumulation upon repeat dosing. MMAE PK was linear with minimal accumulation after repeat dosing. The elimination was estimated by its apparent release from enfortumab vedotin with an elimination half-life of ~2.44 days (58.5 h). MMAE was distributed within central vascular and peripheral tissue compartments with moderate binding to plasma proteins. MMAE is metabolized predominantly by CYP3A4 and is excreted mainly by hepatobiliary routes.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:

Weight-based dosing for enfortumab vedotin is supported by population pharmacokinetic modeling and simulation analyses, which indicate that weight-based dosing resulted in lower variances in pharmacokinetic parameters as compared to fixed dosing.

Enfortumab vedotin was dosed every 3 weeks in the first-in-human study; however, preliminary pharmacokinetic results indicated a relatively short half-life that supported dosing on a weekly basis. Therefore, further evaluation with dosing on days 1, 8 and 15 of a 28-day cycle was conducted in subsequent clinical studies. A relatively short half-life (3.35 days) was confirmed with a population pharmacokinetic analysis.

The phase 1 Study EV-101 evaluated the weekly dosing schedule at doses ranging from 0.5 mg/kg to 1.25 mg/kg. An MTD was not reached during dose-escalation; however, further dose escalation was not pursued due to dose reductions and drug-related rash and diarrhea, which occurred at higher frequencies relative to subjects treated at lower dose levels at the time the interim data analysis was conducted.

In Study EV-101, responses were observed at all dose levels, but lower rates of response were observed at doses < 1.25 mg/kg. Enfortumab vedotin exposure-response analyses of best overall response (BOR) (complete response [CR]/partial response [PR]: responders, and progressive disease [PD]/stable disease [SD]/not evaluable [NE]: non-responders), progression-

free survival (PFS) and overall survival (OS) outcomes demonstrated an efficacy plateau at higher systemic exposure levels (Q2 to Q4), therefore, further increases in enfortumab vedotin exposures at doses > 1.25 mg/kg may not provide additional efficacy benefit.

The estimate of relative dose intensity among subjects treated at 1.25 mg/kg was 81.2%, indicating that subjects generally received study treatment as planned. For subjects requiring dose modification, responses to enfortumab vedotin are anticipated based on the PFS and OS observed in subjects at doses < 1.25 mg/kg during the dose-escalation phase of Study EV-101.

Dose reductions remain more frequently required at 1.25 mg/kg (31.6% for 1.25 mg/kg enfortumab vedotin safety analysis group) than at lower dose levels (0% at 0.75 mg/kg and 10% at 1 mg/kg in Study EV-101). This is supported by exploratory exposure-safety analyses, which suggested enfortumab vedotin exposure predicts the occurrence of key safety events. The higher rate of dose reductions at 1.25 mg/kg compared to the lower doses suggests that higher doses may result in lower relative dose intensity compared to the intended dose.

Overall, enfortumab vedotin administered by intravenous infusion at 1.25 mg/kg, up to an absolute dose of 125 mg, on days 1, 8 and 15 of each 28-day cycle demonstrates a favorable benefit-risk profile for subjects with locally advanced or metastatic UC.

The Applicant's Position:

Enfortumab vedotin administered by intravenous infusion at 1.25 mg/kg on days 1, 8 and 15 of each 28-day cycle. This regimen was selected based on the benefit/risk ratio observed in the phase 1 clinical studies, where a range of doses were tested. While activity was observed at all dose levels, 1.25 mg/kg was associated with greater antitumor activity compared to lower doses.

Enfortumab vedotin, administered by intravenous infusion of 1.25 mg/kg (up to a maximum dose of 125 mg), on days 1, 8, and 15 of each 28-day cycle, is supported by the pharmacokinetic characteristics of enfortumab vedotin, as well as its clinical efficacy with a manageable safety profile. The use of weight-based dosing for enfortumab vedotin was supported by population PK modeling and simulation analyses.

The integration of enfortumab vedotin exposure-response findings for both efficacy and safety support the recommended dose of 1.25 mg/kg administered on days 1, 8 and 15 of a 28-day cycle.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

6.2.2.2. Therapeutic Individualization

Data:
Enfortumab vedotin has been administered based on subject body weight, with the exception of subjects >100 kg for which a dose cap (125 mg) was implemented via protocol amendments for Studies EV-101, EV-102, and EV-201 following serious drug-related AEs in obese subjects. In addition, population PK modeling and simulation analyses were used to support weight-based dosing for enfortumab vedotin.

Impact of intrinsic factors on enfortumab vedotin and MMAE PK was assessed in the population PK model. The model identified body weight, sex, hemoglobin, sum of tumor diameters at baseline and cancer type as covariates for enfortumab vedotin PK and albumin, Eastern Cooperative Oncology Group (ECOG) score, hemoglobin, bilirubin, race, body weight and sex as covariates for MMAE PK. The model-predicted Cycle 1 $AUC_{0\text{-}28d}$ and C_{max} evaluated for these covariates following 1.25 mg/kg enfortumab vedotin (up to a maximum dose of 125 mg for subjects with body weight > 100 kg) were within 0.86 to 1.29-fold of enfortumab vedotin exposures and 0.77 to 1.46-fold of free MMAE exposures for a reference population. The model-predicted Cycle 1 C_{trough} was within 0.71 to 1.44-fold of enfortumab vedotin exposures and 0.66 to 1.47-fold of free MMAE exposures for a reference population. The range of effects relative to a reference population was within the observed variability in the modeling dataset for both enfortumab vedotin and free MMAE. Based on these results, it was concluded that the effects of these covariates were not clinically meaningful.

The assessment of renal impairment was based on estimated creatinine clearance (CrCl) at baseline as determined using the Cockcroft-Gault Formula (Cockcroft and Gault, 1976). In Study EV-101, the PK of enfortumab vedotin and free MMAE in subjects with mild, moderate or severe renal impairment were comparable to subjects with normal renal function at 1.25 mg/kg dose of enfortumab vedotin on days 1, 8, and 15 on a 28-day cycle. In addition, a population PK analysis of the effects of renal function on enfortumab vedotin and free MMAE was conducted in subjects with varying degrees of renal impairment at baseline. No significant differences in AUC exposure of enfortumab vedotin and MMAE were observed in patients with mild (CrCl > 60 to < 90 mL/min; n = 150), moderate (CrCl 30 to < 60 mL/min; n = 132) or severe renal impairment (CrCl < 30 mL/min; n = 9) compared to patients with normal renal function.

A population PK analysis of the effects of hepatic function on enfortumab vedotin and free MMAE was conducted in subjects with mild hepatic impairment at baseline, as determined by the criteria of the National Cancer Institute of Organ Dysfunction Working Group. Population PK modeling and simulation demonstrated that no significant differences in enfortumab vedotin or MMAE exposures were observed in patients with mild hepatic impairment (bilirubin of 1 to 1.5 × ULN and AST < ULN, or bilirubin ≤ ULN and AST > ULN, n=31) compared to patients with normal hepatic function.

Formal drug-drug interaction studies with enfortumab vedotin have not been conducted. To characterize the drug-drug interaction potential of free MMAE, clinical studies with another ADC that contains MMAE are described below. In vitro data and clinical drug-drug interaction study data from brentuximab vedotin (6), an ADC structurally similar to enfortumab vedotin, were used to support the clinical pharmacology evaluations of enfortumab vedotin. In the clinical DDI study with brentuximab vedotin, concomitant use of ketoconazole led to a 34% increase in free MMAE AUC exposure, while concomitant use of rifampicin was associated with a 46% decrease in free MMAE AUC exposure. The pharmacokinetics of enfortumab vedotin were unchanged by either drug [Han et al, 2013]. Concomitant use of strong inhibitors or inducers of CYP3A4 with enfortumab vedotin would likely result in similar effects on circulating concentrations of enfortumab vedotin and free MMAE.

The Applicant's Position:

Dose individualization is recommended on the basis of body weight, up to a maximum dose of 125 mg for subjects treated at 1.25 mg/kg with body weight of 100 kg or greater. In addition, population PK modeling and simulation analyses demonstrated body weight-based dosing is appropriate.

No dose adjustment is required based on age, race, or sex. No dose adjustment is required in patients with mild, moderate or severe renal impairment. No dose adjustment is required in patients with mild hepatic impairment. Enfortumab vedotin has not been evaluated in patients with moderate or severe hepatic impairment. No dose adjustment is required with concomitant administration of enfortumab vedotin with strong inhibitors/inducers of CYP3A4. Closely monitor for adverse reactions when enfortumab vedotin is given concomitantly with strong CYP3A4 inhibitors. The safety and effectiveness of enfortumab vedotin in pediatric patients has not been established.

The FDA's Assessment:

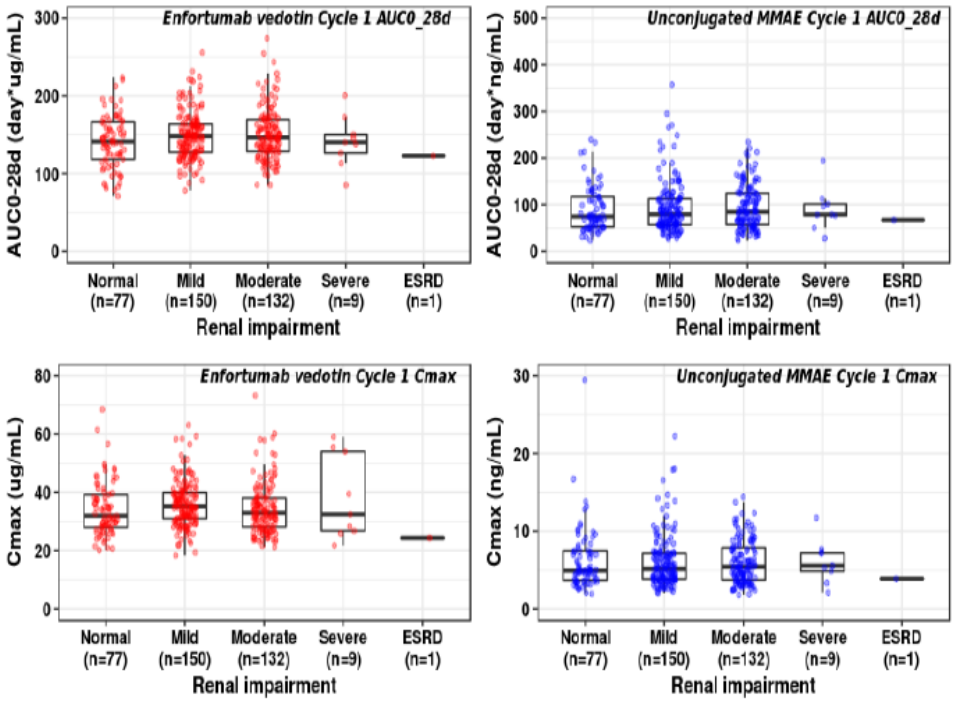
(b) (4)

Enfortumab vedotin has not been evaluated in patients with moderate or severe HI. However, in a dedicated hepatic impairment trial with another ADC that contains MMAE (brentuximab vedotin), the frequency of ≥ Grade 3 adverse reactions and deaths was higher in patients with moderate or severe hepatic impairment (Child-Pugh B or C) compared to patients with normal hepatic functions. Due to the observed safety signals with another ADC that contains the same microtubule-disrupting agent MMAE, enfortumab vedotin should be avoided in patients with moderate or severe hepatic impairment (Child-Pugh B or C).

The FDA agrees that no dose adjustment is required in patients with renal impairment. Based on population PK analysis, enfortumab vedotin and MMAE exposures were comparable in

patients with mild, moderate and severe renal insufficiency (**Figure 5**). Study EV-101 has a dedicated renal cohort to assess the safety, PK, and efficacy in mUC patients with severe renal impairment (CrCL ≥ 15 to < 30 mL/min) (N=18). There was no trend of increased exposures in patients with renal impairment. The 90-day safety update provide to FDA included updated safety information for patients with renal impairment (**Table 45**). There was no signal of increased incidence of adverse events in patients with renal insufficiency.

Figure 5: Renal function vs. model-predicted Cycle 1 exposures of enfortumab vedotin and unconjugated MMAE



Source: Adapted from Figure 2 on page 9 from Applicant's population PK report addendum 1

Table 45. Overview of TEAEs in patients with urothelial cancer who received 1.25 mg/kg enfortumab vedotin on Days 1, 8, 15 based on renal function (90-day safety update)

Treatment-Emergent Adverse Events (TEAE)	Patients with normal renal function (n=47)	Patients with mild RI (n=112)	Patients with moderate RI (n=126)	Patients with severe RI (n=15)
Serious TEAE	21 (45%)	49 (44%)	55 (44%)	4 (27%)
TEAE leading to death	3 (6%)	9 (8%)	4 (3%)	0
TEAE leading to drug discontinuation	10 (21%)	22 (20%)	22 (18%)	1 (7%)

TEAE leading to dose reduction	19 (40%)	36 (32%)	42 (33%)	1 (7%)
TEAE leading to dose interruption	30 (64%)	62 (55%)	80 (64%)	9 (60%)

Source: based on Table 12.6.1.6.1.7 from Applicant's 90-day safety update

6.2.2.3. Outstanding Issues

Data:
N/A

The Applicant's Position:
N/A

The FDA's Assessment:
There are no outstanding issues.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:
The clinical pharmacology of enfortumab vedotin has been studied in subjects with malignant solid tumors who received enfortumab vedotin by intravenous infusion administration once weekly for 3 weeks of each 28-day cycle or once every 3 weeks. Levels of ADC, TAb, and free MMAE were measured using validated methods to evaluate PK parameters.

Enfortumab vedotin exhibited linear, approximately dose-proportional PK at doses ranging from 0.5 to 1.25 mg/kg on days 1, 8, and 15 of each 28-day cycle. Peak concentrations of enfortumab vedotin were attained near the end of infusion with an estimated terminal half-life of 3.35 days (80.5 h). By contrast, plasma concentrations of free MMAE continued to increase until ~2 days after enfortumab vedotin dosing when peak levels were reached. Elimination of MMAE appeared to be limited by its formation, with an estimated terminal half-life of 2.44 days (58.5 h). Upon repeated enfortumab vedotin administration, minimal accumulation of enfortumab vedotin and free MMAE occurred after the first treatment cycle.

A total of 365 subjects were tested for antitherapeutic antibody (ATA); 4 subjects (1%) were confirmed to be transiently positive for ATA, and 1 subject (0.3%) was confirmed to be persistently positive for ATA at any post-baseline time point. The ADC concentrations in this subject were within the range of observed concentrations. However, due to the very low ATA

rate, conclusions regarding impact of ATA on pharmacokinetics could not be made. No clinically meaningful impact was observed on endpoints of enfortumab vedotin efficacy, safety or pharmacokinetics in subjects with positive ATA.

Based on population PK analyses, enfortumab vedotin and MMAE PK in subjects with mild, moderate, or severe renal impairment were comparable to subjects with normal renal function. The PK of enfortumab vedotin and MMAE in subjects with mild hepatic function were comparable to that of subjects with normal hepatic function.

The potential for metabolism-based drug-drug interactions that could involve MMAE were assessed in vitro and by evaluation of the clinical experience with brentuximab vedotin, an ADC structurally similar to enfortumab vedotin. Circulating concentrations of free MMAE after enfortumab vedotin infusion are not likely to cause clinically significant changes in the PK of drugs metabolized by CYP3A4/5. Concomitant use of strong inhibitors of CYP3A4 with enfortumab vedotin may increase free MMAE exposures to a magnitude similar to that observed with brentuximab vedotin (34% increase). Concomitant use of strong inducers of CYP3A4 with enfortumab vedotin may decrease free MMAE exposures to a magnitude similar to that observed with brentuximab vedotin (46% decrease).

The relationship between enfortumab vedotin exposure and efficacy endpoints of BOR (CR/PR as responders and PD/SD/NE as non-responders), PFS, OS suggest that treatment with 1.25 mg/kg enfortumab vedotin on days 1, 8, and 15 of a 28-day cycle was associated with clinically meaningful efficacy across the entire range of concentrations in subjects who had received a prior PD-1/PD-L1 inhibitor and a platinum-containing chemotherapy in the locally advanced or metastatic disease setting (Study EV-201, Cohort 1 and Study EV-101 Part C).

Enfortumab vedotin exposure and safety relationships were evaluated by univariate logistic regression in a safety population comprising subjects treated at the 1.25 mg/kg dose. Model-predicted Cycle 1 exposures (AUC and C_{max}) positively correlated with key safety endpoints of ≥ Grade 3 treatment-emergent adverse events (TEAEs), ≥ Grade 3 rash and hyperglycemia and ≥ Grade 2 peripheral neuropathy. However, the respective increases in odds ratios were relatively minor, ranging from 1.006 for ≥ Grade 3 TEAEs to 1.129 for ≥ Grade 3 hyperglycemia. Within the same safety population, relationships between model predicted free MMAE exposures and ≥ Grade 3 TEAEs, rash and hyperglycemia were not considered clinically meaningful. Grade 2 or higher peripheral neuropathy events positively correlated with MMAE C_{max}; however, the odds ratio was minor (0.895) and not considered clinically meaningful. Although logistic regression analyses revealed relationships between enfortumab vedotin exposures and reported safety outcomes, the 1.25 mg/kg dose was tolerated with a manageable safety profile. Subjects generally received study treatment as planned with relative dose intensities of approximately 80%.

The Applicant's Position:

Enfortumab vedotin exhibited linear PK with an estimated terminal half-life of 3.35 days and minimal accumulation after repeat dose administration. Elimination of free MMAE was limited by its formation with an estimated terminal half-life of 2.44 days and minimal accumulation after repeat enfortumab vedotin dosing.

The incidence of ATA was low with no apparent effect on enfortumab vedotin PK, efficacy or safety.

No dedicated clinical drug–drug interaction studies with enfortumab vedotin in humans have been conducted. However, A clinical drug-drug interaction study was conducted with another ADC that contains MMAE, and similar effect would be expected for enfortumab vedotin.

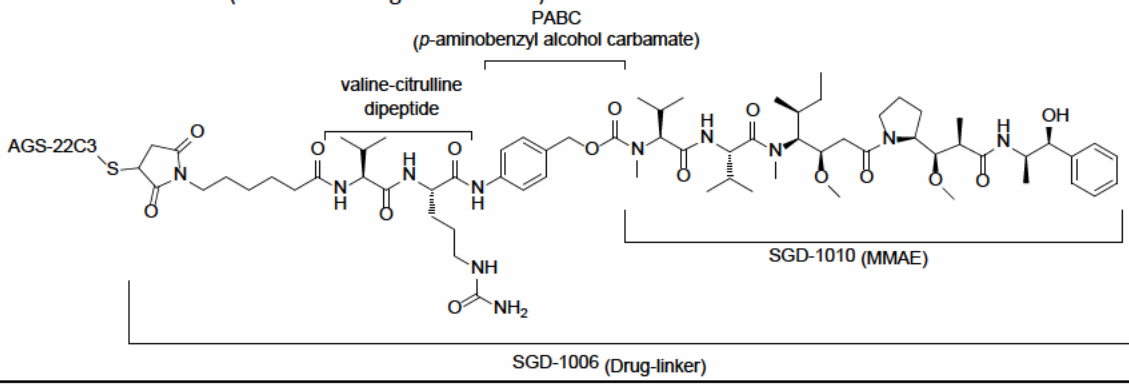
Based on clinical data of brentuximab vedotin, concomitant use of strong inhibitors of CYP3A4 with enfortumab vedotin may result in an increase in free MMAE exposure. However, MMAE exposure-safety analyses indicated that MMAE concentrations were not predictive of safety responses. To be cautious, monitoring for adverse reactions when enfortumab vedotin is given concomitantly with strong CYP3A4 inhibitors is still recommended.

Overall, enfortumab vedotin administered by intravenous infusion at 1.25 mg/kg, up to a maximum dose of 125 mg, on days 1, 8, and 15 of each 28-day cycle demonstrated a favorable benefit-risk profile for patients with locally advanced or metastatic UC.

The FDA's Assessment:

Summary details of enfortumab vedotin ADME and clinical PK information are presented in **Table 46** below.

Table 46. Highlights of enfortumab vedotin clinical pharmacology

PHYSICOCHEMICAL PROPERTIES	
Chemical structure and molecular weight	Enfortumab vedotin (molecular weight ≈ 152 kDa) 

<table>
<tr><td>Aqueous solubility</td><td>Not applicable (enfortumab vedotin is formulated for IV administration).</td></tr>
<tr><td colspan="2">PHARMACOLOGY</td></tr>
<tr><td>Mechanism of action</td><td>Enfortumab vedotin is an antibody-drug conjugate (ADC). The antibody is a human IgG1 directed against Nectin-4, an adhesion protein located on the cell surface. The antibody is conjugated to MMAE, a small molecule microtubule-disrupting agent, via a protease-cleavable linker. Non-clinical data suggest enfortumab vedotin binds to Nectin-4-expressing cells, following by internalization of the ADC-Nectin-4 complex, then release of MMAE via proteolytic cleavage. MMAE disrupts the microtubule network within the cell, which induces cell cycle arrest and apoptotic cell death.</td></tr>
<tr><td>Active moiety</td><td>MMAE.</td></tr>
<tr><td>QT/QTc prolongation</td><td>No large QTc prolongation (>20 ms) identified at the recommended dose of enfortumab vedotin.</td></tr>
<tr><td colspan="2">GENERAL INFORMATION</td></tr>
<tr><td>Bioanalysis</td><td>Validated bioanalytical assays were developed to measure enfortumab vedotin, MMAE, total antibody, anti-therapeutic antibody, and neutralizing antibody concentrations and/or titers. (see Appendix).</td></tr>
<tr><td>Patient PK vs. healthy subject (HS) PK</td><td>Enfortumab vedotin has not been administered to healthy subjects.</td></tr>
<tr><td>Steady-state exposure at the proposed dosing regimen</td><td>Steady-state concentrations of ADC and MMAE were reached after 1 treatment cycle (28 days).

Exposure parameters of ADC and unconjugated MMAE after 1st treatment cycle of 1.25 mg/kg enfortumab vedotin on Days 1, 8, 15 of a 28-day cycle:
<table>
<tr><th></th><th>ADC‡
Mean (± SD)†</th><th>Unconjugated MMAE
Mean (± SD)†</th></tr>
<tr><td>C_{max}</td><td>27.7 (6.76) (µg/mL)</td><td>4.79 (2.68) (ng/mL)</td></tr>
<tr><td>$AUC_{0\text{-}21d}$</td><td>108 (36.4) (day*µg/mL)</td><td>61.1 (36.4) (day*ng/mL)</td></tr>
<tr><td>$AUC_{0\text{-}28d}$ #</td><td>111 (38.3) (day*µg/mL)</td><td>68.6 (41.9) (day*ng/mL)</td></tr>
<tr><td>$C_{avg0\text{-}21d}$</td><td>5.13 (1.74) (µg/mL)</td><td>2.91 (1.73) (ng/mL)</td></tr>
<tr><td>$C_{avg0\text{-}28d}$ #</td><td>3.98 (1.37) (µg/mL)</td><td>2.45 (1.50) (ng/mL)</td></tr>
<tr><td>C_{21d}</td><td>0.94 (0.604) (µg/mL)</td><td>1.83 (1.47) (ng/mL)</td></tr>
<tr><td>C_{trough} #</td><td>0.267 (0.218) (µg/mL)</td><td>0.566 (0.584) (ng/mL)</td></tr>
</table>
C_{max} = maximum concentration, $AUC_{0\text{-}21d}$ = area under the concentration-time curve from time zero to 21 days, $AUC_{0\text{-}28d}$ = area under the concentration-time curve from time zero to 28 days, $Cavg0_{\text{-}21d}$ = average concentration from time zero to 21days, $Cavg0_{\text{-}28d}$ = average concentration from time zero to 28days, C_{21d} = concentration on Day 21. C_{trough} = pre-dose concentration on Day 28.
[a]After first treatment cycle of 1.25 mg/kg enfortumab vedotin-ejfv dose on Days 1, 8, 15
‡ADC concentration data are presented in µg/mL for consistency with data presented in the BLA
† Mean (SD) at 1.25 mg/kg based on population PK modeling and simulation
# $AUC_{0\text{-}28d}$, $Cavg_{0\text{-}28d}$ and C_{trough} were reported because 1 cycle = 28 day
Source: Applicant's Table 1 from their response to FDA's Information Request (dated 11-07-19)</td></tr>
<tr><td>Minimal effective dose or exposure</td><td>Limited activity was observed at doses lower than 1.25 mg/kg on Days 1, 8, 15 of a 28-day cycle. Due to limited activity, a lower starting dose is not recommended.</td></tr>
<tr><td>Maximum tolerated dose or exposure</td><td>MTD has not been identified. The maximum tested dose was the recommended dose of 1.25 mg/kg on Days 1, 8, 15 of a 28-day cycle.</td></tr>
</table>

<table>
<tr><td>Dose proportionality</td><td>Following multiple-dosing, ADC exposures (AUC) and MMAE exposures (AUC, C_{MAX}) generally increased dose-proportionally from 0.5 to 1.25 mg/kg on Days 1, 8, 15 of a 28-day cycle.

Statistical assessment of dose proportionality for ADC (power model)
<table>
<tr><th>Dose Range</th><th>Dosing</th><th>Parameter</th><th>Slope Estimate (SE)</th><th>90% CI of Slope</th></tr>
<tr><td rowspan="4">0.5 mg/kg – 1.25 mg/kg</td><td rowspan="2">Cycle 1 1st dose</td><td>$AUC_{(d0-7)}$ (day·µg/mL)</td><td>0.891 (0.139)</td><td>(0.660, 1.12)</td></tr>
<tr><td>C_{max} (µg/mL)</td><td>0.637 (0.152)</td><td>(0.384, 0.890)</td></tr>
<tr><td rowspan="2">Cycle 1 3rd dose</td><td>$AUC_{(d0-7)}$ (day·µg/mL)</td><td>1.01 (0.158)</td><td>(0.740, 1.27)</td></tr>
<tr><td>C_{max} (µg/mL)</td><td>0.529 (0.169)</td><td>(0.246, 0.812)</td></tr>
</table>
ADC: antibody-drug conjugate; PKAS: pharmacokinetic analysis set.
Source: Applicant's Table 12.4.3.1 from Study EV-101 CSR

Statistical assessment of dose proportionality for MMAE (power model)
<table>
<tr><th>Dose Range</th><th>Dosing</th><th>Parameter</th><th>Slope Estimate (SE)</th><th>90% CI of Slope</th></tr>
<tr><td rowspan="4">0.5 mg/kg – 1.25 mg/kg</td><td rowspan="2">Cycle 1 1st dose</td><td>$AUC_{(d0-7)}$ (day·ng/mL)</td><td>1.74 (0.459)</td><td>(0.964, 2.51)</td></tr>
<tr><td>C_{max} (ng/mL)</td><td>0.996 (0.283)</td><td>(0.525, 1.47)</td></tr>
<tr><td rowspan="2">Cycle 1 3rd dose</td><td>$AUC_{(d0-7)}$ (day·ng/mL)</td><td>0.946 (0.313)</td><td>(0.422, 1.47)</td></tr>
<tr><td>C_{max} (ng/mL)</td><td>0.952 (0.295)</td><td>(0.458, 1.45)</td></tr>
</table>
MMAE: monomethyl auristatin E.
Source: Applicant's Table 12.4.3.2 from Study EV-101 CSR</td></tr>
<tr><td>Accumulation</td><td>Based on population PK analysis, minimal accumulation of ADC and free MMAE was observed. The accumulation ratio (C_{TROUGH} after Cycle 3 / C_{TROUGH} after Cycle 1) was 1.14 for ADC and 1.05 for free MMAE.</td></tr>
<tr><td>Variability</td><td>Based on pivotal Study EV-201 (Cohort 1) at 1.25 mg/kg on Days 1, 8, 15 of a 28-day cycle, the following inter-subject variabilities (%CV) were observed:
▪ ADC: 25-31% for C_{MAX}, 34-40% for AUC
▪ MMAE (free): 57-65% for C_{MAX}, 57-64% for AUC</td></tr>
<tr><td colspan="2">ABSORPTION</td></tr>
<tr><td>Bioavailability</td><td>Not applicable (enfortumab vedotin is formulated for IV administration).</td></tr>
<tr><td>T_{MAX}</td><td>Median T_{MAX} = end of infusion (ADC), 2 days (free MMAE).</td></tr>
<tr><td>Food Effect</td><td>Not applicable (enfortumab vedotin is formulated for IV administration).</td></tr>
<tr><td colspan="2">DISTRIBUTION</td></tr>
<tr><td>Volume of distribution (Vd)</td><td>Free MMAE is 68-82% bound to human plasma proteins. Based on population PK modeling, mean VSS was approximately 11 and 218 L for ADC and free MMAE, respectively.</td></tr>
<tr><td>Substrate of transporter systems</td><td>MMAE is a substrate of P-gp.</td></tr>
<tr><td colspan="2">ELIMINATION</td></tr>
</table>

Terminal elimination half-life and clearance	ADC and MMAE exhibited multi-exponential declines with an elimination half-life of 3.4 and 2.4 days, respectively. The mean CL of ADC and free MMAE in patients was 0.10 and 2.7 L/h, respectively, in patients. Elimination of MMAE appeared to be limited by its rate of release from the ADC.
Metabolism	Enfortumab vedotin catabolism has not been studied in humans; however, it is expected to undergo catabolism to small peptides, amino acids, free MMAE, and free MMAE-related catabolites. Enfortumab vedotin releases MMAE via proteolytic cleavage, and MMAE is primarily metabolized by CYP3A4.
Excretion	The excretion of enfortumab vedotin is not fully characterized. Following a single-dose of another ADC that contains MMAE< 17% of the total MMAE administered was recovered in feces and 7% in urine over a 1-week period, primarily as unchanged drug. A similar excretion profile of MMAE is expected after enfortumab vedotin administration.
Drug interaction liability	No clinical studies evaluating the drug-drug interaction (DDI) potential of enfortumab vedotin have been conducted. To characterize the DDI potential of free MMAE, clinical studies with another ADC that contains MMAE were previously conducted: ▪ Strong CYP3A4 inhibitors: another ADC that contains MMAE (brentuximab vedotin) co-administered with ketoconazole (a strong CYP3A4 inhibitor) increased MMAE C_{MAX} by 25% and AUC by 34%, with no change in ADC exposure. The concomitant use of strong CYP3A4 inhibitors with enfortumab vedotin would likely result in similar effects on free MMAE and ADC. ▪ Strong CYP3A4 inducers: another ADC that contains MMAE (brentuximab vedotin) co-administered with rifampin (a strong CYP3A4 inducer) decreased MMAE C_{MAX} by 44% and AUC by 46%, with no change in ADC exposure. The concomitant use of strong CYP3A4 inducers with enfortumab vedotin would likely result in similar effects on free MMAE and ADC. ▪ Sensitive CYP3A4 substrates: another ADC that contains MMAE (brentuximab vedotin) co-administered with midazolam (a sensitive CYP3A4 substrate) did not affect the exposure of midazolam. Similarly, enfortumab vedotin is not expected to alter the exposure of drugs that are metabolized by CYP3A4 enzymes.

6.3.2. Clinical Pharmacology Questions

6.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes, the clinical pharmacology program provides supportive evidence of enfortumab vedotin effectiveness in patients with locally advanced or metastatic UC.

Data:

Evidence of effectiveness was obtained from pivotal Study EV-201, Cohort 1 which included 125 subjects with locally advanced or metastatic UC who received prior treatment with a PD-1/PD-L1 inhibitor and a platinum-based chemotherapy. Efficacy was established based upon confirmed ORR by blinded independent central review (BICR). The ORR was 44% (55/125 subjects; 95% CI: 35.1, 53.2), the median duration of response (DOR) was 7.6 months (95% CI: 6.34, -; range: 0.95, 11.30+), and the majority of subjects (92/110 subjects [84%]) who were evaluable for target lesion response had target lesion size reductions (Figure 10). The median time to response was 1.84 months (range: 1.2, 9.2).

To support the clinical efficacy observed with enfortumab vedotin dosed at 1.25 mg/kg on days 1, 8, and 15 of each 28-day cycle, exposure-efficacy relationship was evaluated in subject populations separately by study and as a combined population (EV-101, Part C plus EV-201, Cohort 1) for the primary endpoint of BOR (CR/PR as responder, PD/SD/NE as non-responder) and secondary endpoints of PFS, OS, and DOR [Module 2.7.2, Section 3.6.4.2]. Similar analyses of free MMAE exposure were conducted, but relationships with efficacy outcomes were not considered clinically meaningful.

Univariate logistic regression analysis determined a positive relationship between enfortumab vedotin exposures and model-predicted BOR response (CR/PR). Exposure-efficacy modeling results for the combined efficacy population predicted a probability of response (CR/PR) of ~50% among subjects in the upper 3 exposure quartiles (Q2 to Q4) and 29% (15/51 subjects) in the lower exposure quartile, Q1, which is ~3-fold higher than the historical ORR of 10% for taxanes. Enfortumab vedotin at the dose of 1.25 mg/kg was well-tolerated with a manageable safety profile. Subjects generally received study treatment as planned with relative dose intensities of approximately 80%. Taken together, these results suggest enfortumab vedotin administered by intravenous infusion at 1.25 mg/kg on days 1, 8 and 15 of each 28-day cycle demonstrates a favorable benefit-risk profile for subjects with metastatic UC.

The Applicant's Position:
The relationships between enfortumab vedotin exposure and efficacy endpoints show that treatment with 1.25 mg/kg enfortumab vedotin on days 1, 8, and 15 of a 28-day cycle was associated with clinically meaningful efficacy across the entire range of concentrations in subjects with locally advanced or metastatic UC.

The FDA's Assessment:
The FDA agrees that the clinical pharmacology program provides supportive evidence of effective for enfortumab vedotin in the proposed indication.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, enfortumab vedotin administered by intravenous infusion at 1.25 mg/kg, up to a maximum dose of 125 mg, on days 1, 8 and 15 of each 28-day cycle is appropriate for patients with locally advanced or metastatic UC. The proposed dosing regimen is supported by the observed efficacy, safety, and PK data.

Data:
During phase 1, enfortumab vedotin doses higher than 1.25 mg/kg were not evaluated due to dose reductions and drug-related rash and diarrhea, which occurred at higher frequencies relative to subjects treated at lower dose levels. An MTD for enfortumab vedotin was not reached. Enfortumab vedotin doses were administered based on subject body weight, except for subjects > 100 kg, as discussed in Section 6.2.2.2.

Enfortumab vedotin exposure-response analyses of BOR (CR/PR), PFS, and OS outcomes suggested an apparent efficacy plateau at higher systemic exposure levels for subjects with locally advanced or metastatic UC previously treated with a PD-1/PD-L1 inhibitor in Study EV-201, Cohort 1. The predicted probability of response was similar across the 3 upper exposure quartiles (~50% in quartiles Q2 to Q4), whereas the predicted probability of response was lower (28%; 9/32 subjects) among subjects in the lowest exposure quartile in Study EV-201, Cohort 1. The probability of response in subjects within quartile Q1 of EV-201, Cohort 1 was ~3-fold higher than the historical control, where the lower bound of the 95% CI of confirmed ORR for all subjects (44% [95% CI: 35.1, 53.2]) excluded the historical ORR. The overlapping efficacy outcomes for subjects within the upper 3 exposure quartiles indicate an apparent efficacy plateau at these enfortumab vedotin concentrations, suggesting increases in enfortumab vedotin dose above 1.25 mg/kg may not provide added benefit.

Subjects generally received study treatment as planned, as supported by relative dose intensities of 83% among subjects in EV-101 Part C, 78.7% in EV-201 Cohort 1, and 89.2% in EV-201 Cohort 2. For subjects requiring dose modification, responses to enfortumab vedotin are anticipated based on the PFS and OS observed in subjects at doses < 1.25 mg/kg during the dose-escalation phase of Study EV-101.

Enfortumab vedotin exposure and safety relationships were evaluated by univariate logistic regression in a safety population comprising subjects treated at the 1.25 mg/kg dose.

Model-predicted Cycle 1 exposures (AUC and C_{max}) positively correlated with key safety endpoints of ≥ Grade 3 TEAEs, ≥ Grade 3 rash and hyperglycemia and ≥ Grade 2 peripheral neuropathy. However, the respective increases in odds ratios were relatively minor, ranging from 1.006 for ≥ Grade 3 TEAEs to 1.129 for ≥ Grade 3 hyperglycemia. Within the same safety population, relationships between model predicted free MMAE exposures and ≥ Grade 3 TEAEs, rash and hyperglycemia were not considered clinically meaningful. Grade 2 or higher peripheral neuropathy events positively correlated with MMAE C_{max}; however, the odds ratio was minor (0.895) and not considered clinically meaningful.

The Applicant's Position:
Enfortumab vedotin administered by intravenous infusion at 1.25 mg/kg, up to a maximum dose of 125 mg, on days 1, 8, and 15 of each 28-day cycle demonstrates a favorable benefit-risk profile for patients with locally advanced or metastatic UC.

The FDA's Assessment:
We agree with that the recommended dosing of 1.25 mg/kg (up to a maximum dose of 125 mg) on Days 1, 8, 15 of a 28-day cycle is appropriate for the proposed patient population and is approvable from a clinical pharmacology perspective.

In the process of the review, the clinical pharmacology review team expressed concerns regarding the dose cap threshold of 125 mg for patients greater than 100 kg. An information request was sent to the Applicant asking for justifications of the dose cap and evaluation whether a lower weight cutoff for dosing cap is needed. Additional simulations using a dose cap for subjects > 85 kg was conducted with the final population pharmacokinetic model. Compared to the weight cutoff of 100 kg (**Table 47**), there is more variability and less consistency of exposures, particularly for subjects > 100 kg when a lower weight cutoff of 85 kg is used. A lower dose cap may result in under-dosing of higher body weight subjects (**Table 48**). The reviewers concur with the analyses and agree that 125 mg is an appropriate dose cap that ensures consistent exposure of subjects to enfortumab vedotin across all weight groups.

Table 47: Comparison of Simulated Cycle 1 Exposures for Enfortumab Vedotin and Free MMAE Using Dose Cap Based on Weight > 100 kg (125 mg)

Body Weight	n (%)	Enfortumab Vedotin			Free MMAE		
		$AUC_{0\text{-}28d}$† (day*µg/mL)	C_{max}† (µg/mL)	C_{trough}† (µg/mL)	$AUC_{0\text{-}28d}$† (day*ng/mL)	C_{max}† (ng/mL)	C_{trough}† (ng/mL)
≤ 85 kg	203 (67)	114 (79, 160)	26 (19, 39)	0.27 (0.068, 0.67)	66 (28, 176)	4.3 (2.1, 11)	0.49 (0.19, 1.8)
> 85 kg	97 (33)	125 (89, 177)	29 (21, 45)	0.30 (0.088, 0.69)	66 (35, 146)	4.2 (2.4, 8.2)	0.53 (0.22, 2.4)
≤ 100 kg	278 (93)	117 (82, 173)	27 (19, 41)	0.28 (0.073, 0.69)	66 (30, 171)	4.2 (2.2, 11)	0.49 (0.20, 2.1)
> 100 kg	22 (7)	114 (67, 140)	26 (17, 34)	0.25 (0.085, 0.45)	81 (43, 151)	4.9 (2.9, 8.3)	0.66 (0.27, 3.4)
≥ 85 kg and ≤ 100 kg	76 (25)	128 (96, 179)	29 (21, 45)	0.33 (0.097, 0.72)	64 (33, 129)	4.2 (2.4, 8.1)	0.51 (0.21, 2.2)

Weight Range: 36.9-145 kg; N = 300
†Exposures were represented as median (5^{th} and 95^{th} percentile).

Source: Table 4 on page 8 of Applicant's response to information request from the mid-cycle meeting minutes

Table 48: **Comparison of Simulated Cycle 1 Exposures for Enfortumab Vedotin and Free MMAE Using Dose Cap Based on Weight > 85 kg (106 mg)**

Body Weight	n (%)	Enfortumab Vedotin			Free MMAE		
		$AUC_{0\text{-}28d}$† (day*µg/mL)	C_{max}† (µg/mL)	C_{trough}† (µg/mL)	$AUC_{0\text{-}28d}$† (day*ng/mL)	C_{max}† (ng/mL)	C_{trough}† (ng/mL)
≤ 85 kg	203 (67)	114 (79, 160)	26 (19, 39)	0.27 (0.068, 0.67)	66 (28, 176)	4.3 (2.1, 11)	0.49 (0.19, 1.8)
> 85 kg	97 (33)	113 (80,160)	26 (17, 40)	0.26 (0.075, 0.65)	60 (32, 130)	3.8 (2.3, 7.7)	0.48 (0.21, 2.2)
≤ 100 kg	278 (93)	115 (81, 161)	27 (19, 40)	0.28 (0.073, 0.66)	65 (30, 169)	4.2 (2.1, 10)	0.48 (0.19, 2.0)
> 100 kg	22 (7)	97 (57, 118)	22 (15, 29)	0.21 (0.072, 0.38)	68 (36, 128)	4.2 (2.5, 7.0)	0.50 (0.23, 2.9)
≥ 85 kg and ≤ 100 kg	76 (25)	122 (89, 162)	27 (20, 40)	0.31 (0.096, 0.66)	59 (31, 123)	3.8 (2.3, 7.7)	0.47 (0.20, 2.1)

Weight Range: 36.9-145 kg; N = 300
†Exposures were represented as median (5^{th} and 95^{th} percentile).

Source: Table 5 on page 8 of Applicant's response to information request from the mid-cycle meeting minutes

6.3.2.2. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No, enfortumab vedotin administered by intravenous infusion at 1.25 mg/kg, up to a maximum dose of 125 mg, on days 1, 8, and 15 of each 28-day cycle is appropriate for subpopulations based on intrinsic patient factors.

Data:
The effects of sex, race, age, body weight, albumin, hemoglobin, bilirubin, disease status (as assessed by sum of tumor diameters at baseline and ECOG score), renal and hepatic impairment on enfortumab vedotin and free MMAE PK were evaluated by population PK modeling and simulation. Although some of these covariates were included in the population PK model, their impact on enfortumab vedotin and free MMAE exposures was not clinically meaningful, except for body weight. Population PK modeling and simulation analyses determined a fixed dose of enfortumab vedotin would result in relatively higher enfortumab vedotin and free MMAE exposures for subjects with lower body weight than for subjects with higher body weight. The differences in enfortumab vedotin and free MMAE exposures based on body weight are addressed by weight-based dosing.

The assessment of renal impairment was based on estimated CrCL at baseline. In Study EV-101, systemic exposures of ADC, MMAE, and TAb in subjects with mild, moderate, or severe renal impairment were comparable to exposures in subjects with normal renal function. In addition, population PK modeling and simulation showed that enfortumab vedotin and free MMAE exposures were independent of baseline renal function.

A population PK model analysis of the effects of hepatic function on enfortumab vedotin and free MMAE PK was conducted in subjects with mild hepatic impairment, as determined by the criteria of the National Cancer Institute Organ Dysfunction Working Group. Population PK modeling and simulation demonstrated that no significant differences in enfortumab vedotin or MMAE exposures were observed in subjects with mild hepatic impairment (bilirubin of 1 to 1.5 × ULN and AST < ULN, or bilirubin ≤ ULN and AST > ULN, n = 31) compared to subjects with

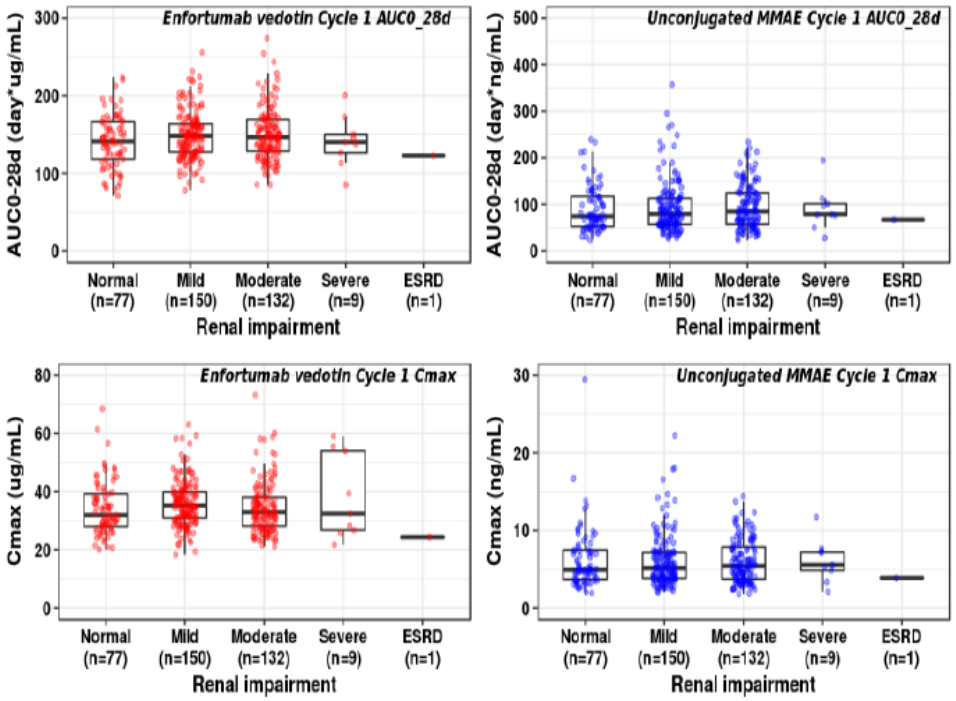
normal hepatic function. These model analyses suggest that enfortumab vedotin dose adjustment is not required for subjects with mild hepatic impairment. The effects of moderate or severe hepatic impairment on enfortumab vedotin PK have not been studied.

The Applicant's Position:
Enfortumab vedotin dose adjustment is not required for subjects with mild, moderate or severe renal impairment. Dose adjustment is also not required for subjects with mild hepatic impairment. Enfortumab vedotin has not been evaluated in subjects with moderate or severe hepatic impairment. Based on population PK analysis, no dose adjustment is required for the intrinsic factors of age, sex, race, hemoglobin, albumin, bilirubin, and disease status (as assessed by sum of tumor diameters at baseline and ECOG score).

The FDA's Assessment:
(b) (4)
Enfortumab vedotin has not been evaluated in patients with moderate or severe HI. However, in a dedicated hepatic impairment trial with another ADC that contains MMAE (brentuximab vedotin), the frequency of ≥ Grade 3 adverse reactions and deaths was higher in patients with moderate or severe hepatic impairment (Child-Pugh B or C) compared to patients with normal hepatic functions. Due to the observed safety signals with another ADC that contains the same microtubule-disrupting agent MMAE, enfortumab vedotin should be avoided in patients with moderate or severe hepatic impairment (Child-Pugh B or C).

The FDA agrees that no dose adjustment is required in patients with renal impairment. Based on population PK analysis, enfortumab vedotin and MMAE exposures were comparable in patients with mild, moderate and severe renal insufficiency (**Figure 5**). Study EV-101 has a dedicated renal cohort to assess the safety, PK, and efficacy in mUC patients with severe renal impairment (CrCL ≥ 15 to < 30 mL/min) (N=18). There was no trend of increased exposures in patients with renal impairment. The 90-day safety update provide to FDA included updated safety information for patients with renal impairment (**Table 45**). There was no signal of increased incidence of adverse events in patients with renal insufficiency.

Figure 6: Renal function vs. model-predicted Cycle 1 exposures of enfortumab vedotin and unconjugated MMAE



Source: Adapted from Figure 2 on page 9 from Applicant's population PK report addendum 1

Table 49. Overview of TEAEs in patients with urothelial cancer who received 1.25 mg/kg enfortumab vedotin on Days 1, 8, 15 based on renal function (90-day safety update)

Treatment-Emergent Adverse Events (TEAE)	Patients with normal renal function (n=47)	Patients with mild RI (n=112)	Patients with moderate RI (n=126)	Patients with severe RI (n=15)
Serious TEAE	21 (45%)	49 (44%)	55 (44%)	4 (27%)
TEAE leading to death	3 (6%)	9 (8%)	4 (3%)	0
TEAE leading to drug discontinuation	10 (21%)	22 (20%)	22 (18%)	1 (7%)
TEAE leading to dose reduction	19 (40%)	36 (32%)	42 (33%)	1 (7%)
TEAE leading to dose interruption	30 (64%)	62 (55%)	80 (64%)	9 (60%)

Source: based on Table 12.6.1.6.1.7 from Applicant's 90-day safety update

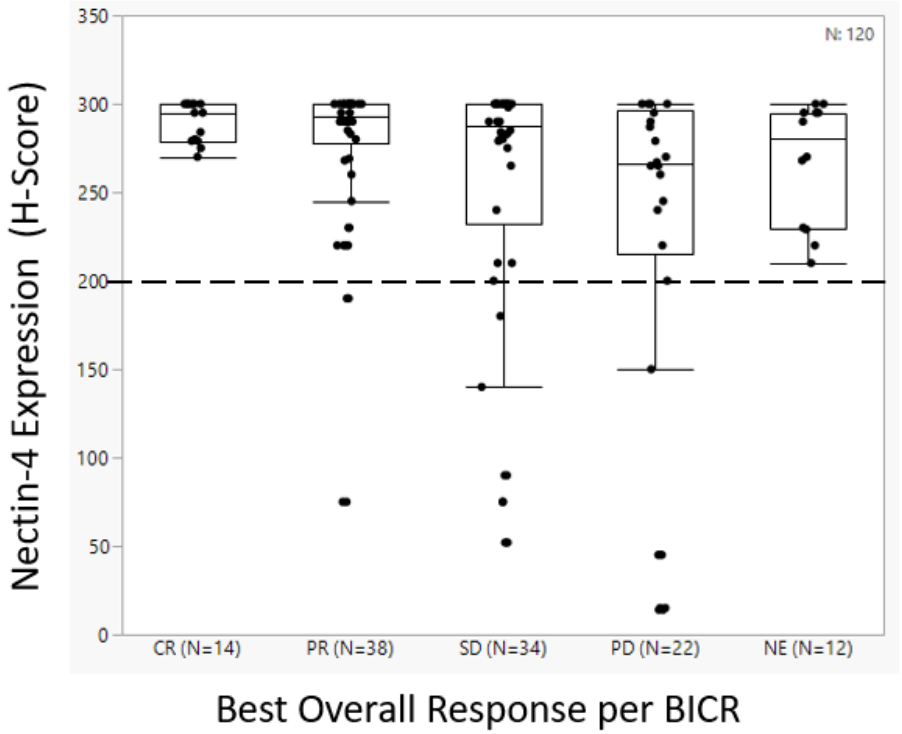
FDA also evaluated the effects of Nectin-4 protein expression and other biomarkers on treatment response to determine if the patient selection approach was supported.

Nectin-4 protein expression was retrospectively assessed by immunohistochemistry (IHC) in

fresh or archival tumor samples from 120 patients (96%) included in the efficacy population (N=125). IHC H-scores (0-300) were used to determine expression, and ranged from 14-300, with a median H-score of 290 in the tested patients' samples. Although exploratory analyses by the reviewer of best overall response (BIRC) by Nectin-4 expression showed a trend toward higher H-scores (mostly above 200) in responders (ORR 48% H-score > 200 vs 15% H-score ≤ 200), responses were also observed in patients with lower H-scores (**Figure 7**). Also in Study EV-101, a patient with an H-score of 45 achieved a CR and a patient with an H-score of 0 achieved a PR. Based on these results, patient selection for treatment with enfortumab vedotin based on Nectin-4 expression levels is not warranted.

RNA-sequencing was used to categorize available tumor samples (N=40) of patients enrolled in Study EV-201 Cohort 1 (N=125) into one of the 5 TCGA bladder cancer molecular subtypes (luminal papillary N=19, luminal infiltrated N=4, basal-squamous N=15, neuronal N=1, or luminal N=1) [Robertson et al, 2017]. Responses were observed across subtypes except for luminal, which only included one patient. No action is indicated based on the results of the analysis.

Figure 7. Nectin-4 Expression (H-Score) by Best Overall Response per BICR in EV-201, Cohort 1



Source: Reviewer Figure. CR: Complete Response, PR: Partial Response, SD: Stable Disease, PD: Progressive Disease, NE: Not Evaluable, BICR: Blinded Independent Central Review. H-scores were calculated by the applicant by summing the products of the percentage of cells stained at a given staining intensity and the staining intensity, resulting in a possible continuous range of H-scores from 0 to 300.

6.3.2.3. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

No, based on available data there is a low potential for clinically relevant interactions between enfortumab vedotin and concomitant medications. Enfortumab vedotin is intended for intravenous infusion administration; therefore, food-drug interactions are not expected.

Data:

Coadministration of CYP3A4 Substrates with Enfortumab Vedotin

In a clinical DDI study, the PK of midazolam was not affected by concomitant brentuximab vedotin administration, suggesting free MMAE is not a clinically significant inhibitor or inducer of CYP3A4/5 activity (6). A comparison of free MMAE PK after brentuximab vedotin and enfortumab vedotin dose administration suggests that concomitant enfortumab vedotin administration would be predicted to have limited effects on the PK of midazolam. These data suggest that circulating concentrations of free MMAE that result from enfortumab vedotin are not likely to cause clinically significant changes in the PK of drugs metabolized by CYP3A4/5.

Coadministration of CYP3A4/5 Inhibitors with Enfortumab Vedotin

Concomitant administration of ketoconazole with brentuximab vedotin led to a 34% increase in free MMAE AUC exposure (6). By contrast, the PK of brentuximab vedotin were unchanged by concomitant use of ketoconazole. Based on clinical data of brentuximab vedotin, concomitant use of strong inhibitors of CYP3A4 with enfortumab vedotin may result in a similar increase in free MMAE exposure.

Coadministration of CYP3A4/5 Inducers with Enfortumab Vedotin

Concomitant administration of rifampin with brentuximab vedotin led to a 46% decrease in free MMAE AUC exposure (6). By contrast, the PK of brentuximab vedotin were unchanged by concomitant use of rifampin. The concomitant use of strong inducers of CYP3A4/5 such as rifampin with enfortumab vedotin would likely result in similar effects of free MMAE and enfortumab vedotin.

The Applicant's Position:

No formal DDI studies have been conducted with enfortumab vedotin. Enfortumab vedotin is an antibody-based therapeutic and DDI involving antibodies are not anticipated. MMAE, the microtubule disrupting agent of enfortumab vedotin, is not expected to produce DDIs via CYP inhibition or induction, and concomitant use of strong inducers or inhibitors of CYP3A4/5 is not predicted to result in clinically meaningful changes in MMAE exposure.

The FDA's Assessment:

The FDA agrees with Applicant's position. To clarify, no dose adjustments are required in patients who are on concomitant strong CYP3A4/5 inhibitors or inducers. In clinical drug-drug

interaction trials with another ADC that contains MMAE (brentuximab vedotin), concomitant ketoconazole (a strong CYP3A4 inhibitor) increased MMAE C_{MAX} by 25% and AUC by 34% with no change in ADC exposure while concomitant rifampin (a strong CYP3A4 inducer) decreased MMAE C_{MAX} by 44% and AUC by 46% with no change in ADC exposure. No dose adjustment is recommended in patients who are on concomitant strong CYP3A4 inhibitors, rather patients should be closely monitored for signs of toxicity. No dose adjustment is recommended in patients who are on concomitant strong CYP3A4 inducers, as concomitant strong CYP3A4 inducers enhanced the metabolism of the circulating MMAE rather than the intracellular MMAE that is relevant to the efficacy of enfortumab vedotin.

X X

X X

X X

X X

Primary Reviewer Team Leader

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:
An overview of the clinical studies supporting the efficacy and safety of enfortumab vedotin is presented in Table 50.

Table 50: Listing of Clinical Trials Relevant to the BLA for Enfortumab Vedotin

Trial Identity [NCT no.]	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	Subjects enrolled / dosed	Study Population	Centers and Countries
	Primary Study to Support Efficacy and Safety						
EV-201 (SGN22E-001) [NCT03219333]	Phase 2, open-label, multicenter trial of efficacy and safety as monotherapy/ single arm	Enfortumab vedotin 1.25 mg/kg IV infusion over ~30 min on days 1, 8, and 15 of each 28-day cycle	Primary: ORR per RECIST by BICR Secondary: DOR, DCR at week 16, PFS, OS, PK, immunogenicity, safety, tolerability	Until disease progression, unacceptable toxicity, investigator decision, consent withdrawal, start of subsequent anticancer therapy, pregnancy or study termination by the sponsor.	Total: 156/152 Cohort 1: 128/125 Cohort 2: 28/27	Adults with la/mUC with prior PD-1/PD-L1 inhibitor Cohort 1: Prior treatment with platinum-containing chemotherapy Cohort 2: No prior platinum-containing chemotherapy and cisplatin ineligible at the time of enrollment	46 centers 4 countries
	Additional Studies to Support Safety and Efficacy						
EV-101 (ASG-22CE-13-2) [NCT02091999]	Phase 1, open-label, dose escalation to evaluate safety, determine RP2D, PK, and efficacy/3-part study	Enfortumab vedotin 0.5, 0.75, 1.0, or 1.25 mg/kg IV infusion over ~30 min on days 1, 8, and 15 of each 28-day cycle	Primary: safety and PK Secondary: immunogenicity and antitumor activity	Until disease progression, intolerability of enfortumab vedotin, investigator decision or consent withdrawal	Total: 201/201 Part A: 87/87 Part B: 40/40 Part C: 74/74	Adults with metastatic UC with or without prior PD-1/PD-L1 inhibitor or severe renal insufficiency; NSCLC; ovarian cancer, and other malignant solid tumors expressing Nectin-4	21 centers 2 countries
EV-102 (7465-CL-0101) [NCT03070990]	Phase 1, open-label, multicenter, safety and PK of enfortumab	Enfortumab vedotin 1.0 or 1.25 mg/kg; IV infusion over ~30 min on days 1,	Primary: safety, tolerability, PK Secondary: immunogenicity	Until disease progression, clinically significant toxicity of enfortumab vedotin, investigator decision	Total: 19/17 Arm A: 10/9 Arm B:	Adults with la/mUC	8 centers 1 country

	vedotin in Japanese subjects/randomized 2-arm	8, and 15 of each 28-day cycle	and antitumor activity	or informed consent withdrawal	9/8		
	Studies to Support Safety						
AGS-22M6E-11-1 [NCT01409135]	Phase 1, open-label, nonrandomized, multicenter, dose escalation and bridging trial to assess safety and PK of AGS-22M6E and enfortumab vedotin/single arm	0.6 or 1.2 mg/kg 30 min IV infusion once every 3 weeks	Primary: safety and PK Secondary: immunogenicity and effectiveness	Until disease progression, intolerability of enfortumab vedotin, investigator decision or consent withdrawal	Total: 9/9[a]	Nectin-4-expressing malignant solid tumors	9 centers 2 countries
	Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)						
None							

BICR: blinded independent central review; DCR: disease control rate; DOR: duration of response; IV: intravenous; la/mUC: locally advanced or metastatic urothelial carcinoma; No.: number; NSCLC: non-small cell lung cancer; ORR: objective response rate; OS: overall survival; PD-1/PD-L1: programmed death receptor-1/programmed death ligand 1; PFS: progression-free survival; PK: pharmacokinetics; UC: urothelial carcinoma; RP2D: recommended phase 2 dose.
a An additional 25 subjects were treated with the (b) (4) AGS-22M6E.

The Applicant's Position:

The primary evidence of efficacy and safety is based on data from an ongoing phase 2 Study EV-201, which included 2 cohorts. The data presented reflect a cut-off date of 01 Mar 2019. Reported response rates for Cohort 1 are from the full analysis set (FAS) with response rates for Cohort 2 from the FAS and the efficacy evaluable (EE) set as supporting data. The EE analysis set was considered the most accurate reflection of the efficacy of enfortumab vedotin in Cohort 2 at the data cut-off point due to its ongoing enrollment and the fact that not all subjects in the FAS had undergone response assessments to determine objective responses by that time point.

Safety endpoints for Study EV-201 included adverse events (AEs), clinical laboratory abnormalities, and ATA incidence. Peripheral neuropathy, rash, hyperglycemia, corneal events, and infusion-related reactions (IRRs) were prespecified for analysis as AEs of special interest for enfortumab vedotin.

Supportive evidence for efficacy and safety is from Study EV-101 Part C checkpoint inhibitor (CPI)-treated expansion cohort. These subjects represent a patient population that is comparable to Study EV-201 Cohort 1. All subjects in Part C had metastatic UC and previously received therapy with a PD-1/PD-L1 inhibitor. They were treated with the recommended clinical dose of 1.25 mg/kg enfortumab vedotin IV infusion on days 1, 8, and 15 of each 28-day cycle and had their responses assessed by BICR.

Additional supportive efficacy evidence is from Study EV-102, conducted in Japan. Subjects enrolled to this trial had locally advanced or metastatic UC and prior treatment with platinum-based chemotherapy. They were randomized between 2 dose levels, 1 or 1.25 mg/kg, administered on days 1, 8, and 15 of each 28-day cycle.

Supportive evidence for safety analyses are provided by data from EV-101, EV-102, and AGS-22M6E-11-1, including subjects treated with any dose of enfortumab vedotin and regardless of prior treatment with a PD-1/PD-L1 inhibitor.

The FDA's Assessment:

The FDA agrees with the applicant's table of studies of enfortumab vedotin. EV-201 formed the basis for evaluation of the efficacy of enfortumab vedotin in the indicated population.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study EV-201

Trial Design

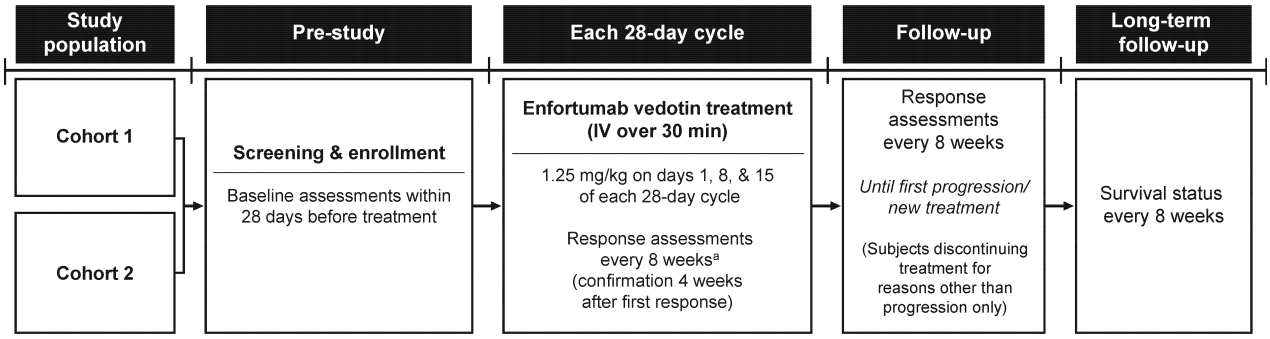
The Applicant's Description:

Basic Study Design

Study EV-201 is a phase 2 single-arm, open-label, multicenter study to evaluate the efficacy and safety of enfortumab vedotin as a single agent in subjects with locally advanced or metastatic UC, who previously received systemic therapy with a PD-1/PD-L1 inhibitor (Figure 8). There are 2 distinct cohorts in this study:

- **Cohort 1**: Subjects who previously received a PD-1/PD-L1 inhibitor and platinum-containing chemotherapy
- **Cohort 2**: Subjects who previously received a PD-1/PD-L1 inhibitor without prior platinum-containing chemotherapy and are cisplatin-ineligible at enrollment

Figure 8: EV-201 Study Schema



a After 1 year on study, the frequency of assessments was reduced to every 12 weeks

Trial Location

This study is being conducted globally, including the US, EU, and Asia.

Choice of Control Group

This study uses an external historical control based on data from taxanes or vinflunine in the treatment of locally advanced or metastatic UC. There are very limited data for any therapy

following progression after both a PD-1/PD-L1 inhibitor and a platinum-based therapy, but a recent phase 3 trial included a small subgroup of subjects treated with docetaxel after platinum-based therapy and a PD-1/PD-L1 inhibitor.

Diagnostic Criteria

Subjects had histologically documented UC that was metastatic or locally advanced and unresectable. For the purposes of this study, platinum-treated was defined as having received a platinum-based chemotherapy in the locally advanced or metastatic setting, or in the neoadjuvant or adjuvant setting with progression within 12 months of completion. Cisplatin ineligible was defined as CrCl ≥30 and <60 mL/min, Grade 2 or greater hearing loss, or ECOG performance status score of 2 or greater. The definition of cisplatin ineligible is standard and based on (7), with the exception of grade 2 or higher peripheral neuropathy and NYHA class III heart failure, as these subject are otherwise excluded from EV-201. Uncontrolled diabetes was defined as hemoglobin A1C (HbA1c) ≥8% or HbA1c 7% to <8% with associated diabetes symptoms (polyuria or polydipsia) that were not otherwise explained.

Key Inclusion/Exclusion Criteria

The eligibility criteria were appropriate for the selection of subjects that would be typical of those receiving treatment for UC and reflective of the patient population for the proposed indication. Subjects with CrCl <30 mL/min were excluded due to the lack of data in this setting at the time the study was designed. This exclusion is no longer considered necessary based on more recent data in subjects with severe renal insufficiency. Subjects with ECOG performance status score of >1 were excluded at the time the study was designed; however, subjects with ECOG performance status score of 2 are now eligible for enrollment onto Cohort 2 (no prior platinum treatment and cisplatin ineligible at enrollment).

The key inclusion criteria are as follows:

- Histologically documented locally advanced or metastatic UC.
- Prior therapy with a PD-1/PD-L1 inhibitor.
- Prior treatment with platinum-containing chemotherapy (Cohort 1) or no prior platinum-containing chemotherapy and ineligible for cisplatin treatment at the time of enrollment (Cohort 2).
- Measurable disease according to Response Evaluation Criteria in Solid Tumor (RECIST) Version 1.1.
- Progression during or following the most recent prior therapy.

The key exclusion criterion is as follows:

- Uncontrolled diabetes.
- Ongoing ≥ Grade 2 sensory or motor neuropathy

Dose Selection

The recommended phase 2 dose chosen for this study was 1.25 mg/kg based on the balance of observed safety and efficacy from the phase 1 Study EV-101 that evaluated doses of enfortumab vedotin ranging from 0.5 to 1.25 mg/kg on Days 1, 8, and 15 of each 28-day cycle. An MTD was not reached; however, there were successively more dose reductions for TEAEs with increasing dose levels, suggesting that dosing above 1.25 mg/kg would be associated with a higher proportion of dose reductions. Although efficacy was lower in subjects with the lowest exposures, they still received meaningful therapeutic benefit from enfortumab vedotin monotherapy. The predicted probability of response was 29% in subjects within exposure quartile Q1 (the lowest exposure quartile) of EV-201, Cohort 1; ~3-fold higher than the historical ORR of 10% for taxanes. Additionally, responses were observed at all dose levels, with a higher proportion of responders at 1.25 mg/kg than the lower dose levels. Additional details on dose rationale can be found in Section 6.2.2.

Study Treatments

Subjects received enfortumab vedotin 1.25 mg/kg intravenously over ~30 minutes on days 1, 8, and 15 of a 28-day cycle. Dosing was calculated using the subject's actual body weight, except for subjects weighing greater than 100 kg for whom doses were based on 100 kg. The maximum dose of enfortumab vedotin permitted on this study was 125 mg. There was no maximum number of cycles and treatment continued until disease progression, unacceptable toxicity, investigator decision, consent withdrawal, start of subsequent anticancer therapy, pregnancy, or study termination by the sponsor.

Assignment to Treatment

This was a single-arm study. The planned treatment for all subjects was enfortumab vedotin 1.25 mg/kg on days 1, 8, and 15 of each 28-day cycle.

Blinding

N/A. This was an open-label, single-arm study.

Dose Modifications and Dose Discontinuation

Intrapatient dose reduction to 1 mg/kg (dose level –1), and to 0.75 mg/kg (dose level –2) were allowed depending on the type and severity of toxicity. Dose modification recommendations for enfortumab vedotin-associated toxicity are presented in Table 51 and Table 52. In general, dose modifications for hematologic and non-hematologic enfortumab vedotin-associated toxicity were consistent with standard medical practice. Due to the potential for more significant clinical consequences with neuropathy and corneal events, enfortumab vedotin-associated toxicities of this type required discontinuation at Grade 3 and withholding of drug at Grade 2. Dose reduction for these toxicities was required after more than one Grade 2 occurrence.

Table 51: Study EV–201 Recommended Dose Modifications for Enfortumab Vedotin-Associated Hematologic Toxicity

Grade	Recommended Dose Modification
Grade 1	Continue at same dose level.
Grade 2	Continue at same dose level. For Grade 2 thrombocytopenia, withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at the same dose level.
Grade 3	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. Transfusions or growth factors may be used as indicated per institutional guidelines.
Grade 4	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 institutional guidelines. For anemia, treatment discontinuation should be strongly considered.

Table 52: Study EV–201 Recommended Dose Modifications for Enfortumab Vedotin-Associated Nonhematologic Toxicity

Grade	Recommended Dose Modification
Grade 1	Continue at same dose level. If ocular symptoms and/or changes in vision are identified, the subject should be evaluated by a qualified optometrist or ophthalmologist.
Grade 2	Continue at same dose level, except in the event of Grade 2 neuropathy or corneal AEs. For Grade 2 neuropathy or corneal AEs, withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at the same dose level. For the second occurrence of Grade 2 neuropathy or corneal AEs, withhold dose until toxicity is ≤ Grade 1, then reduce the dose by 1 dose level and resume treatment. If ocular symptoms and/or changes in vision are identified, the subject should be evaluated by a qualified optometrist or ophthalmologist.

Grade 3	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.[a] For Grade 3 neuropathy or corneal AEs, discontinue treatment. For Grade 3 hyperglycemia/elevated blood glucose withhold enfortumab vedotin treatment. Resume treatment once hyperglycemia/elevated blood glucose has improved to ≤ Grade 2 and subject is clinically and metabolically stable. If ocular symptoms and/or changes in vision are identified, the subject should be evaluated by a qualified optometrist or ophthalmologist.
Grade 4	For Grade 4 AEs, discontinue treatment.[a] Grade 4 vomiting and/or diarrhea that improves to ≤ Grade 2 within 72 hours with supportive management does not require discontinuation.

a Grade ¾ electrolyte imbalances/laboratory abnormalities, except hyperglycemia, that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset do not require discontinuation (e.g., Grade 4 hyponatremia). Grade 3 rash that is not limiting self-care activities of daily living or associated with infection requiring systemic antibiotics does not require treatment interruption, provided symptoms are not severe and can be managed with supportive treatment.

Administrative Structure

Astellas Pharma US, Inc. (Astellas) and Seattle Genetics, Inc. are collaborators and co-developers of enfortumab vedotin. Study SGN22E-001 (EV-201) is a global, multicenter study sponsored by Seattle Genetics, Inc. (Bothell, WA) and conducted under US IND 116360. Astellas is the holder of this IND. (b) (4) provides CRO services for clinical operations and medical monitoring in Europe and South Korea, as well as medical monitoring in Japan. Astellas (Tokyo, Japan) manages clinical operations in Japan.

The study sponsor developed the statistical analysis plan (SAP), performed the statistical analyses, and prepared the clinical study report (CSR), which describes the results of the primary analysis of Cohort 1, with a data cutoff date of 01 Mar 2019.

An independent data monitoring committee (IDMC) performed periodic reviews of accumulating safety data and was charged with recommending modifications to the conduct of the study, if needed, to safeguard the interests of study participants while preserving the integrity of the study data. An independent, third-party statistics group was responsible for preparing analyses for IDMC review. The IDMC communicated their recommendations to the study sponsor; the final decision to act on the IDMC recommendations was made by the study sponsor.

Procedures and Schedule

Table 53 describes the schedule of events and Table 54 the schedule of procedures.

Table 53: Study EV–201 Schedule of Events

		Screening/ Baseline		Enrollment	Every 28-day cycle						EOT	Follow-up	LTFU
	Day	D –28 to 1	D –7 to 1	Within 7D of 1st dose	D1	D3[a]	D8	D15	D17[a]	D22	Within 30–37d of last dose[b]	Every 8 weeks	Every 8 weeks
	Visit window				±2d	±24h	+2d	+2d	–24h /+48h			±7 d	±7 d
Screening/baseline assessments	Inclusion/exclusion, medical history	X		Submit confirmation of eligibility prior to treatment									
	Informed consent	X											
	Acquire and submit tumor specimen[c]	X											
	Complete eye examination[d]	X											
	Slit lamp eye examination[d]									X[e]	X[P]		
	Brain scan	X								X[f]	X[f]	X[f]	
	Bone scan	X								X[f]	X[f]	X[f]	
	INR/PT/PTT	X											
	Hepatitis B and C screening	X											
	Urinalysis with microscopic analysis	X											
	HbA1c[o]	X											
	Pregnancy test (females of childbearing potential)[g]		X		X						X		
Safety assessments	Physical exam (including weight)[q]		X		X[h]						X	X[i]	

	Height		X										
	Vital signs		X		X[h]		X	X			X		
	CBC with differential[q]		X		X[h]		X	X			X		
	Chemistry panel[q]		X		X[h]		X	X			X		
	CrCl		X										
	ECOG performance status[q]		X		X[h]						X	X[i]	
	ECG		X								X		
	Concomitant medications	Related to study procedures from time of informed consent			Collect from Day 1 predose to EOT or 30 days post last dose, whichever is later								
	Adverse event collection												
PRO/QoL	QLQ-C30 and EQ-5D				X						X		
Treatment	Study drug administration[j]				X		X	X					
PK/ATA/biomarker	Blood sample collection	See PK, ATA and Biomarker Table for sample collection details											
Response assessment	CT scan with contrast of chest, abdomen, pelvis and any other region of known or suspected disease[r]	X								X[k,l]	X[k,m]	X[i,k]	
	Survival status												X[n]

INR: international normalized ratio; LTFU: long-term follow-up; PTT: partial thromboplastin time.

a Cycles 1 and 2. See PK, ATA and Biomarker Table (Table 54) for sample collection details.

b EOT evaluations must be obtained before the initiation of subsequent anticancer therapy, with the exception of slit lamp examinations. If EOT evaluations are completed before 30 days following the last study treatment, conduct a phone screen 30–37 days following the subject's last study treatment to ensure that no changes in AE profile have occurred.

c Pretreatment tumor tissue (from primary or metastatic site) for biomarker studies must be available for submission to the sponsor prior to study treatment. A minimum of 10 freshly sectioned, unstained charged slides are required. Either archival tissue or pre-treatment fresh tumor tissue (obtained from a fresh biopsy) was acceptable.

d Repeated as clinically indicated throughout the study.

e Cycle 2 Day 22 (±1 week) and Cycle 6 Day 22 (±1 week) on at least the first 60 enrolled subjects (from Cohorts 1 and/or 2). The sponsor may require Cycle 2 Day 22 and/or Cycle 6 Day 22 slit lamp examinations in the remaining subjects if warranted.
f Repeated at disease assessment timepoints if disease present at baseline, or as clinically indicated throughout the study.
g Either serum or urine pregnancy test. Not required for Cycle 1 if baseline assessment performed within 7 days. Repeat every month (±1 week) for 6 months after EOT.
h Not required for Cycle 1 if baseline assessments performed within 1 day.
I Subjects who discontinue study treatment for reasons other than objective disease progression by RECIST Version 1.1 will continue to have physical exams (no weight collection was required), ECOG, and response assessments 8 weeks (±1 week) after the previous response assessment scan and every 8 weeks (±1 week) following the previous visit thereafter. After 1 year on study the frequency of follow-up visits and response assessments was reduced to every 12 weeks (±1 week). The tumor assessments continue until the subject has radiologically confirmed disease progression per RECIST Version 1.1 as determined by the investigator, initiates a new anticancer therapy, subject death, study closure, or withdrawal of consent, whichever comes first.
j At least 1 week must elapse between doses of enfortumab vedotin.
k Responses were confirmed with repeat scans at 4 weeks after first documentation of response (+1 week). 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 was suspected.
l Response assessment were performed every 8 weeks (±1 week). After 1 year on study, response assessments were 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 subject's study activities; timepoints for response assessments should be calculated from Cycle 1 Day 1 during treatment.
m Not required if conducted <4 weeks prior to EOT.
n Contact subject for survival status and collection of subsequent anticancer treatment information every 8 weeks (±1 week) after EOT (or 8 weeks from previous protocol visit, whichever was later) until death, study closure, or withdrawal of consent, or subject was lost to follow-up, whichever occurs first. After 1 year on study the frequency of follow-up contacts were reduced to every 12 weeks (±1 week).
o If HbA1c was elevated (≥6.5%), refer subject to appropriate provider during Cycle 1 for glucose management.
p EOT slit lamp examination required for all subjects who experience corneal adverse events during the study and must be performed ≥4 weeks from last dose.
q May be collected or conducted up to 1 day prior to dosing.
r If contrast is contraindicated, see EV-201 Protocol Appendix F.

Source: EV-201 CSR

Table 54: Study EV–201 Pharmacokinetic, ATA, and Biomarker Blood Sample Collection Timepoints

	Study Day	Time	Window	Relative Time	Blood						
							Biomarkers				
							Plasma			PBMC	
					PK	ATA	Cytokines	Research 1	Research 2	Immuno-phenotyping	Research
Cycles 1 and 2	Day 1	Pre-dose	within 24 h	START of infusion	X	X	X	X	X	X	X
		End of infusion	within 15 min	END of infusion	X						
	Day 3	48 h	±24 h	END of Day 1 infusion	X		X[a]		X[a]	X[a]	X[a]
	Day 8	Pre-dose	within 24 h	START of infusion	X		X[a]	X[a]	X[a]	X[a]	X[a]
		End of infusion	within 15 min	END of infusion	X						
	Day 15	Pre-dose	within 24 h	START of infusion	X		X[a]		X[a]	X[a]	X[a]
		End of infusion	within 15 min	END of infusion	X						
	Day 17	48 h	–24 h/+48 h	END of Day 15 infusion	X						
	Day 22	168 h	±48 h	END of Day 15 infusion	X						
Subsequent dosing cycles	Day 1	Pre-dose	within 24 h	START of infusion	X[b]	X[b]	X[c]	X[c]	X[c]	X[c]	X[c]
End of Treatment (within 30–37 days of last dose)					X	X	X	X	X	X	X

PBMC: peripheral blood mononuclear cell

a Cycle 1 only.

b Cycles 3 and 4 and every even-numbered cycle thereafter.

c Cycles 3 and 4 only.

Dietary Restrictions
N/A. No dietary restrictions.

Concurrent Medications
No concomitant medications were required, expected or encouraged. Concomitant medications that were permitted included chronic prednisone (or equivalent) at a dose of ≤ 20 mg/day, higher doses of prednisone (or equivalent) for limited duration to treat acute conditions that arose during the study, anti-emetics, premedications for IRRs, growth factors, and transfusions. Other medications not specifically prohibited were allowed.

Prohibited concomitant medications included other investigational drugs, radiotherapy (except palliative radiotherapy on nontarget bone lesions), and systemic anti-neoplastic therapy during the treatment period. Subjects were required to have a 2-week washout period from prior therapy before enrollment to limit the potential for prior therapy to impact the safety or pharmacology results of the study.

Treatment Compliance
Study drug administration was performed by study site staff and documented in source documents and the case report form.

Rescue Medication
N/A

Subject Completion, Discontinuation, or Withdrawal
Subjects were considered to have completed the study when they were no longer being followed. Subject completion could occur for the following reasons: subject withdrawal of consent, lost to follow-up, death, or study termination by the sponsor. All subjects treated with enfortumab vedotin were included in the analyses as specified in the SAP. After subjects had completed the study, no further study procedures or assessments were performed. No subjects were replaced, regardless of the reason for study discontinuation or withdrawal.

The FDA's Assessment:

The following eligibility criteria may not be typical of those receiving treatment for UC and reflective of the real-world population for the proposed indication:

- Exclusion of patients with ECOG performance status > 1;
- History of cerebral vascular event including transient ischemic attack, unstable angina, or congestive heart failure NYHA Class III-UIV within prior 6 months;
- Uncontrolled diabetes mellitus (HbA1c ≥8%)

in the context of the demographics of the intended patient population: 90% of the U.S. metastatic UC patient population is >55 years old, and average age at diagnosis being 73 when including early-stage UC.

Refer to safety section x. regarding hyperglycemia with enfortumab vedotin. Ultimately, the fact that patients with elevated HbA1c >8% at baseline were excluded from EV-201 was included in product labeling to inform clinician decision-making for patients meeting this criteria.

Additionally, EV-201 excluded patients with immunotherapy related myocarditis (an addition in amendment 1 in response to request under Voluntary Harmonisation Procedure), colitis, uveitis, or pneumonitis; and patients with immunotherapy-related hypothyroidism or panhypopituitarism. The risk-benefit ratio in these patients is unknown, although the mechanism of toxicity of enfortumab vedotin do not appear to be similar to immune-mediated mechanisms typical of immunotherapy-related toxicities.

Study Endpoints

The Applicant's Description:

Primary Endpoint
The primary endpoint for this study was confirmed ORR, defined as the proportion of subjects who achieved a confirmed CR or PR as assessed by a BICR using RECIST Version 1.1. This endpoint was chosen because this is a single arm study and confirmed ORR is a direct measure of anti-tumor activity. There are several recent examples of regulatory approvals on the basis of ORR in UC, including erdafitinib, atezolizumab, pembrolizumab, nivolumab, durvalumab, and avelumab. Prior to protocol finalization, the confirmed ORR primary endpoint was discussed with FDA on 21 April 2017 (Face-to-Face Type B EOP1 Meeting), and there was agreement that the confirmed ORR may predict clinical benefit and be an acceptable endpoint for accelerated approval pending review of the data.

Response assessments were performed every 8 weeks, a typical timeframe for response assessment, which was considered adequate time to observe a significant change in tumor measurements. Responses were confirmed with repeat scans at least 4 weeks after initial documentation of response as required by RECIST version 1.1 criteria. The imaging data were centrally read and adjudicated by independent radiologists following the independent review charter. The BOR of each subject was derived by the sponsor based on the timepoint assessments by BICR following RECIST v1.1.

Surrogate Endpoint
The primary endpoint, confirmed ORR, is considered a surrogate endpoint of efficacy and has been previously established as a basis for accelerated approval by FDA. DOR is an important

secondary endpoint to demonstrate clinical benefit. Confirmed ORR with response duration is reasonably likely to predict the effect on clinical outcome.

Composite Endpoints
N/A

Secondary
Important secondary efficacy endpoints of this study, detailed in the SAP, include DOR and PFS as assessed by the BICR and investigator, confirmed ORR as assessed by the investigator, and OS. These secondary endpoints are appropriate, as they are considered standard measures of efficacy; however, it is recognized that the interpretation of time-to-event endpoints (e.g. OS) is limited in a single arm study.

DOR was defined as the time from the first documented CR or PR until disease progression per RECIST v1.1 or death due to any cause, whichever occurred first. DOR per BICR is proposed to be included in the label, as this provides important information regarding the character of the response and contributes to the understanding of clinical benefit. PFS was defined as the time from start of study treatment to first documentation of PD per RECIST Version 1.1 or death due to any cause, whichever came first. OS was defined as the time from start of study treatment to date of death due to any cause. In the absence of death, OS was censored at the date the subject was last known to be alive or at the analysis cutoff date, whichever was earlier. Subjects who died after the analysis cutoff date were censored at the analysis cutoff date. Subjects lacking data beyond the start of study treatment had their survival time censored on the date of first dose.

Exploratory Endpoints:
Assessment of biomarkers of biological and clinical activity, including Nectin-4 and PD-L1 expression.

The FDA's Assessment:
Confirmed ORR and DoR are appropriate efficacy endpoints for a single arm study. Time-to-event endpoints (e.g., progression-free survival and overall survival) results are uninterpretable in a single arm study without a comparator arm.

Statistical Analysis Plan and Amendments

The Applicant's Description:
The current version of the SAP, version 2, was finalized on 01 Feb 2019, prior to the database lock and before results of the primary endpoint became available. The initial SAP was updated to reflect changes in protocol amendments and add additional details to the analysis.

The study was designed to estimate the confirmed ORR in all treated subjects and to detect an improvement over the historical response rate of 10%. Approximately 200 subjects were to be enrolled, including ~100 or more subjects in Cohort 1 and up to ~100 subjects in Cohort 2. With 100 subjects in Cohort 1, there is a 98% chance of observing an ORR with the lower-limit of the exact 95% CI excluding a historical response rate of 10% if the true ORR is 25%.

The SAP outlined the following key analysis populations:

- FAS includes all enrolled subjects who received any amount of enfortumab vedotin.
- EE set includes all subjects in the FAS who had at least one post-baseline response assessment or discontinued study without undergoing a response assessment.
- Safety analysis set includes all enrolled subjects who received any amount of enfortumab vedotin and thus is equivalent to the FAS.

The primary analysis of the ORR per BICR was performed based on the FAS. Subjects who did not have post-baseline response assessment were considered non-responders. The exact 95% CI using the Clopper-Pearson method for the ORR was calculated. At the time of the primary analysis of each cohort, the primary endpoint is considered to be met if the lower-limit of the exact 95% CI for ORR excludes a historical response rate of 10%. Sensitivity analysis of the ORR per BICR was also performed for the EE population.

Subgroup analyses of the ORR were performed for selected demographic and disease characteristics as specified in the SAP: age (<65, ≥65 yrs; <75, ≥75 yrs), sex (female, male), race (white, non-white), ECOG performance score at baseline (0, 1–2), Bellmunt risk score (0–1, ≥2), baseline weight (≤100, >100 kg), primary tumor sites (upper tract, bladder/other), liver metastasis (yes, no), number of prior systemic therapy in locally advanced or metastatic setting (1–2, ≥3), best response to prior CPI (responder, non-responder), PD-L1 (CPS <10, ≥10). Subgroups without sufficient number of subjects (e.g., < 5) were not analyzed. At the time of the primary analysis of Cohort 1, subgroup analysis of Cohort 2 were not planned to be performed due to limited number of subjects.

DOR was calculated for responders only. Subjects who had not progressed or died at the time of analysis were censored to the last response assessment showing no evidence of disease progression. The Kaplan-Meier estimate of the median DOR and the 95% CI calculated using a complementary log-log transformation were to be presented.

PFS was analyzed for the FAS. Subjects who had not progressed or died at the time of analysis were censored to the last response assessment showing no evidence of disease progression. Subjects with no post-baseline response assessment were censored to the date of first study dose. The Kaplan-Meier method was used to estimate PFS.

OS was analyzed for the FAS. Subjects who were alive at the time of analysis were censored to the last date known to be alive. The Kaplan-Meier method was used to estimate OS.

This is a single-arm study with one primary endpoint. No multiple comparisons were planned, and multiplicity adjustment is not applicable.

Interim Analyses: No interim analysis was planned for Cohort 1. Three analysis timepoints were specified for Cohort 2: at the time of the Cohort 1 primary analysis, after ~50 subjects in Cohort 2 have been followed for at least 6 months, and after all subjects in Cohort 2 have been followed for at least 6 months.

Missing data was not imputed unless otherwise specified. For time-to-event endpoints (e.g., DOR, PFS, and OS), subjects who had no specified event were censored as specified for each respective endpoint. Subjects who did not have at least two (initial response and confirmation scan) post-baseline response assessments were counted as non-responders for the analysis of primary endpoint. Missing prior therapy dates were imputed for the purpose of calculating the time from prior therapy to first dose of study drug. Missing subsequent anticancer therapy start dates were imputed for the purpose of deriving the time-to-event endpoints as applicable.

For adverse events of interest, the peripheral neuropathy event rate adjusted by subject-year was analyzed ad hoc to evaluate the impact of exposure duration on the rate of peripheral neuropathy observed in Cohort 1 and Cohort 2. In addition, time to first dose reduction and time to treatment discontinuation due to TEAEs were analyzed ad hoc to further characterize dose modifications as a result of AEs.

The FDA's Assessment:
The statistical analysis plan is acceptable in general. Please note that no statistical inference can be made from a single-arm study and results presented would be considered descriptive. The efficacy evaluation was based on the magnitude of response rate and adequate duration of response.

Protocol Amendments

The Applicant's Description:
A summary of important changes implemented under each amendment are provided in Table 55, together with the number of subjects enrolled under each amendment. In addition, a country-specific protocol amendment was issued for South Korea (Amendment 4a). This amendment consisted of minor changes that were included in Amendment 4 for all other countries.

The sponsors do not believe that any of the amendments impacted the integrity of the trial or the interpretation of the results.

Table 55: Study EV-201 Protocol Amendments

EV-201 Protocols	Subjects Enrolled	Changes
Original 24 May 2017	26	
A01 14 Nov 2017	49	• Added an exclusion criterion for subjects with uncontrolled diabetes • Added dose modifications and other guidance for management of hyperglycemia • Added assessment of hemoglobin A1c (HbA1c) at screening • Revised cap on weight-based dosing from 120 kg to 100 kg Rationale: To address treatment-related, fatal serious events reported in 3 subjects in Part C of EV-101. Changes were made to all EV study protocols to ensure subject safety.
A02 13 Feb 2018	60	• Cycle 6 slit lamp examinations for at least the first 60 subjects enrolled Rationale: Added for safety per FDA request.
A03 13 Apr 2018	0	• No significant changes affecting endpoints and methods of assessing them, safety measurements, interim assessments, or statistical plan
A04 16 Apr 2018	20	• Revised the study design to consist of 2 separate cohorts to be analyzed separately: subjects who had received a prior PD-1/PD-L1 inhibitor and platinum-containing chemotherapy in the locally advanced or metastatic setting (Cohort 1), and subjects who had received a prior PD-1/PD-L1 inhibitor, had not received prior platinum-containing chemotherapy in the locally advanced or metastatic setting, and were cisplatin ineligible (Cohort 2) Rationale: To strengthen our ability to interpret study results. Specifically, these 2 cohorts were already being enrolled with plans to analyze as subgroups. Splitting them into cohorts preserved the ability to analyze each group separately and increased the number of subjects to be enrolled in group.
A05 14 Nov 2018	3	• Revised the eligibility criteria to allow subjects with an ECOG 2 performance status to enroll in Cohort 2 • Revised statistical analysis to remove the per protocol analysis set, revise the definition of the PK analysis set, and simplify the subgroup analyses Rationale: To expand Cohort 2 enrollment opportunities, streamline subgroup analyses, and harmonize the analysis set definitions with other studies.

The FDA's Assessment:
The FDA agrees with the applicant's summary of the protocol and amendments. "Subjects enrolled" in Table 56 above refers to the number of patients enrolled subsequent to the amendment, prior to the next amendment.

8.1.2. Study Results

Compliance with Good Clinical Practices

Data:
The following investigator sites (Table 56) and service provider (Table 57) audits were conducted by Seattle Genetics, Inc. to assess compliance with Good Clinical Practice (GCP) and the protocol:

Table 56: Study EV–201 Investigator Site Audits

Investigator	Audit Location	Audit Dates
Peter O'Donnell, MD	University of Chicago 5841 S. Maryland Ave, MC2115, Chicago, IL 60637	26 to 28-Feb-2018
Arjun Balar, MD	New York University (NYU) Cancer Institute, 550 First Avenue New York, NY 10016	06 to 08-Mar-2018
Bradley McGregor, MD	Dana Farber Cancer Institute 450 Brookline Avenue Boston, MA 02215	05 to 07-Nov-2018
Jingsong Zhang, MD	H. Lee Moffitt Cancer Center and Research Institute 12902 Magnolia Drive Tampa, FL 33612	11 to 12-Dec-2018

Table 57: Study EV–201 Service Provider Audits

Service Provider	Audit Location	Audit Dates
[redacted]	[redacted]	(b) (4)

(b) (4)

The Applicant's Position:
The protocol for this study was designed in accordance with the general ethical principles outlined in the Declaration of Helsinki (Brazil 2013). The conduct of all aspects of the study, including methods for obtaining informed consent, were also in accordance with principles enunciated in the declaration, the ICH GCP, and applicable regional regulations/guidelines.

The FDA's Assessment:
FDA agrees with the applicant's assessment. According to FDA's Office of Scientific Investigations, no significant GCP compliance deficiencies were identified in the clinical inspection of the three clinical sites.

Financial Disclosure

Data:
Financial interest was disclosed by one investigator who enrolled (b) (6) subjects in the EV-201 study.

The Applicant's Position:
It is unlikely that the significant payments of other sorts disclosed biased the EV-201 study results based on the following:

- Primary efficacy analysis was performed by BICR
- Study was conducted at 46 sites, and (b) (6) subjects were enrolled at this investigator's site
- Frequent monitoring of clinical trial sites
- Validity of the data was confirmed by standard monitoring procedures

The FDA's Assessment:

The FDA generally agrees with the applicant's assessment that it is unlikely that payments significantly impacted the study's results.
FDA disagrees with a minor point. The study was conducted at 46 sites, and **2** sites had financial interests. "Financial interest" is defined as financial arrangements (i), payments (ii), interest (iii), or equity (iv) paid to "the investigator or the institution to support activities of the investigator that have a monetary value of more than $25,000," according to 21 Code of Federal Regulations (CFR) 54.2. The applicant reports above that one site primary investigator disclosed financial interest who enrolled (b)(6) patients. FDA's assessment is that another site had a cumulative financial interest $42,754, primarily due to a sub-investigator (payments were $22,950), while the primary investigator (PI)'s financial interest was $15,094. This site enrolled (b)(6) patients. Review of this site's safety and efficacy data showed no data irregularities. Therefore, FDA agrees with the applicant that the data reliability is adequate and payments are unlikely to have significantly impacted the study's results.

Patient Disposition

Data:
Enrollment for Cohort 1 was completed on 02 Jul 2018 with a total of 128 subjects enrolled, of whom 125 (98%) received at least 1 dose of enfortumab vedotin. The disposition of subjects in Study EV-201 is summarized in Table 58. Three subjects discontinued from the study prior to receiving study treatment; 1 due to clinical deterioration, 1 per subject decision, and 1 due to low hemoglobin levels after screening and enrollment. Enrollment for Cohort 2 is ongoing.

Table 58: Study EV–201 Subject Disposition

	Cohort 1 N (%)	Cohort 2 N (%)
Subjects Treated	125	27
On treatment	20 (16)	14 (52)
Off treatment	105 (84)	13 (48)
Reason for discontinuing treatment		
Progressive disease	66 (53)	7 (26)
Adverse event	22 (18)	5 (19)
Subject decision	13 (10)	1 (4)
Physician decision	4 (3)	0
Subjects in long-term follow-up	45 (36)	7 (26)

Source: Study EV-201 CSR

The Applicant's Position:
Subjects who did not receive treatment with enfortumab vedotin were excluded from the FAS. This is appropriate because this is a single arm study and these subjects cannot contribute to interpretation of the efficacy or safety of enfortumab vedotin.

As of the 01 Mar 2019 data cut off, the majority (84%) of Cohort 1 subjects had discontinued treatment, with progression being the primary reason. This is an indication of the maturity of Cohort 1. Fewer than half of Cohort 2 subjects had discontinued treatment. Enrollment for Cohort 2 is ongoing.

The FDA's Assessment:
The FDA agrees with the applicant's assessment.

Protocol Violations/Deviations

Data:
Important protocol deviations (IPDs) are the subset of protocol deviations that may represent a divergence from the protocol that could have a significant effect on the integrity of study data, or on a subject's rights, safety, or welfare. A total of 6% (8/125) of Cohort 1 subjects and 15% (4/27) Cohort 2 subjects had an IPD (Table 59).

Table 59: Study EV–201 Summary of Important Protocol Deviations

	Cohort 1 N = 125 n (%)	**Cohort 2 N = 27 n (%)**
Any important protocol deviation[a]	8 (6)	4 (15)
Reason for important protocol deviation[a]		
Exclusion criterion	1 (1)[b]	1 (4)[c]
Study drug administration	2 (2)	0
Concomitant medications	1 (1)	0
Study conduct	4 (3)[d]	2 (7)[e]
Informed consent	0	1 (4)

a Subjects may be counted in more than one category.
b Cerebrovascular event within 6 months of Cycle 1 Day 1.
c Other malignancy within 3 years of the first dose of study treatment.
d Confirmatory response scans were either not done or were performed earlier than the 4-week window specified in the protocol and responses were not subsequently confirmed.
e Confirmatory scan not done with the response unable to be subsequently confirmed (1 subject) and Week 8 and 16 scans done without IV contrast due to site error, which rendered the responses not evaluable at these timepoints (1 subject).
Source: Study EV-201

The Applicant's Position:
Study conduct deviations were the most frequently reported IPDs and had the potential to impact the primary endpoint. Confirmatory scans that were not performed as specified, with responses that were not subsequently confirmed, had the potential to lower the confirmed

ORR. In Cohort 1, the impact of an additional 4 responses on the study results, had these scans been performed and confirmed the responses, would be minimal. For Cohort 2, the study conduct IPDs had the potential to lower the confirmed ORR (1 case) or impact DOR estimates from the interim analysis as the second case involved a responder with earlier scans that could not be interpreted. However, the potential impact will decrease as subjects continue to enroll in Cohort 2.

Other deviations that did occur were unlikely to impact overall study results.

The FDA's Assessment:
The FDA agrees with the applicant's assessment.

Table of Demographic Characteristics

Data:

Table 60: Study EV-201 Demographic Characteristics

Demographic Parameters	Cohort 1 (N = 125)	Cohort 2 (N = 27)
Sex, n (%)		
Male	88 (70)	20 (74)
Female	37 (30)	7 (26)
Age		
Median (yrs) (Range)	69 (40, 84)	77 (49, 90)
Age Group, n (%)		
< 65 years	45 (36)	5 (19)
≥ 65 years	80 (64)	22 (81)
< 75 years	91 (73)	9 (33)
≥ 75 years	34 (27)	18 (67)
Race, n (%)		
Asian	11 (9)	1 (4)
Black or African American	2 (2)	0
White	106 (85)	26 (96)
Other	1 (1)	0
Not Reported	5 (4)	0
Ethnicity, n (%)		
Hispanic or Latino	5 (4)	0
Not Hispanic or Latino	118 (94)	27 (100)
Geographic Region, n (%)		

United States	117 (94)	24 (89)
Rest of the World[a]	8 (6)	3 (11)
Europe	0	2 (7)
Asia	8 (6)	1 (4)

a Japan, the Netherlands, and Italy.
Source: Study EV-201 CSR

The Applicant's Position:
Demographic characteristics of subjects in Study EV-201 Cohort 1 (Data:
Table 60) are representative of the general metastatic UC population (8, 9). Demographics among Cohort 2 subjects were generally similar with the exception of age.

The FDA's Assessment:
The FDA generally agrees with the applicant's assessment. The patients in cohort 1 were likely younger than most patients with metastatic UC in the U.S., since the average age at diagnosis of bladder cancer is 73 years old, and probably older if limiting to the metastatic population.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

Table 61: Study EV–201 Baseline Characteristics

	Cohort 1 N = 125	Cohort 2 N = 27
Current extent of disease, n (%)		
Metastatic	125 (100)	27 (100)
Primary tumor location, n (%)		
Upper tract[a]	44 (35)	8 (30)
Bladder/other	81 (65)	19 (70)
Histology type, n (%)		
Transitional cell carcinoma (TCC) only	84 (67)	19 (70)
TCC with squamous differentiation	15 (12)	3 (11)
TCC with other histologic variants	26 (21)	5 (19)
Metastasis sites at baseline, n (%)		
Lymph nodes only	13 (10)	5 (19)
Visceral disease[b]	112 (90)	22 (81)
Bone	51 (41)	7 (26)
Liver	50 (40)	10 (37)
Lung	53 (42)	13 (48)
ECOG performance status, n (%)		
0	40 (32)	12 (44)
1	85 (68)	15 (56)
Renal function based on creatinine clearance, n (%)		
Normal: ≥90 mL/min	26 (21)	1 (4)
Mild decrease: ≥60 and <90 mL/min	51 (41)	7 (26)
Moderate decrease: ≥30 and <60 mL/min	47 (38)	19 (70)
Severe decrease: ≥15 and <30 mL/min[c]	1 (1)	0
Number of Bellmunt risk factors[d], n (%)		
0	23 (18)	5 (19)
1	49 (39)	17 (63)
2	35 (28)	3 (11)
3	17 (14)	2 (7)
H-score of Nectin-4 expression[e]		
n[e]	120	21
Median	290.0	290.0
Min, Max	14, 300	200, 300

a Includes renal pelvis, ureter, and kidney.
b Subjects may have metastatic disease in more than one location.
c Subject was enrolled based on local 24-hour urine collection.

d Bellmunt risk factors include ECOG performance status >0, hemoglobin <10 g/dL, and presence of liver metastasis (Bellmunt 2010). One subject in Cohort 1 had a missing baseline hemoglobin due to central laboratory value not being available. Bellmunt risk factors is missing for this subject.
e Number of subjects with evaluable data.

The Applicant's Position:
Disease characteristics of subjects in Study EV-201 (Table 61) are representative of the range of characteristics among advanced UC patients, including those with poor prognosis as exemplified by the percent of subjects with liver metastases. All subjects enrolled in Study EV-201 had metastatic disease, although subjects with locally advanced disease were eligible for the study. Both bladder primary sites and upper tract disease were well represented.

Table 62: Study EV–201 Summary of Prior Therapies in Locally Advanced or Metastatic Setting[a]

	Cohort 1 (N = 125)	Cohort 2 (N = 27)
Number of prior systemic therapies		
1	4 (3)[b]	19 (70)
2	58 (46)	7 (26)
≥ 3	63 (50)	1 (4)
Median	3.0	1.0
Min, Max	1, 6	1, 4
Prior treatment, n (%)		
PD-1/PD-L1 containing therapies	125 (100)	27 (100)
Prior platinum-based therapies[c]	125 (100)	0
Cisplatin-based regimen	92 (74)	0
Carboplatin-based regimen	43 (34)	0
Taxane	32 (26)	0
Pemetrexed	7 (6)	1 (4)[d]
FGFR inhibitor	3 (2)	1 (4)
Time from completion/discontinuation of most recent prior therapy to 1st study dose (months)		
≤ 3 Months	101 (81)	21 (78)
> 3 Months	24 (19)	6 (22)
Median	1.54	1.71
Min, Max	0.5, 14.3	0.6, 4.7
Best Response to PD-1/PD-L1 containing therapy, n (%)		

Complete Response	2 (2)	0
Partial Response	23 (18)	8 (30)
Stable Disease	37 (30)	6 (22)
Progressive Disease	63 (50)	13 (48)

a Includes prior systemic therapies in the locally advanced or metastatic setting, or anti PD-1/PD-L1 containing therapy in the neoadjuvant/adjuvant setting and the subject progressed within 3 months of therapy completion, or platinum-based therapy in the neoadjuvant/adjuvant setting and the subject progressed within 12 months of therapy completion.
b These subjects received platinum and PD-1/PD-L1 inhibitors in combination.
c Subjects may have prior treatment with both cisplatin and carboplatin.
d Subject enrolled prior to Amendment 4 (which excluded subjects previously treated with chemotherapy).
Source: Study EV-201 CSR

The Applicant's Position:

All subjects received prior therapy as required per the protocol. Fifty percent of subjects in Cohort 1 received at least 3 prior therapies (Table 62). Responses to prior PD-1/PD-L1 inhibitor therapy were consistent with what has previously been reported for this treatment in both Cohort 1 (post-platinum use of PD-1/PD-L1 inhibitors) [Bellmunt et al, 2017; Keytruda Prescribing Information, Merck; Tecentriq Prescribing Information, Genentech Inc.]. These characteristics reflect a study population that is representative of the intended patient population.

The FDA's Assessment:

FDA agrees that the treatment history characteristics reflect a study population representative of the intended patient population. To ensure that a broad categorization of PD-1/PD-L1 inhibitors would be justified in the indication, FDA conducted an independent analysis of the range of PD-1/PD-L1 inhibitors received in EV-201 Cohort 1 prior to trial enrollment. See Table 16b below.

About half of patients received PD-1 inhibitor and half received PD-L1 inhibitor prior to trial enrollment. The most common agents received were pembrolizumab (47%, including those who had PD-L1 inhibitor exposure as well), and atezolizumab (50%, including those who had PD-1 inhibitor exposure as well).

Table 63: Summary of Prior PD-1/PD-L1 Inhibitors in Cohort 1

	Cohort 1 (N = 125)
PD-1 inhibitor, n (%)	
Any PD-1 (without PD-L1) inhibitor	57 (46)
Pembrolizumab[a]	59 (47)
PD-L1 inhibitor, n (%)	
Any PD-L1 (without PD-1) inhibitor	52 (42)

Atezolizumab[b]	62 (50)
Both PD-1 and -L1 inhibitor, n (%)	16 (13)

[a] including patients who received pembrolizumab only and patients who also had PD-L1 inhibitor exposure in addition to pembrolizumab
[b] including patients who received atezolizumab only and patients who also had PD-L1 inhibitor exposure in addition to atezolizumab

Additionally, FDA conducted an independent analysis of the platinum exposure in EV-201 Cohort 1 prior to trial enrollment. Sixty-six percent of patients received prior cisplatin-based regimens, 26% received prior carboplatin-based regimens, and an additional 8% received both cisplatin and carboplatin-based regimens. This is generally consistent with the breakdown of prior platinum seen in other clinical trials in the later line metastatic urothelial cancer setting.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:
N/A

The Applicant's Position:
There are no applicable data because EV-201 is a single-arm trial.

The FDA's Assessment:
FDA disagrees that there is no applicable data. On October 16, FDA sent an information request for data on healthcare utilization. Given that the most common grade 3-4 treatment-emergent AEs in Cohort 1 were anemia (14%) and neutropenia (9%), transfusion and growth factor usage data were requested. Within the first cycle of enfortumab treatment, 10% of patients required RBC transfusion and 3% of patients required granulocyte colony-stimulating factors. Additionally, 46% of patients required antiemetics (compared to 24% at baseline) and 18% of patients required antidiarrheal medication (compared to 7% at baseline).

Efficacy Results – Primary Endpoint

Data:

Primary Efficacy
The confirmed ORR per BICR assessment for Cohort 1 was 44% (55/125; 95% CI: 35.1, 53.2), of which 15 subjects (12%) achieved CR (Table 64). The lower bound of the 95% CI excluded the historical ORR of 10% for taxanes as specified per protocol.

Cohort 2 continues to enroll. The confirmed ORR per BICR assessment for Cohort 2 was 33% (9/27; 95% CI: 16.5, 54.0), including 3 subjects (11%) who achieved CR (Table 67). A prespecified efficacy evaluable analysis was conducted to evaluate the ORR excluding the

subjects who remained on treatment and had not yet undergone any post-baseline disease assessment. This analysis is more comparable to that of Cohort 1 and included 22 subjects. The confirmed ORR per BICR assessment for efficacy evaluable subjects in Cohort 2 was 41% (9/22; 95% CI: 20.7, 63.6); see Table 64.

Table 64: Study EV–201 Summary of Best Overall Response per BICR

	Cohort 1 FAS N = 125 n (%)	**Cohort 2 FAS N = 27 n (%)**	**Cohort 2 EE N = 22 n (%)**
Best Overall Response[a]			
Complete Response (CR)	15 (12)	3 (11)	3 (14)
Partial Response (PR)	40 (32)	6 (22)	6 (27)
Stable Disease (SD)	35 (28)	10 (37)	10 (45)[b]
Progressive Disease (PD)	23 (18)	2 (7)	2 (9)
Not Evaluable (NE)	12 (10)[c]	6 (22)[e]	1 (5)[f]
Confirmed ORR (CR or PR)	55 (44)	9 (33)	9 (41)
95% CI[d] for ORR	(35.1, 53.2)	(16.5, 54.0)	(20.7, 63.6)

CI: confidence interval; CR: complete response; EE: efficacy evaluable; FAS: full analysis set; NE: not evaluable; ORR: objective response rate; PD: progressive disease; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumor; SD: stable disease

a Best overall response according to RECIST v1.1. CR or PR were confirmed with repeat scans ≥ 28 days after initial response.

b Includes 3 subjects whose initial response (CR or PR) was pending confirmation at the time of data cutoff.

c Includes 10 subjects who did not have response assessment post-baseline, 1 subject who had uninterpretable post-baseline assessment, and 1 subject whose post-baseline assessment did not meet the minimum interval requirement for stable disease.

d Computed using the Clopper-Pearson method (Clopper 1934).

e Five subjects have not reached the first response assessment visit and 1 subject did not have a response assessment postbaseline.

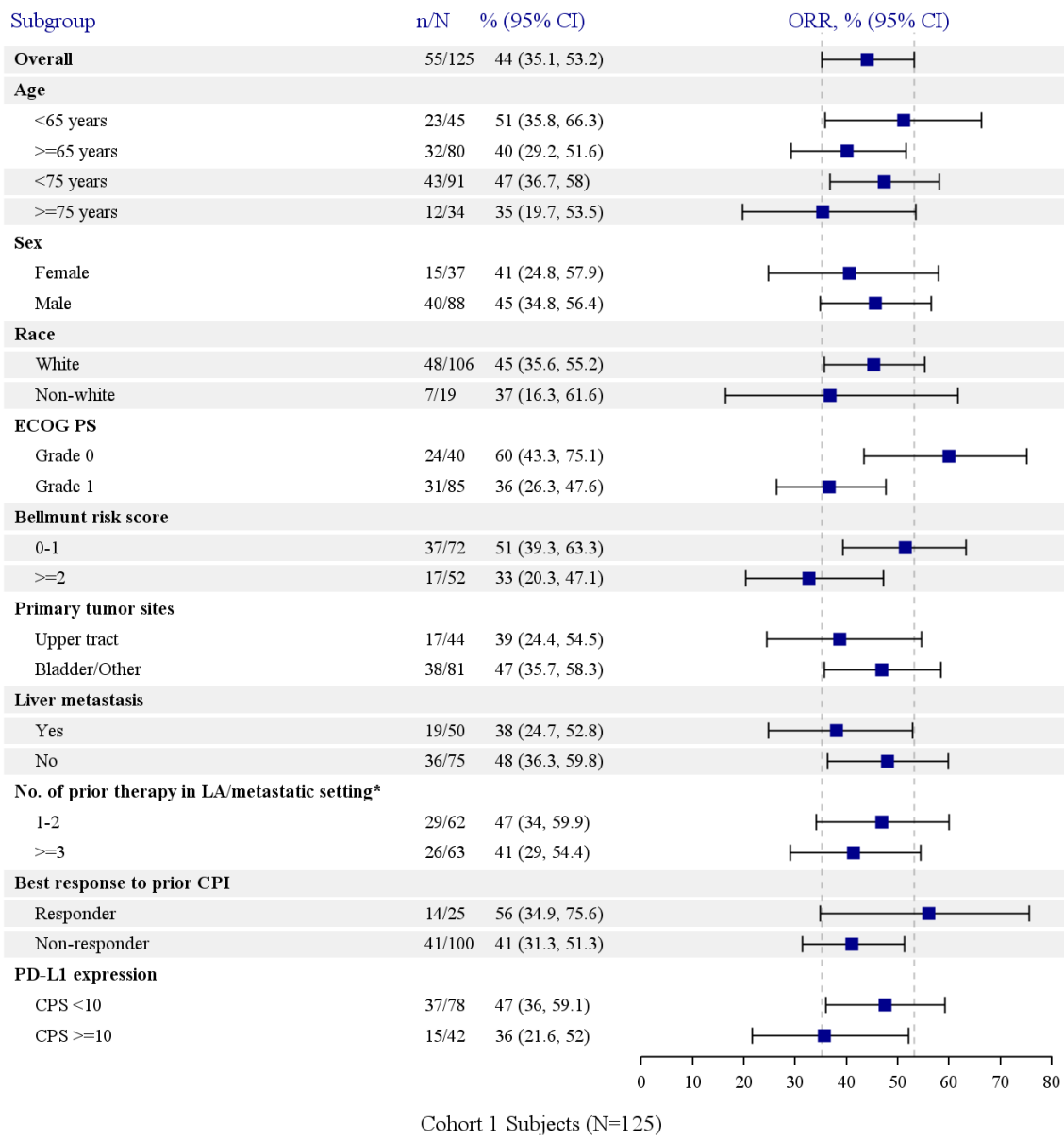
f One subject did not have a response assessment postbaseline.

Source: EV-201 CSR

Effects in Subpopulations

A forest plot of subgroup analyses of ORR per BICR by selected baseline characteristics and prognostic factors as pre-specified in the SAP is presented in Figure 9. The ORR for each subgroup was similar to that of the overall Cohort 1 population; in each case, the CIs of each subgroup overlapped with the overall outcome.

Figure 9: Objective Response Rate per BICR and 95% CI by Subgroups, Study EV-201 Cohort 1 (Full Analysis Set)

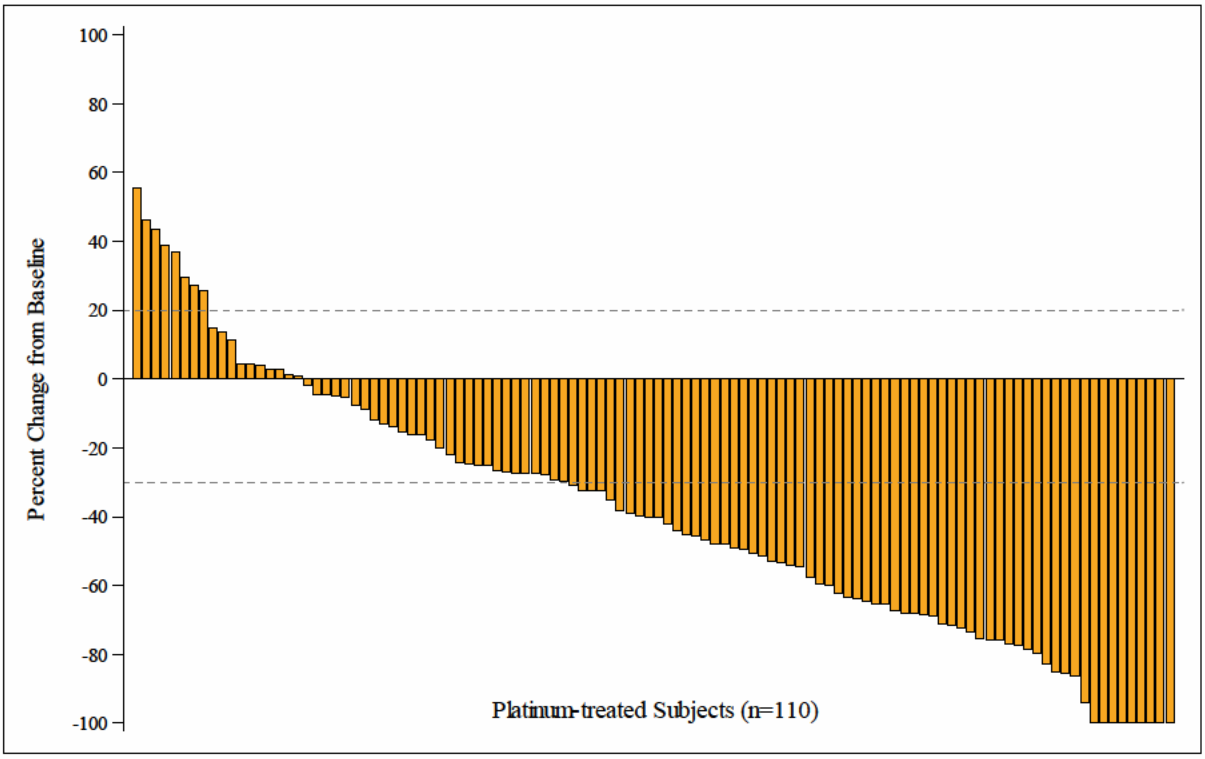


Source: EV-201 CSR

Maximum Percent Reduction from Baseline in Sum of Diameters Target Lesions per BICR

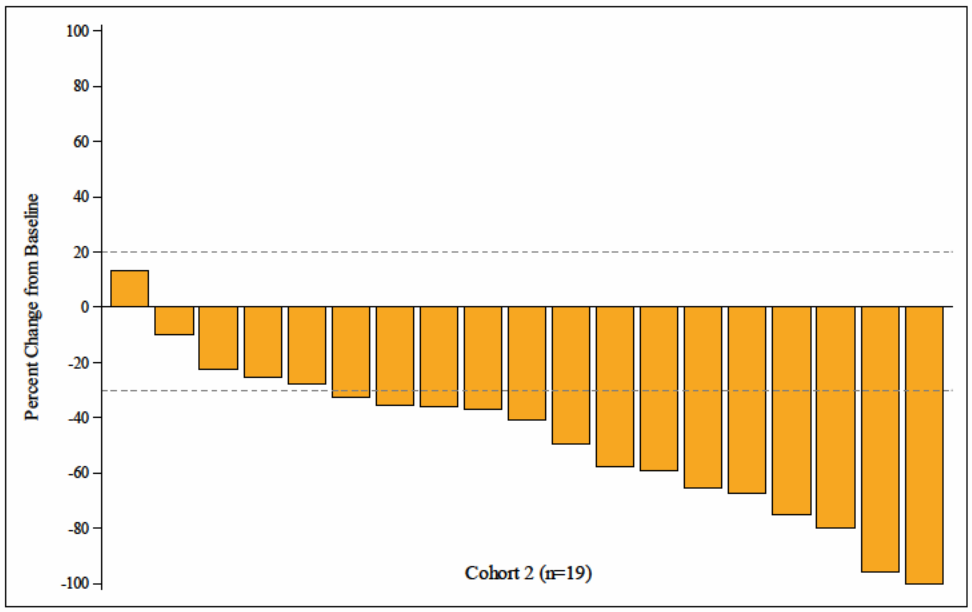
In both cohorts, the majority of subjects who were evaluable for target lesion response had a reduction of target lesion size per BICR: 84% in Cohort 1 (92/110; Figure 10) and 95% in Cohort 2 (18/19; Figure 11).

Figure 10: Maximum Percent Reduction from Baseline in Sum of Diameters of Target Lesions per BICR, Study EV-201 Cohort 1 (Full Analysis Set)



Source: EV-201 CSR

Figure 11: Maximum Percent Reduction from Baseline in Sum of Diameter of Target Lesions Per BICR, Study EV-201 Cohort 2 (Full Analysis Set)



Source: EV-201 CSR

Time to Objective Response: The median time to objective response for the 55 responders in Cohort 1 was 1.8 months (range, 1.2 to 9.2 months). Eighty-four percent of the responders (46/55) responded by the time of their first scheduled disease response assessment. An additional 15% (8/55) responded by their second response assessment. There was no meaningful difference in the median time to response (TTR) for subjects who did versus those who did not previously respond to a PD-1/PD-L1 inhibitor. Results in Cohort 2 were similar.

Investigator Assessed ORR: The confirmed ORR per investigator assessment for Cohort 1 subjects was similar to the BICR assessment at 39% (49/125 in the FAS;95% CI: 30.6, 48.3).

For Cohort 2, the confirmed ORR per investigator assessment was similar to Cohort 1 (41% (11/27 in the FAS; 95% CI: 22.4, 61.2).

A summary of the concordance between investigator and BICR assessment is provided in Table 65. The percent agreement was calculated as the percent agreement = (number of matched responders + number of matched non-responders)/total number of subjects assessed. Concordance between BICR and investigator assessment of response was 83% in Cohort 1, indicating good general agreement between the investigator and independent assessments. Concordance in Cohort 2 was lower (71%) than in Cohort 1, likely reflecting greater variability due to the smaller sample size in Cohort 2.

Table 65: Study EV-201 Concordance Between BICR and Investigator Assessments: EV-201

	Best Overall Response per Investigator		Concordance Rate
Best Overall Response per BICR	Responder	Non-Responder	
	Cohort 1 (N = 115)[a]		
Responder	42	13	95/115 (83%)
Non-Responder	7	53	
	Cohort 2 (N = 21)[a]		
Responder	7	2	15/21 (71%)
Non-Responder	4	8	

a Only subjects who were assessed by both BICR and investigator are included in the calculation of concordance rate. Ten subjects in Cohort 1 and 6 subjects in Cohort 2 did not have any response assessment post-baseline and were not assessed by the BICR. These subjects were considered non-responders for the primary endpoint ORR.

Source: EV-201 CSR

The Applicant's Position:

Treatment with enfortumab vedotin resulted in clinically meaningful efficacy in subjects with locally advanced or metastatic UC who had received a PD-1 or PD-L1 inhibitor and had either received a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting, or were not eligible for cisplatin-containing chemotherapy.

For subjects who had previously received platinum treatment (Cohort 1), the confirmed ORR per BICR was 44% (95% CI: 35.1, 53.2), which is ~4-fold higher than has previously been reported with taxanes in this setting. The lower bound of the 95% CI (35%) was ~3-fold higher than the 10% historical ORR reported for taxanes. The CR rate of 12% was also notable in this patient population, as the CR rate for taxanes has been reported to range from 1% to 3%; (2, 3, 8). Results of subgroup analyses of ORR per BICR were consistent with the overall study results. Notably, responses were observed in subjects with poor prognosis, including those who did not respond to prior PD-1/PD-L1 inhibitor therapy and in those with liver metastases. Responses occurred early in treatment, with most occurring by the time of the first response assessment; however later responses have also occurred. Most subjects evaluable for changes in target lesions had reduction of these lesions.

For subjects who had not received prior platinum chemotherapy and were cisplatin ineligible at enrollment (Cohort 2), the confirmed ORR per BICR was similar to that of Cohort 1 at 33% overall and 41% among efficacy-evaluable subjects. The CR rate of 11% overall and 14% among efficacy-evaluable subjects was also similar to that of Cohort 1. As with Cohort 1, most

responses to enfortumab vedotin were observed at the first response assessment and most subjects had reduction in target lesion size. Cohort 2 continues to enroll.

Overall, these data demonstrate that enfortumab vedotin provides a meaningful clinical benefit compared with other available treatments for patients with locally advanced or metastatic UC.

The FDA's Assessment:

1. Overall, FDA agrees that the demonstrated ORR is meaningful in the enrolled patient population.

2. The Applicant presented tumor response data from both cohorts; however, please note that only data from cohort 1 (platinum treated population) are considered as the pivotal evidence supporting the efficacy claim in this BLA submission. (b) (4)

   In September 2019, under IND 116360, the applicant requested FDA's advice regarding the data (b) (4)

3. As this is a single arm study, no statistical inference can be made, and results presented would be descriptive. The efficacy evaluation was based on the magnitude of response rate and adequate duration of response. FDA agrees with the efficacy results on tumor response of Cohort 1 presented by the Applicant.

4. FDA conducted additional subgroup analyses on ORR and the results are summarized in Table 66. No apparent outliers were observed in these subgroup analyses.

5. The Applicant also provided the waterfall plots of maximum percentage change in

summed diameter of target lesions from baseline to nadir based on BICR. The use of waterfall plots to visually convey the benefit seen in cancer clinical trial has gained popularity over time; however, it is noted that the waterfall plot has its own limitations. Not every bar below the -30% line is a response and may have stable disease, partial response, etc. In addition, the waterfall plots may visually bias the estimate of response rate upward and misrepresent response rates, given that neither confirmatory scan results nor non-target lesion and new lesion status are reflected.

Table 66: Additional FDA Subgroup Analyses of ORR per BICR assessment: EV201

	Number of patients	Number of Responders	BICR ORR % (95% CI)
Overall	125	55	44 (35, 53)
Prior use of cisplatin-based regimen			
Yes	92	47	51 (40, 62)
No	33	8	24 (10, 39)
Prior use of Carboplatin-based regimen			
Yes	43	14	33 (19, 49)
No	82	41	50 (39, 61)
Anti-PD-(L)1 as most recent therapy			
Yes	86	40	47 (36, 58)
No	39	15	38 (23, 55)
Prior Pembrolizumab use			
Yes	59	27	46 (33, 59)
No	66	28	42 (30, 55)
Prior Atezolizumab use			
Yes	62	26	42 (30, 55)
No	63	29	46 (33, 59)
Prior CPI use			
Anti PD-1 only	57	26	46 (32, 59)
Anti PD-L1 only	52	23	44 (30, 59)
Both anti PD-1 and anti PD-L1	16	6	38 (15, 65)
Smoking Status			
Current/Former	82	36	44 (33, 55)
Never	43	19	44 (29, 60)
Histology type			
Transitional cell carcinoma (TCC) only	84	35	42 (31, 53)
TCC with other histologic variants	41	20	49 (33, 65)

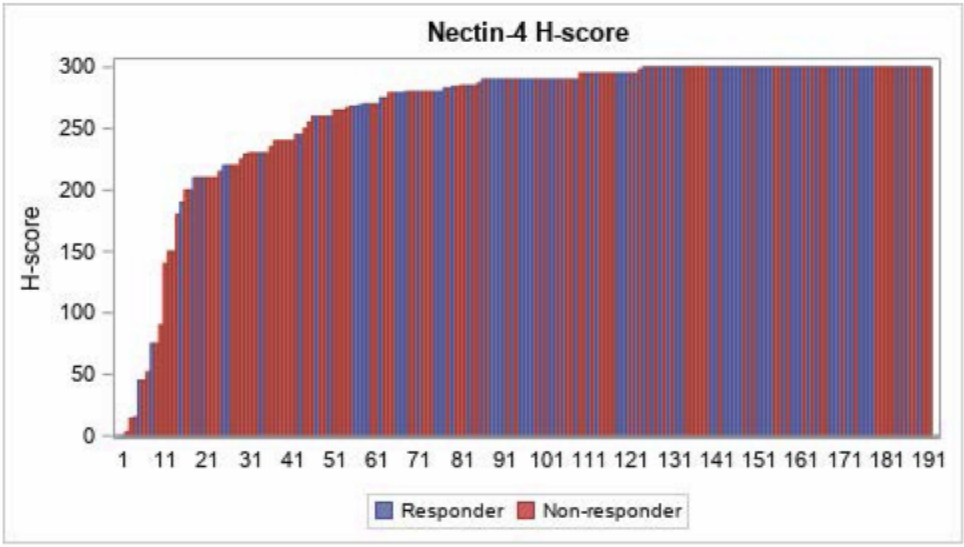
Nectin-4 H-score[a]			
<265[b]	29	7	24 (10, 44)
[265, 290)	27	11	41 (22, 61)
[290, 300)	21	11	52 (30, 74)
300	43	23	53 (38, 69)

[a]Nectin-4 H-score missing for 5 patients including 3 responders.
[b]Two partial responders had H-score less than 200.

6. Nectin-4 expression was not a requirement for enrollment on EV-201 due to high expected Nectin-4 expression overall in the enrolled population. For comparison of staining among tissues, the results were quantified by calculation of a complete H-score (histoscore) that considers both staining intensity and the percentage of cells stained at a specific range of intensities. A complete H-score was calculated by summing the products of the percentage of cells stained at a given staining intensity (0–100) and the staining intensity (0–3). We note the expression of Nectin-4 in all patients on EV-201 with tissue available for testing (120 out of 125 patients), and that efficacy was observed in all quartiles of Nectin-4 expression based on H-score (Table 67).

In a combined analysis pooling EV-201 and EV-101 data together (n=191 with 8 patients missing H-scores), responders were seen throughout expression levels of Nectin-4 (Figure 12). We note that one patient with an H-score of 0 had a partial response (not viewable on this plot). Based on these data, we conclude that there is likely no lower H-score cutoff for Nectin-4 expression below which patients would not be expected to benefit from treatment with enfortumab vedotin.

Figure 12: H-score of Nectin-4 Expression at Baseline, EV201 Cohort 1 + EV101 Part C



Data Quality and Integrity

Data:
N/A

The Applicant's Position:

There are no issues regarding data integrity and submission quality.

The FDA's Assessment:
The electronic submission for this BLA, including protocols, Statistical Analysis Plan (SAP), Clinical Study Reports (CSRs) and SAS transport datasets, is located in the network path: \\CDSESUB1\EVSPROD\BLA761137\0001\m5.

The overall data quality and integrity were acceptable to the reviewers. The submitted datasets were generally consistent, and variables were clearly labeled and/or explained. Based on the submitted data and reports, the reviewers believe that the analyses and results are reliable for regulatory decision making.

FDA sent an information request after learning from the central imaging CRO, (b) (4) of issues related to incomplete data transmission between their imaging software and their software system that captures numerical measurements and response assessments. The applicant responded that all affected images in EV-201 were re-read prior to the data cutoff on 01 Mar 2019. FDA agrees that there was no impact of the data transmission issue on the data submitted as part of the BLA.

Efficacy Results – Secondary and other relevant endpoints

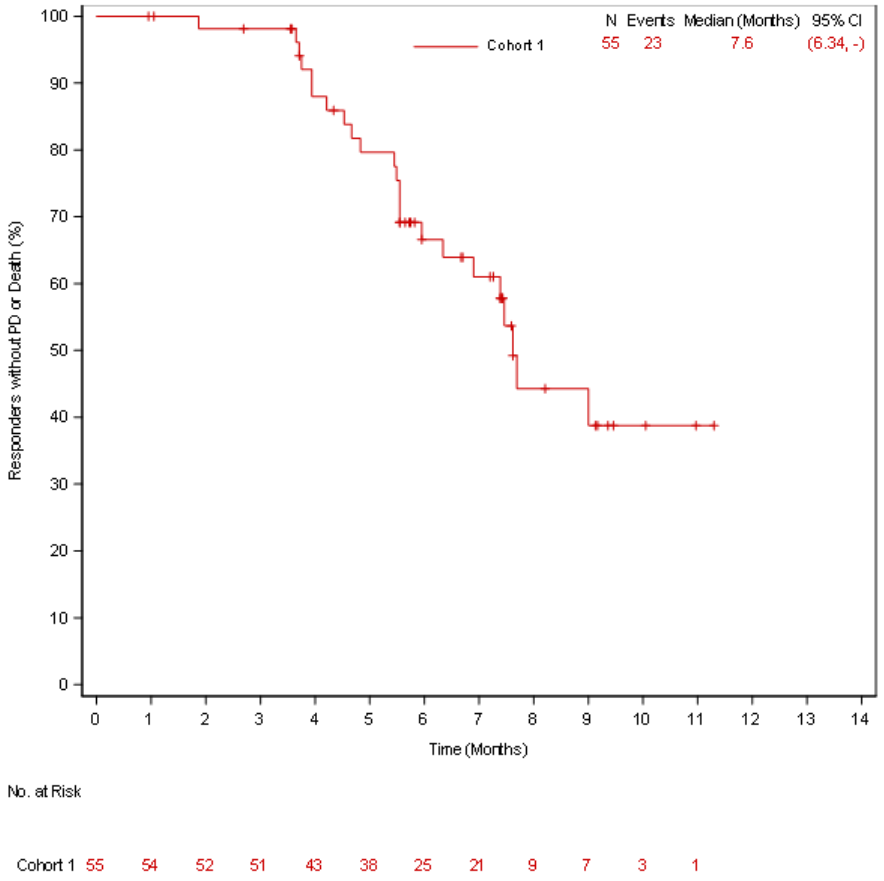
Data:

Duration of response

Responses to enfortumab vedotin were durable. As of the data cutoff date, the median DOR for the 55 Cohort 1 subjects who had confirmed CR or PR per BICR was 7.6 months (95% CI: 6.34, -; range, 0.95 to 11.30+; Figure 13); Overall 44% (24/55) of responders had ongoing responses at the time of the data cutoff.

Cohort 2 continues to enroll subjects, and there is not sufficient follow-up time for calculation of a mature response duration in Cohort 2. As of the data cutoff date, 56% (5/9) of responders had ongoing response. The range of response duration among the 9 responders is 1.02 to 5.85+ months.

Figure 13: Duration of Objective Response per BICR, EV-201 Cohort 1 (Full Analysis Set)

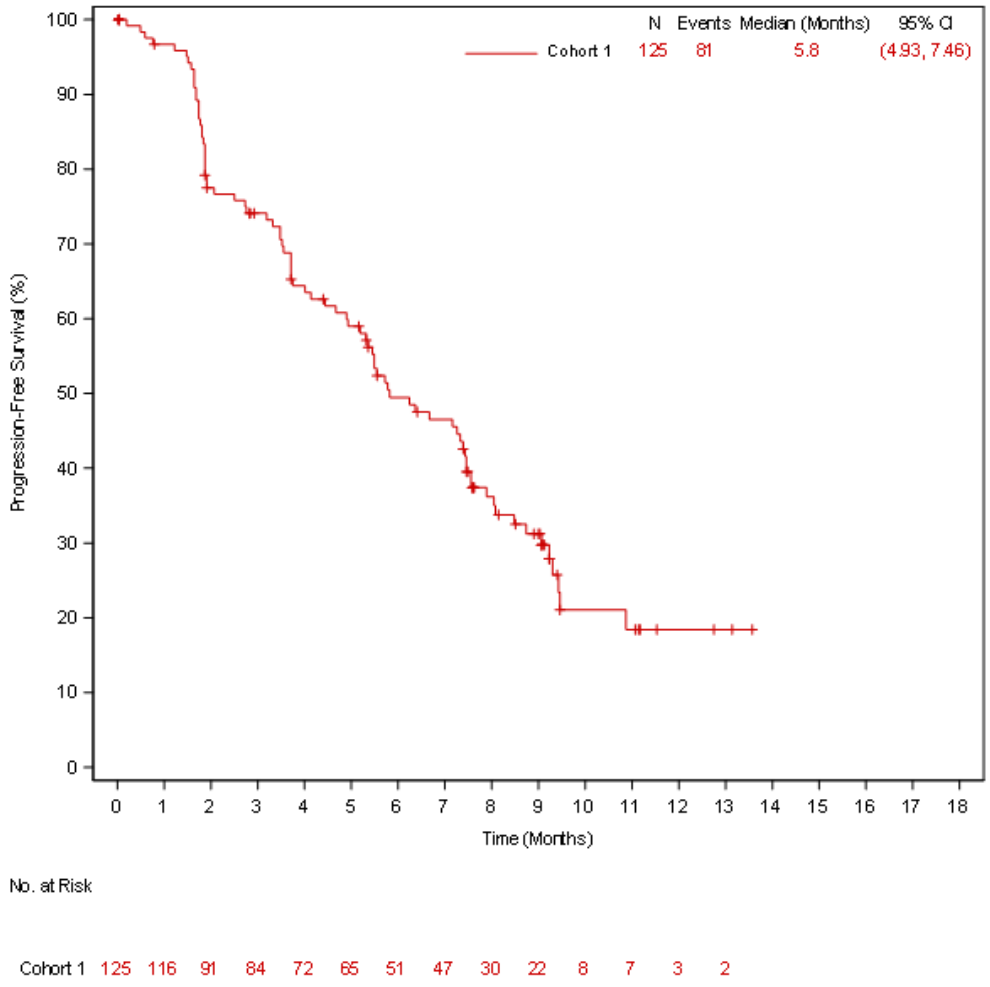


Source: EV-201 CSR

Progression-free survival

As of the data cutoff date, for Cohort 1, the median PFS per BICR was 5.8 months (95% CI: 4.9, 7.5 months; Figure 14). A total of 44 subjects (35%) were censored; of these, 28 (64%) remained in follow-up and 16 (36%) had started new anticancer therapy or discontinued from the study prior to PD or death. Cohort 2 continues to enroll. As of the data cutoff date, 17 subjects (63%) were censored; of these, 11 had not progressed and are continuing on study, 1 had started subsequent anticancer therapy, and 5 had not yet reached the first response assessment visit.

Figure 14: Progression-free Survival per BICR, EV-201 Cohort 1 (Full Analysis Set)



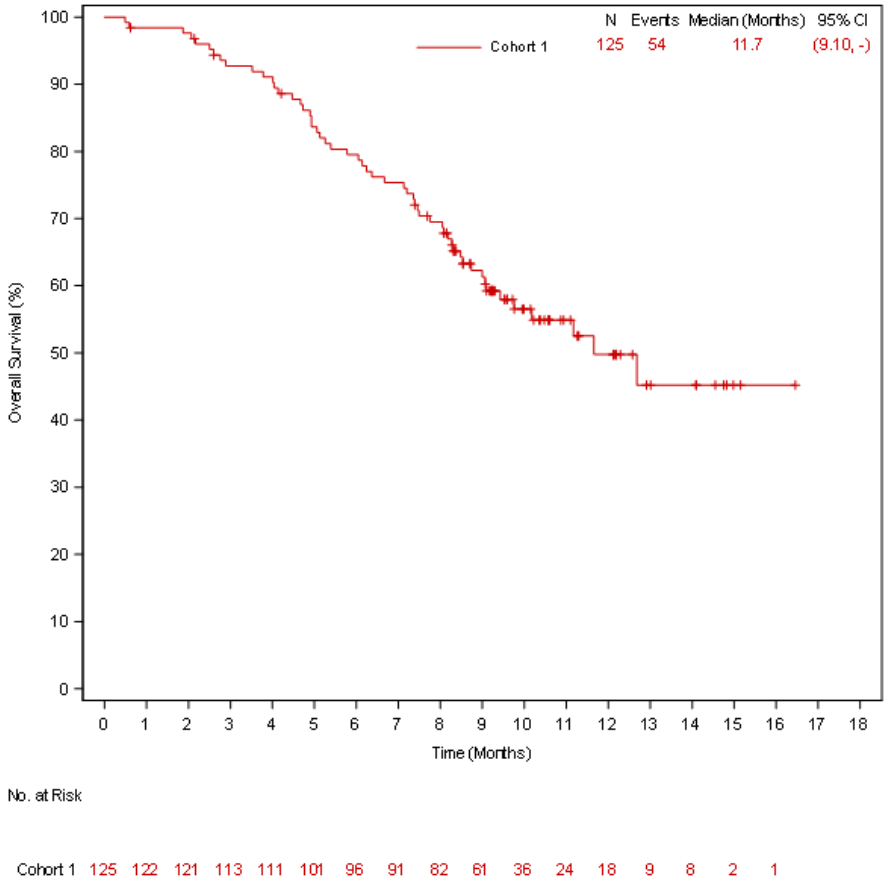
Source: EV-201 CSR

Overall survival

With a median follow-up time of 10.2 months (range: 0.5, 16.5) for Cohort 1, the estimated median OS was 11.7 months (95% CI: 9.1, -; Figure 15). As of the data cutoff date, a total of 71

subjects (57%) were censored; of these, 65 subjects (92%) remained in follow-up. Cohort 2 continues to enroll and the median follow-up time for currently enrolled subjects is 5.8 months (95% CI: 3.1, 8.1; range: 0.3, 16.5). As of the data cutoff date, a total of 21 subjects (78%) were censored and remained in follow-up.

Figure 15: Overall Survival, EV-201 Cohort 1 (Full Analysis Set)



Source: EV-201 CSR

The Applicant's Position:

The observed median DOR is 7.6 months in Cohort 1, which is clinically meaningful and supports the overall benefit of enfortumab vedotin in patients previously treated with both platinum-based chemotherapy and a PD-1/PD-L1 inhibitor.

DOR is proposed to be included in the label. The median DOR for Cohort 1 subjects was ~3 months longer than reported for taxanes in 2 recent large, phase 3 trials (4.2 and 4.3 months) and similar to that of a third trial (7.4 months) (2, 3, 8). As Cohort 2 is still enrolling, the data cutoff date for the Cohort 1 primary analysis does not provide sufficient follow-up time for calculation of a mature response duration; however durable responses were observed to 5.85+

months.

Other secondary efficacy endpoints included PFS and OS. The median PFS per BICR was 5.8 months (95% CI: 4.9, 7.5 months), and the median OS was 11.7 months (95% CI: 9.1, -) for Cohort 1. Although interpretation is limited by the single-arm trial design, both the PFS and OS outcomes compare favorably to historical data for taxanes. The median PFS for Cohort 1 subjects was ~2 months longer than the 2.8 to 4.0 months reported for taxanes in 3 recent large, phase 3 trials (2, 3, 8) and the median OS was ~4 months longer than the 7.4 to 8.0 months reported for taxanes in these same trials. The data cutoff date for the Cohort 1 primary analysis does not provide sufficient follow-up time for calculation of a mature PFS or OS for Cohort 2; median estimates of PFS and OS are anticipated to change as new subjects enroll and all subjects are followed for a longer duration.

The FDA's Assessment:

The FDA has confirmed that the estimated median duration of response in Cohort 1 was 7.6 months (95% CI: 6.3, NE), and the range was 0.95+ to 11.30+ months. The symbol "+" means ongoing response. Of the 32 responders censored in the duration of response evaluation, eight patients were censored due to receiving a new anti-cancer therapy, including two patients who were censored at around 1 month after the initial response date; and 24 responders are still under follow-up for response duration assessment as of the data cutoff date. The new anti-cancer therapies were given based on disease progression determined by investigator assessment; however, the progression was not confirmed by the BICR.

Please note the results of progression-free survival and overall survival are uninterpretable due to lack of a comparator arm in a single-arm study.

Cohort 2 data are considered supportive only, and data are immature at the current cutoff date.

Dose/Dose Response

Data:

Data on dose/dose response is presented from multiple studies in Section 8.1.2.

The Applicant's Position:

N/A

The FDA's Assessment:

See Section 6.3.2, Clinical Pharmacology Questions.

Durability of Response

Data:
DOR is presented as a secondary endpoint.

The Applicant's Position:
See secondary endpoint: DOR

The FDA's Assessment:
See results of DOR above. FDA agrees that the demonstrated duration of response is meaningful in the enrolled patient population.

Persistence of Effect

Data:
N/A

The Applicant's Position:
See Section 8.1.3, Subsection Persistence of Effect.

The FDA's Assessment:
Persistence of efficacy was demonstrated in EV-201 Cohort 1 based on the observed duration of response. Please note the results from progression-free survival and overall survival are uninterpretable due to lack of a comparator arm in a single-arm study.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints
Data:
Patient-reported outcome data were assessed from baseline to end of treatment (EOT).

Of the 125 treated subjects in Cohort 1, 120 (96%) completed the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) at baseline.

At baseline, the mean global QoL score was 63.0 (Cohort 1), and the mean functional domain score was above 70, indicating moderate-to-good functioning. No notable changes were observed over time for any of the domain scores, inclusive of general quality of life, functioning, and symptom scores. Some domains demonstrated signals of potential improvement across the study; however, the small sample size and variability across timepoints complicated comprehensive interpretation of the results.

The mean baseline visual analog scale and utility scores from the EQ-5D were 66.9 and 0.795, respectively for Cohort 1. During the treatment period, both visual analog scale and utility scores remained stable with little-to-no change from baseline throughout the study period.

The Applicant's Position:

The overall PRO data from the EORTC QLQ-C30 and EQ-5D questionnaires support the efficacy and safety results of this study and demonstrate that quality of life was maintained for subjects receiving enfortumab vedotin treatment. Some improvements in symptoms and functioning may exist, but interpretation of the data was limited by the small sample size and variability in the results.

The FDA's Assessment:

In a single arm study, the PRO data were analyzed descriptively only, and no statistical inference can be made. PRO data from two questionnaires, EORTC-QLQ-C30 and EQ-5D, were collected. Per the study protocol, PRO data were to be collected at day 1 of each treatment cycle until the end of study treatment. These data were reviewed and were not considered part of the efficacy analysis but were considered as important data for the review of safety and tolerability.

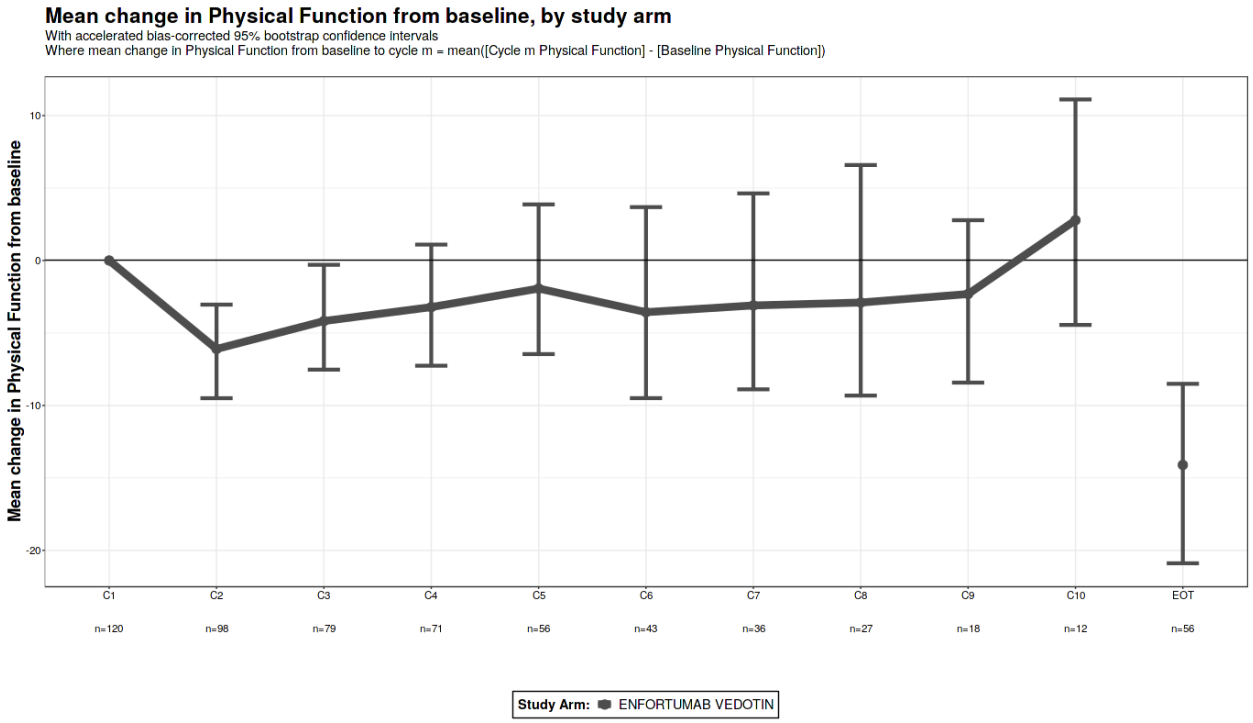
The EQ-5D is a generic preference-based measure intended to provide a single health utility index value for use in economic analyses and lacks evidence of content validity for use in estimating clinical benefit. However, we acknowledge that the EQ-5D may be necessary for other regulatory authorities and/or payers. The EORTC QLQ-C30 is a widely used patient-reported outcome instrument that is modular in its design, with individual symptom scales and items as well as global HRQL and 5 functional scales scored separately. It is noted that the global QoL score (items 29 and 30) may not be representative of the complete patient experience and we recommend assessing core disease and treatment symptoms and its associated impacts (i.e., physical function).

FDA reviewed the submitted PRO data and focused on analyzing physical function scale of EORTC QLQ-C30. Among patients who were expected to complete the questionnaire at each scheduled assessment, the compliance rate in the first 6 months on treatment was higher than 90%. It is noted that approximately two thirds of the patients have discontinued study treatment by cycle 6 and PRO data were not planned to be collected after patients have discontinued study treatment.

Figure 16 shows the mean change from baseline in physical function score over the scheduled assessments. The higher score represents better physical function. As shown in

Figure 16, by average, patients appeared to have worse physical function score compared to baseline during treatment, but the mean values were around 5 points deterioration which may not represent a clinically meaningful worsening.

Figure 16 Mean of Change in EORTC QLQ-C30 Physical Function from Baseline



[FDA analysis, data source: adqs]

Additional Analyses Conducted on the Individual Trial

Data:
N/A

The Applicant's Position:
N/A

The FDA's Assessment:

N/A

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:

See Section 8.1.4.

8.1.4. Assessment of Efficacy Across Trials

Primary Endpoints

Data:
The data presented compares efficacy results across Cohort 1 of EV-201, Cohort 2 of EV-201, and Part C of EV-101, which is most similar to EV-201 Cohort 1. All subjects in these 3 groups had prior treatment with PD-1/PD-L1 inhibitors in the locally advanced or metastatic UC setting and outcomes were assessed by BICR. Nearly all subjects enrolled to EV-101 Part C had prior treatment with platinum-based chemotherapy, but the setting of this treatment could not be determined for all subjects. Other data from EV-101 and data from EV-102 are not presented here due to differences in prior treatment (most subjects did not receive a PD-1/PD-L1 inhibitor) and response assessment (most were not by BICR).

Table 67: Comparative Efficacy Analysis Endpoints

	EV-201 Cohort 1 (N = 125)	EV-201 Cohort 2		EV-101 Part C (N = 74)
	FAS	FAS (N = 27)	EE (N = 22)	FAS
Primary efficacy endpoint				
Confirmed ORR[a] (CR or PR), n (%)	55 (44)	9 (33)	9 (41)	33 (45)
95% CI[b] for ORR	(35.1, 53.2)	(16.5, 54.0)	(20.7, 63.6)	(33.0, 56.6)
Secondary efficacy endpoints				
DOR[c] (months), median (95% CI[d])	7.6 (6.34, -)	-[e]	-[e]	7.5 (5.78, -)
PFS[c] (months), median (95% CI[d])	5.8 (4.93, 7.46)	-[e]	-[e]	6.6 (5.32, 8.15)
OS[c] (months), median (95% CI[d])	11.7 (9.10, -)	-[e]	-[e]	12.2 (8.15, 16.85)

BICR: blinded independent central review; CI: confidence interval; CR: complete response; DOR: duration of response; EE: efficacy evaluable; FAS: full analysis set; NE: not evaluable; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumor.

a Response assessed per BICR according to RECIST v1.1.
b Computed using the Clopper-Pearson method (Clopper 1934).
c As estimated using the Kaplan-Meier method.
d Calculated using the complementary log-log transformation method (Collett, 1994).
e Median DOR, PFS, and OS are not reported for EV-201 Cohort 2 due to shorter follow-up time.

The Applicant's Position:

The ORR per BICR was similar across populations (Table 67), regardless of prior treatment. Together, these results demonstrate consistent efficacy across independent clinical trials. In all 3 groups across 2 trials, the ORR was at least 3- to 4-fold higher than the historical ORR of ~10% for taxanes, with a CR rate that was ~4-fold higher than the recently reported rates of 1% to 3% for taxanes (2, 3, 8).

The FDA's Assessment:

The population in the 3 cohorts have differences, and sample sizes are generally small, particularly in Cohort 2. While the results across these cohorts appear similar, It is difficult to draw definitive conclusions

Secondary and Other Endpoints

Data:

Duration of Objective Response per BICR: Durable responses to enfortumab vedotin were observed across all studies. Median DOR among subjects in EV-201 Cohort 1 and EV-101 Part C was similar (~ 7.5 months; Table 67).

The maximum response duration was longest for EV-101 Part C (14.78+ months), reflecting the relative length of follow-up for each group. In all 3 groups, the maximum response duration reflected subjects with ongoing response at the time of the data cutoff.

Progression-free survival per BICR: The median PFS per BICR among subjects in EV-201 Cohort 1 and EV-101 Part C was similar at ~6 months (Table 67).

The maximum PFS was longest for EV-101 Part C (18.07+ months), reflecting the relative length of follow-up for each group. In all 3 groups, the maximum PFS reflected subjects with ongoing PFS at the time of the data cutoff.

Overall Survival: At the time of the data cutoff the median follow-up was 10.1 and 15.3 months for subjects in EV-201 Cohort 1 and EV-101 Part C, respectively. The estimated median OS was ~12 months for both groups (Table 67).

The Applicant's Position:
Data from secondary endpoints demonstrates that enfortumab vedotin has durable responses in a heavily pre-treated population, with a median DOR of ~7.5 months estimated from 2 independent trials. Although the OS and PFS benefits associated with enfortumab vedotin relative to currently available therapies cannot be determined from single-arm trials, the available data strongly support the clinical benefit of enfortumab vedotin in previously treated UC.

The FDA's Assessment:
The FDA generally agrees that the duration of response in Cohort 1 and Part C appear similar in cross-study comparisons; however, the FDA also noted that OS and PFS results are not interpretable in a single-arm study without a randomized comparator.

Subpopulations

Data:
The ORR as determined by BICR was analyzed by subgroups based on demographics and key baseline disease characteristics across studies (Table 68). Subgroup analyses were not performed for EV-201 Cohort 2 due to the limited number of subjects at the time of the data cutoff.

Table 68: Subgroup Analysis of Confirmed Objective Response Rate per BICR (Full Analysis Set)

	EV-201 Cohort 1 (N = 125)		EV-101 Part C (N = 74)	
	n/N	ORR (95% CI)	n/N	ORR (95% CI)
Age				
< 65 years	23/45	51 (35.8, 66.3)	13/35	37.1 (21.47, 55.08)
≥ 65 years	32/80	40 (29.2, 51.6)	20/39	51.3 (34.78, 67.58)
< 75 years	43/91	47 (36.7, 58.0)	27/61	44.3 (31.55, 57.55)
≥ 75 years	12/34	35 (19.7, 53.5)	6/13	46.2 (19.22, 74.87)
Sex				
Female	15/37	41 (24.8, 57.9)	8/20	40.0 (19.12, 63.95)
Male	40/88	45 (34.8, 56.4)	25/54	46.3 (32.62, 60.39)
Race				
White	48/106	45 (35.6, 55.2)	30/68	44.1 (32.08, 56.68)
Non-white	7/19	37 (16.3, 61.6)	2/5	40.0 (5.27, 85.34)
ECOG performance status				
0	24/40	60 (43.3, 75.1)	14/23	60.9 (38.54, 80.29)
1	31/85	36 (26.3, 47.6)	19/51	37.3 (24.13, 51.92)
Primary tumor site				
Upper tract	17/44	39 (24.4, 54.5)	6/13	46.2 (19.22, 74.87)
Bladder/Other	38/81	47 (35.7, 58.3)	27/61	44.3 (31.55, 57.55)
Liver metastases				
Yes	19/50	38 (24.7, 52.8)	12/29	41.4 (23.52, 61.06)
No	36/75	48 (36.3, 59.8)	21/45	46.7 (31.66, 62.13)
Best response to prior PD-1/PD-L1 inhibitor				
Responder	14/25	56 (34.9, 75.6)	6/12	50.0 (21.09, 78.91)
Non-responder	41/100	41 (31.3, 51.3)	27/60	45.0 (32.12, 58.39)

CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; ORR: objective response rate; n: number of subjects who achieved confirmed CR/PR; N: number of subjects in the respective subgroup; PD-1: programmed cell death 1; PD-L1: programmed cell death-ligand 1

The Applicant's Position:

Results of subgroup analyses were consistent across trials, with no meaningful differences in ORR observed for any of the subgroups assessed. In both studies, responses were consistent across all subgroups evaluated, including in subjects with liver metastases and subjects with poor response to prior PD-1/PD-L1 inhibitor.

The FDA's Assessment:

The FDA agrees that no apparent outliers were observed in these subgroup ORR analyses from both studies. The FDA also noted that in study EV-101 Part C, one complete responder had Nectin-4 H-score of 45 and one partial responder had Nectin-4 H-score of 0. Except for these two responders, all responders had Nectin-4 H-score >200. Combining EV-201 Cohort 1 and EV-101 Part C, a total of 15 patients had Nectin-4 H-score less than 200 and 4 out of the 15 were responders.

Persistence of Effect

Data:
The median DOR per BICR among subjects in EV-201 Cohort 1 (55 responders) and EV-101 Part C (33 responders) was similar at ~7.5 months. The maximum response duration was 14.78+ months in EV-101 Part C. The median PFS per BICR among subjects in EV-201 Cohort 1 and EV-101 Part C was similar at ~6 months. The estimated median OS for subjects in EV-201 Cohort 1 and EV-101 Part C was ~12 months with median follow-up of 10.1 and 15.3 months, respectively.

The Applicant's Position:
Single arm studies EV-201 Cohort 1 and EV-101 Part C demonstrate persistence of efficacy as reflected in favorable longer-term outcomes, including DOR, PFS, and OS. However, no controlled clinical studies specifically designed to collect long-term efficacy data have been conducted.

The FDA's Assessment:
The FDA agrees that persistence of efficacy was demonstrated in EV-201 Cohort 1 and EV-101 Part C based on the observed duration of response, though acknowledges limitation of cross study comparison and small sample sizes. Please note the results from progression-free survival and overall survival are uninterpretable due to lack of a comparator arm in a single-arm study.

Additional Efficacy Considerations

The FDA's Assessment:
N/A

8.1.5. Integrated Assessment of Effectiveness

Data:
Treatment with enfortumab vedotin resulted in clinically meaningful efficacy in heavily pretreated subjects with locally advanced or metastatic UC who had received a prior PD-1/PD-L1 inhibitor and had either received a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally

advanced or metastatic setting, or subjects who had received a prior PD-1/PD-L1 inhibitor and were not eligible for cisplatin-containing chemotherapy. In 3 cohorts from 2 independent trials (Study EV-201 Cohorts 1 and 2 and EV-101 Part C), ORR were consistently 3- to 4-fold higher than those associated with currently available therapies (33% to 45% versus ~10%) (2, 3, 8). The ORR across populations was even more consistent (range of 41% to 45%) when considering the efficacy-evaluable subjects from EV-201 Cohort 2, an analysis set that excluded subjects still on study who had not yet undergone a post-baseline disease assessment. CR rates ranged from 11% to 12% overall across all 3 cohorts and were similar (14%) when considering only efficacy-evaluable subjects from EV-201 Cohort 2.

Responses were consistent across all subgroups evaluated, including in subjects with liver metastases and subjects with poor response to prior PD-1/PD-L1 inhibitor.

Responses to enfortumab vedotin occurred early in treatment, with most subjects who achieved objective response doing so by the time of the first response assessment at 8 weeks; however, later responses also occurred.

Responses to enfortumab vedotin treatment were also durable, with a median DOR of ~7.5 months estimated from 2 independent trials. Although cross-trial comparisons may be confounded, the observed DOR with enfortumab vedotin is similar to or better than the 4 to 7 months associated with taxanes (2, 3, 8). Cohort 2 continues to enroll subjects and the data cutoff date for the Cohort 1 primary analysis does not provide sufficient follow up time for calculation of a mature response duration. Although DOR was not estimated in EV-201 Cohort 2 due to shorter follow-up time and small sample size, ongoing responses in 5 of 9 responders at the time of the data cutoff indicate that DOR may evolve to be similar among subjects in this cohort.

While OS and PFS benefits associated with enfortumab vedotin relative to currently available therapies cannot be concluded from single-arm trials, the available data are supportive of the clinical benefit of enfortumab vedotin in this setting.

The Applicant's Position:

The totality of the efficacy data demonstrates that enfortumab vedotin has a clinically meaningful treatment effect, resulting in rapid and durable responses in subjects with locally advanced or metastatic UC who have received prior treatment with a PD-1/PD-L1 inhibitor and a platinum-based chemotherapy. This population has a significant unmet medical need.

The FDA's Assessment:

The FDA generally agrees with the applicant's assessment. FDA notes that these results are from a single arm study. Confirmation of clinical benefit will be required from a randomized

study.

8.2. Review of Safety

8.2.1. Safety Review Approach

The Applicant's Position:
The safety profile summarized in this biologics license application (BLA) consists of data from 1 completed and 3 ongoing clinical studies of enfortumab vedotin monotherapy clinical studies including 379 subjects who received at least one dose of enfortumab vedotin. The primary evidence of safety is derived from the pivotal clinical study, EV-201, Cohort 1. This safety analysis group in the phase 2 trial represents a relevant core safety population for the indication being sought and is representative of the overall safety profile. The focus on Cohort 1 in Study EV-201 serves to align with the primary evidence of efficacy which is also derived from Cohort 1 of the EV-201 study.

Five safety analysis groups are presented in the Summary of Clinical Safety analysis. The primary safety analysis group consists of subjects with locally advanced or metastatic UC (Study EV-201, Cohort 1 [n=125]) who were treated with enfortumab vedotin as a single agent. Cohort 1 subjects had previously received systemic therapy with a PD-1/PD-L1 inhibitor and had received prior treatment with platinum-containing chemotherapy.

Four supportive safety subgroups derived from 3 studies (EV-101, EV-102, and EV-201) evaluating enfortumab vedotin monotherapy in locally advanced or metastatic UC are also presented. These safety subgroups are part of the primary Integrated Summary of Safety (ISS) and include: 1) Cohort 2 (Study EV-201 [n=27]) subjects who received no prior platinum-containing chemotherapy and were ineligible for treatment with cisplatin at the time of enrollment; 2) combined Cohort 1 and 2 (EV-201 [n=152]); 3) the enfortumab vedotin 1.25 mg/kg subgroup (EV-101, EV-102, EV-201 [n=310]) which included all subjects with any solid tumor type who started treatment at the 1.25 mg/kg dose of which the majority had locally advanced or metastatic UC regardless of prior treatment; and 4) the all enfortumab vedotin group (AGS-22M6E-11-1, EV-101, EV-102, EV-201 [n=379]) which included any subject with any tumor type, administered at least 1 dose of enfortumab vedotin at any dose.

The AEs of interest (AEOI) for enfortumab vedotin are rash, peripheral neuropathy, hyperglycemia, extravasation site reaction, IRRs (both local and systemic IRRs), anemia, neutropenia (including associated neutropenic infections), gastrointestinal (GI) disorders (grouped into two categories: diarrhea, nausea and vomiting and all other), ocular toxicity (corneal disorders) and ATAs.

The FDA's Assessment:

The FDA generally agrees with the applicant's assessment. The FDA's safety review approach focused on patients who received the dose recommended by the proposed label, 1.25 mg/kg (n=310, or n=336 after the 90-day safety update). FDA also focuses on grade 3-4 treatment-emergent AEs rather than all-grade AEs.

8.2.2. Review of the Safety Database

Overall Exposure

Data:

In Study EV-201 Cohort 1, the median duration of treatment for subjects was 4.6 months with a median of 12 infusions administered per subject. Thirty-two percent of subjects received ≥ 6 months of treatment. The median duration of treatment for subjects in Cohort 2 was similar to Cohort 1, but only 18.5% of subjects received ≥ 6 months of treatment as a result of ongoing enrollment.

Doses of enfortumab vedotin were administered based on subject weight, except for subjects > 100 kg in Studies EV-101, EV-102 and EV-201 (this weight cap was implemented in each study via protocol amendment). In Study EV-101, 14 subjects weighing > 100 kg were dosed prior to the amendment (dated 27 Nov 2017); and therefore, received > 125 mg (up to a maximum of 150 mg permitted) enfortumab vedotin. No other subjects in EV-101 or EV-201 received > 125 mg of enfortumab vedotin. Subjects > 100 kg are grouped by their assigned initial dose of 1.25 mg/kg, even though the actual dose they received was < 1.25 mg/kg due to the dose cap.

Enfortumab vedotin administration and dose exposure by safety group is summarized in the following table.

Table 69: Study Drug Exposure

Category/Statistic, n (%)	EV-201 Cohort 1 1.25 mg/kg	EV-201 Cohort 2 1.25 mg/kg	EV-201 All Cohorts 1.25 mg/kg	Enfortumab Vedotin 1.25 mg/kg
	(n = 125)	(n = 27)	(n = 152)	(n = 310)

Duration of exposure, months†				
n	125	27	152	310
Mean (std dev)	5.1 (3.5)	3.7 (2.4)	4.9 (3.3)	5.0 (3.8)
Min, max	0.5, 15.6	0.3, 8.1	0.3, 15.6	0.3, 18.5
Median	4.6	3.9	4.1	4.1
Duration of exposure, months				
< 1	14 (11.2)	6 (22.2)	20 (13.2)	50 (16.1)
≥ 1 and < 6	71 (56.8)	16 (59.3)	87 (57.2)	166 (53.5)
≥ 6	40 (32.0)	5 (18.5)	45 (29.6)	94 (30.3)
Number of infusions				
n	125	27	152	310
Mean (std dev)	13.9 (9.5)	10.7 (6.6)	13.3 (9.1)	13.5 (10.3)
Min, max	1, 39	2, 24	1, 39	1, 55
Median	12.0	11.0	12.0	12.0
Table continued on next page				
Number of dosing cycles‡				
n	125	27	152	310
Mean (std dev)	5.1 (3.4)	4.0 (2.4)	4.9 (3.2)	5.2 (3.8)
Min, max	1, 15	1, 8	1, 15	1, 20
Median	4.0	4.0	4.0	4.0
Relative dose intensity, %§				
n	125	27	152	310
Mean (std dev)	78.5 (16.8)	81.3 (18.5)	79.0 (17.1)	78.7 (19.0)
Min, max	29.0, 101.8	40.6, 100.5	29.0, 101.8	29.0, 120.0
Median	78.7	89.2	79.9	81.2

Max: maximum; Min: minimum; std dev : standard deviation.
†Duration of exposure =([the minimum of: initial dose date of the last cycle + 27, cutoff date or death date] - first dose date + 1) / 30.4375.
‡Total number of cycles with nonzero dosing in the cycle.
§(Dose intensity/Planned dose intensity) x 100. Relative dose intensity calculation uses subject dose capped for subjects with body weight of > 100 kg. At dose administration, some subjects were not dose capped at 100 kg and as a result, their relative dose intensity may be > 100%.
Source: ISS Supplemental Table 12.2.1.1

The Applicant's Position:

The overall exposure to enfortumab vedotin is adequate to support characterization of the safety profile of enfortumab vedotin. The exposure observed in EV-201 Cohort 1 was representative of the exposure overall across the safety analysis groups. The median duration of treatment for enfortumab vedotin was approximately 4 months across all safety analysis groups with subjects frequently remaining on treatment for 6 months or longer. The relative dose intensity showed that subjects generally received study drug as planned. At the 1.25 mg/kg dose, enfortumab vedotin was tolerable in subjects with metastatic UC, with a

manageable safety profile. No clinically meaningful differences were observed between any safety analysis groups, and the Study EV-201 Cohort 1 is representative of the overall safety profile of the integrated safety population.

The FDA's Assessment:

The FDA agrees with the exposure data the applicant presented. The FDA does not agree with the statement that "No clinically meaningful differences were observed between any safety analysis groups" because this is a non-inferiority claim The small size of some of the safety analysis groups (e.g., 27 patients in Cohort 2 of EV-201) does not permit this definitive conclusion, although the overall safety outcomes appeared concordant between groups.

We also note the fact that among the 310 patients receiving enfortumab vedotin at 1.25 mg/kg, 8% were exposed for ≥12 months.

Relevant characteristics of the safety population:

Data:

Demographic characteristics of subjects in Study EV-201 (Table 70) are representative of the general metastatic UC population (8, 9). Thus, this study enrolled a population appropriate for consideration of approval in the US.

In study EV-201 subjects were predominantly male (71.1%) with a median age of 70 (range: 40 to 90 years). Baseline subject demographics were similar across the safety analysis groups, the median age of subjects being highest in Cohort 2. Subjects in Study EV-201 Cohort 1 were predominately male (70.4%) and White (84.8%) with a median age of 69 years. Consistent with the EV-201 Cohort 1 data, baseline subject demographics were similar across the safety analysis groups, with EV-201 Cohort 2 consisting of older subjects.

Table 70: Demographic Characteristics

Parameter Category/Statistic	**EV-201 Cohort 1 1.25 mg/kg (n = 125)**	**EV-201 Cohort 2 1.25 mg/kg (n = 27)**	**EV-201 All Cohorts 1.25 mg/kg (n = 152)**	**Enfortumab Vedotin 1.25 mg/kg (n = 310)**	**All Enfortumab Vedotin (n = 379)**
Sex, n (%)					
Male	88 (70.4)	20(74.1)	108 (71.1)	208 (67.1)	255 (67.3)
Female	37 (29.6)	7 (25.9)	44 (28.9)	102 (32.9)	124 (32.7)
Age, years, n (%)					
Mean (std dev)	67.4 (10.0)	75.4 (9.8)	68.8 (10.4)	67.0 (10.3)	66.6 (10.3)
Min, max	40, 84	49, 90	40, 90	24, 90	24, 90

Parameter Category/Statistic	EV-201 Cohort 1 1.25 mg/kg (n = 125)	EV-201 Cohort 2 1.25 mg/kg (n = 27)	EV-201 All Cohorts 1.25 mg/kg (n = 152)	Enfortumab Vedotin 1.25 mg/kg (n = 310)	All Enfortumab Vedotin (n = 379)
Median	69.0	77.0	70.0	68.0	67.0
Age group, years, n, (%)					
< 65	45 (36.0)	5 (18.5)	50 (32.9)	123 (39.7)	155 (40.9)
≥ 65 and < 75	46 (36.8)	4 (14.8)	50 (32.9)	107 (34.5)	131 (34.6)
≥ 75	34 (27.2)	18 (66.7)	52 (34.2)	80 (25.8)	93 (24.5)

Source: Source: ISS Supplemental Table 12.1.2.1

In Study EV-201, the majority of subjects in both Cohort 1 and Cohort 2 had ECOG performance score of 1. The majority of subjects in Cohort 1 had normal renal function or mild renal insufficiency while the majority of subjects in Cohort 2 had moderate renal insufficiency. The degree of renal impairment in Cohort 2 was consistent with the cisplatin-ineligibility requirement (Table 71). Selected baseline characteristics noted below were similar across safety analysis groups.

Table 71: Selected Baseline Characteristics

Parameter Category/Statistic	EV-201 Cohort 1 1.25 mg/kg (n = 125)	EV-201 Cohort 2 1.25 mg/kg (n = 27)	EV-201 All Cohorts 1.25 mg/kg (n = 152)	Enfortumab Vedotin 1.25 mg/kg (n = 310)	All Enfortumab Vedotin (n = 379)
ECOG performance status at baseline[a]					
0	40 (32.0)	12 (44.4)	52 (34.2)	107 (34.5)	128 (33.8)
1	85 (68.0)	15 (55.6)	100 (65.8)	202 (65.2)	250 (66.0)
> 1	0	0	0	1 (0.3)	1 (0.3)
Hemoglobin, g/dL[b]					
N	124	27	151	309	378
Mean (std dev)	10.9 (1.4)	11.1 (1.4)	10.9 (1.4)	11.2 (1.6)	11.3 (1.5)
Min, max	8.1, 13.9	8.7, 14.5	8.1, 14.5	8.1, 16.5	8.1, 16.5
Median	10.8	10.9	10.8	11.1	11.2
< 10	35 (28.2)	4 (14.8)	39 (25.8)	69 (22.3)	77 (20.4)
≥ 10	89 (71.8)	23 (85.2)	112 (74.2)	240 (77.7)	301 (79.6)
Missing	1	0	1	1	1
Estimated creatinine clearance, mL/min[c]					
Mean (std dev)	70.3 (25.7)	52.7 (16.8)	67.2 (25.3)	69.6 (26.7)	70.4 (27.8)
Min, max	22.8, 161.5	32.7, 92.7	22.8, 161.5	11.9, 192.1	11.9, 213.0
Median	66.4	46.5	63.8	65.6	66.4
Renal function based on estimated creatinine clearance[c]					
Normal	26 (20.8)	1 (3.7)	27 (17.8)	60 (19.4)	77 (20.3)
Mild	51 (40.8)	7 (25.9)	58 (38.2)	125 (40.3)	153 (40.4)

Parameter Category/Statistic	EV-201 Cohort 1 1.25 mg/kg (n = 125)	EV-201 Cohort 2 1.25 mg/kg (n = 27)	EV-201 All Cohorts 1.25 mg/kg (n = 152)	Enfortumab Vedotin 1.25 mg/kg (n = 310)	All Enfortumab Vedotin (n = 379)
Moderate	47 (37.6)	19 (70.4)	66 (43.4)	119 (38.4)	139 (36.7)
Severe	1 (0.8)	0	1 (0.7)[d]	5 (1.6)	9 (2.4)
ESRD	0	0	0	1 (0.3)	1 (0.3)
Hepatic function group[e]					
Normal	110 (88.0)	23 (85.2)	133 (87.5)	279 (90.0)	345 (91.0)
Mild	14 (11.2)	4 (14.8)	18 (11.8)	30 (9.7)	33 (8.7)
Unknown[f]	1 (0.8)	0	1 (0.7)	1 (0.3)	1 (0.3)

AST: aspartate aminotransferase; ECOG: Eastern Cooperative Oncology Group; ESRD: end-stage renal disease; max: maximum; min: minimum; NCI: National Cancer Institute; stdev: standard deviation; ULN: upper limit of normal.

a One subject in Study EV-101 has ECOG = 1 at Screening, but ECOG = 2 just before first dosing.

b One subject had a missing baseline hemoglobin due to central laboratory value not being available.

c Cockroft-Gault formula was used to estimate creatinine clearance. Normal: ≥ 90 mL/min; mild: ≥ 60 and < 90 mL/min; moderate: ≥ 30 and < 60 mL/min; severe: ≥ 15 and < 30 mL/min; ESRD: < 15 mL/min.

d This subject in EV-201 was enrolled based on local 24-hour urine collection.

e Hepatic function classification based on NCI Organ Dysfunction Working Group criteria: Normal (total bilirubin ≤ ULN and AST ≤ ULN); mild (total bilirubin > 1 to ≤ 1.5 x ULN) or (AST > ULN and total bilirubin ≤ 1 x ULN); moderate (total bilirubin > 1.5 to 3 x ULN); severe (total bilirubin > 3 x ULN).

f This subject had unknown hepatic function due to missing laboratory values at baseline. The missing row is not included in the denominator for the percentage.

Source: ISS Supplemental Table 12.1.2.2

In Study EV-201, all subjects had UC and bladder was the primary location for a majority of subjects. Approximately 40% of subjects had liver metastases at baseline in Study EV-201 Cohorts 1 and 2 (Table 72). In the enfortumab vedotin 1.25 mg/kg safety analysis group, disease history was generally consistent with Study EV-201 Cohort 1, with the exception that 11.3% of subjects had other solid tumor types. The percentage of subjects with liver metastases (37.7%) at baseline was consistent with Study EV-201 Cohort 1.

Table 72: Disease History

Parameter Category/Statistic	EV-201 Cohort 1 1.25 mg/kg (n = 125)	EV-201 Cohort 2 1.25 mg/kg (n = 27)	EV-201 All Cohorts 1.25 mg/kg (n = 152)	Enfortumab Vedotin 1.25 mg/kg (n = 310)	All Enfortumab Vedotin (n = 379)
Time since locally advanced or metastatic disease diagnosis categories[a]					
< 12 months	47 (37.9)	17 (63.0)	64 (42.4)	110 (35.6)	131 (34.7)
≥ 12 months	77 (62.1)	10 (37.0)	87 (57.6)	199 (64.4)	247 (65.3)
Missing	1	0	1	1	1
Type of solid tumor cancer					
Urothelial	125 (100.0)	27 (100.0)	152 (100.0)	275 (88.7)	330 (87.1)
Other	0	0	0	35 (11.3)	49 (12.9)
Location of primary urothelial cancer					
Upper tract[b]	44 (35.2)	8 (29.6)	52 (34.2)	78 (25.2)	98 (25.9)
Bladder/other	81 (64.8)	19 (70.4)	100 (65.8)	197 (63.5)	232 (61.2)

Parameter Category/Statistic	EV-201 Cohort 1 1.25 mg/kg (n = 125)	EV-201 Cohort 2 1.25 mg/kg (n = 27)	EV-201 All Cohorts 1.25 mg/kg (n = 152)	Enfortumab Vedotin 1.25 mg/kg (n = 310)	All Enfortumab Vedotin (n = 379)
NA	0	0	0	35 (11.3)	49 (12.9)
Liver metastasis at baseline					
Yes	50 (40.0)	10 (37.0)	60 (39.5)	117 (37.7)	140 (36.9)
No	75 (60.0)	17 (63.0)	92 (60.5)	193 (62.3)	239 (63.1)

NA: not available.

a Time from metastatic disease for all subjects except subjects who have only locally advanced diagnosis at enrollment. Those diagnosed with both locally advanced disease and metastatic disease, the later date is used.

b Upper tract includes renal pelvis, ureter and kidney.

Source: ISS Supplemental Table 12.1.2.3

Each study and cohort enrolled the intended patient populations as defined by prior therapies. Most subjects had received a prior PD-1/ PD-L1 inhibitor, including all subjects in Study EV-201 (Table 73).

In Study EV-201, as required, all subjects in Cohort 1 had previously received platinum-based therapy. Few subjects in Cohort 2 previously received platinum-based therapy and those who did, received it in the neoadjuvant or adjuvant setting followed by a long (> 12 months) disease free interval. The majority of subjects in Cohort 1 previously received 2 or more prior systemic therapies, while most subjects in Cohort 2 only had 1 prior systemic therapy. Approximately one-quarter to one-third of subjects in each cohort had prior cystectomy, with a similar number in each cohort having prior nephrectomy. Prior cancer treatment history was similar in the enfortumab vedotin 1.25 mg/kg safety analysis group.

Table 73: Prior Cancer Treatment History

Parameter Category/Statistic	EV-201 Cohort 1 1.25 mg/kg (n = 125)	EV-201 Cohort 2 1.25 mg/kg (n = 27)	EV-201 All Cohorts 1.25 mg/kg (n = 152)	Enfortumab Vedotin 1.25 mg/kg (n = 310)	All Enfortumab Vedotin (n = 379)
Prior platinum treatment received in any setting					
Yes	125 (100)	5 (18.5)[c]	130 (85.5)	280 (90.3)	335 (88.4)
Prior cisplatin-based therapy					
Yes	94 (75.2)	5 (18.5)	99 (65.1)	207 (66.8)	247 (65.2)
NA[a]	0	22 (81.5)	22 (14.5)	30 (9.7)	44 (11.6)
Prior CPI treatment received (at any time)					
Yes	125 (100)	27 (100)	152 (100)	262 (84.5)	280 (73.9)
CPI most recent treatment received[b]					

Parameter Category/Statistic	EV-201 Cohort 1 1.25 mg/kg (n = 125)	EV-201 Cohort 2 1.25 mg/kg (n = 27)	EV-201 All Cohorts 1.25 mg/kg (n = 152)	Enfortumab Vedotin 1.25 mg/kg (n = 310)	All Enfortumab Vedotin (n = 379)
Yes	86 (68.8)	23 (85.2)	109 (71.7)	186 (60.0)	198 (52.2)

CPI: checkpoint inhibitor; NA: not available.
Number of prior systemic therapies under metastatic settings included treatments beginning after the date of metastatic diagnosis and do not include treatments in the locally advanced setting.
CPI is defined as a PD-1 or PD-L1 inhibitor as monotherapy or part of a combination therapy.
a NA indicates that a subject did not receive prior platinum-based therapy, and thus, did not receive cisplatin-based therapy. Prior platinum was given prior to diagnosis of metastatic disease and recurrent disease occurred >12 months following the last dose.
b Percentage based on all subjects.
c Prior platinum was given prior to diagnosis of metastatic disease and recurrent disease occurred >12 months following the last dose

Source: ISS Supplemental Table 12.1.4

The Applicant's Position:

Demographic characteristics of subjects in Study EV-201 are representative of the general metastatic UC population (8, 9). Subjects were typically older and male and in the enfortumab vedotin 1.25 mg/kg safety analysis group, baseline characteristics were overall consistent with Study EV-201 Cohort 1. Across the safety analysis groups, most subjects had received prior PD-1/PD-L1 inhibitor therapy and the majority of subjects in all groups received platinum-based therapy with the exception of EV-201, Cohort 2. Baseline characteristics were similar across the safety analysis groups, with more subjects in Cohort 2 having baseline moderate renal dysfunction. The degree of renal impairment in Cohort 2 is consistent with the cisplatin-ineligibility requirement.

The FDA's Assessment:

FDA's independent analyses generally agree with the above statements. See also Tables 17 and 18 in section 8.1.2, for relevant tables summarizing relevant baseline characteristics and prior treatment.

Adequacy of the safety database:

Data:

At the Type B End-of Phase 1 meeting held on 21 April 2017, the sponsors posed a question to the Agency regarding the size of the safety database to support the initial BLA submission for accelerated approval. The sponsors proposed to include safety data from ~200 subjects treated with enfortumab vedotin at the proposed dose and schedule who were previously treated with

CPI therapy, plus additional data from ~180 subjects treated with enfortumab vedotin at varying doses and schedules. The Agency indicated it is possible this safety database will be sufficient to support the BLA submission and indicated it will be a review issue. In the pre-BLA preliminary written responses provided by the Agency in advance of the clinical pre-BLA meeting (dated 14 December 2018), the Agency agreed with the sponsors' proposed Integrated Summary of Safety populations to be presented in the BLA, which were projected to include 229 subjects with locally advanced or metastatic UC who received enfortumab vedotin at 1.25 mg/kg and previously received a CPI, and a total of 365 subjects who received any dose of enfortumab vedotin. At the time of the database lock for the pivotal EV-201 study (01 Mar2019), 379 subjects had received at least one dose of enfortumab vedotin regardless of dose or tumor type in completed and ongoing studies. A total of 310 subjects were treated with the recommended commercial dose of 1.25 mg/kg enfortumab vedotin. As noted in (Table 74), the overall incidence of TEAEs in the enfortumab vedotin 1.25 mg/kg safety analysis group was consistent with that observed in Study EV-201 Cohort 1, with the exception of drug related TEAEs leading to death. All 4 drug-related TEAEs leading to death occurred in Study EV-101, resulting in a higher rate in the enfortumab vedotin 1.25 mg/kg group.

Table 74 Overview of Treatment-emergent Adverse Events

MedDRA (v20.0) Parameter n (%)	EV-201 Cohort 1 1.25 mg/kg (n = 125)	EV-201 Cohort 2 1.25 mg/kg (n = 27)	EV-201 All Cohorts 1.25 mg/kg (n = 152)	Enfortumab Vedotin 1.25 mg/kg (n = 310)	All Enfortumab Vedotin (n = 379)
TEAE	**125 (100)**	**27 (100)**	**152 (100)**	**309 (99.7)**	**376 (99.2)**
Drug-related† TEAE	117 (93.6)	24 (88.9)	141 (92.8)	287 (92.6)	349 (92.1)
Serious TEAE‡	58 (46.4)	8 (29.6)	66 (43.4)	131 (42.3)	161 (42.5)
Drug-related† serious TEAE‡	24 (19.2)	6 (22.2)	30 (19.7)	53 (17.1)	63 (16.6)
TEAE leading to death	7 (5.6)	2 (7.4)	9 (5.9)	19 (6.1)	22 (5.8)
Drug-related† TEAE leading to death	0§	0	0§	4 (1.3) §	4 (1.1) §
TEAE leading to withdrawal of study drug	20 (16.0)	5 (18.5)	25 (16.4)	60 (19.4)	78 (20.6)
Drug-related† TEAE leading to withdrawal of study drug	15 (12.0)	3 (11.1)	18 (11.8)	33 (10.6)	41 (10.8)
TEAE leading to dose reduction	43 (34.4)	7 (25.9)	50 (32.9)	98 (31.6)	105 (27.7)
Drug-related† TEAE leading to dose reduction	40 (32.0)	7 (25.9)	47 (30.9)	94 (30.3)	100 (26.4)
TEAE leading to dose interruption	80 (64.0)	13 (48.1)	93 (61.2)	187 (60.3)	212 (55.9)
Drug-related† TEAE leading to dose interruption	60 (48.0)	12 (44.4)	72 (47.4)	145 (46.8)	159 (42.0)

MedDRA (v20.0) Parameter n (%)	EV-201 Cohort 1 1.25 mg/kg (n = 125)	EV-201 Cohort 2 1.25 mg/kg (n = 27)	EV-201 All Cohorts 1.25 mg/kg (n = 152)	Enfortumab Vedotin 1.25 mg/kg (n = 310)	All Enfortumab Vedotin (n = 379)
TEAE with NCI-CTCAE ≥ Grade 3	91 (72.8)	18 (66.7)	109 (71.7)	198 (63.9)	237 (62.5)
Drug-related† TEAE with NCI-CTCAE ≥ Grade 3	68 (54.4)	15 (55.6)	83 (54.6)	136 (43.9)	158 (41.7)

NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; TEAE: treatment-emergent adverse event; UC: urothelial carcinoma.

†A reasonable possibility that the event may have been caused by the study drug as assessed by the investigator. If relationship was missing, then it was considered drug-related.

‡Includes serious adverse events upgraded by the sponsors based on review of the sponsors' list of Always Serious terms, if any upgrade was done.

§One subject from Study EV-201 had a drug-related AE leading to death (interstitial lung disease) that occurred > 30 days after the last dose of enfortumab vedotin, and therefore did not meet the definition of a TEAE leading to death. This subject is not represented in the table above.

Source: ISS Supplemental Table 12.6.1.1

The Applicant's Position:

The safety database is adequate to assess the safety of enfortumab vedotin. The majority of included subjects had metastatic UC, supporting the safety profile of enfortumab vedotin in subjects with this disease. The overall incidence of TEAEs was similar across the safety analysis groups and the events and rates observed in the EV-201 Cohort 1 are representative of the overall safety profile.

The FDA's Assessment:

FDA's independent analysis generally supports the above assessment.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:

The clinical sites for the safety analysis groups were monitored by clinical research associates following study-specific monitoring plans for consistency. Data were queried per study-specific data management plans. Additionally, external and IDMCs reviewed safety data for EV-102 and EV-201.

The Applicant's Position:

No issues were identified regarding data integrity or submission quality that had an effect on the safety review.

The FDA's Assessment:
Based upon the agency's review and the findings of inspections by OSI, the FDA agrees with the applicant's assessment regarding the quality and integrity of the submitted datasets. Refer to Section 4.1 in this document for further details on inspections.

Categorization of Adverse Event

Data:
N/A, please see The Applicant's position.

The Applicant's Position:
Safety was assessed by the surveillance and recording of AEs (including serious adverse events [SAEs]), recording of concomitant medications, and evaluation of physical examination findings, slit lamp examinations findings, and laboratory test results. Additionally, in EV-201 and EV-102, safety was monitored over the course of the study by an IDMC. Details of the EV-201 safety assessment and associated schedule of assessments are provided below.

Laboratory assessments were performed as per the Schedule of Assessments in EV-201 (see Section 8.1.1). Samples were drawn for central and local labs. Physical examinations included assessments of the following body parts/systems: abdomen, extremities, head, heart, lungs, neck, and neurological. Height was collected at the Baseline visit. Weight was collected at protocol-specified timepoints. Vital sign measurements included heart rate, diastolic and systolic blood pressure, and temperature. Vital sign values were recorded, and any diagnoses associated with clinically significant abnormal vital signs were recorded as an AE or pre-existing condition. ECOG performance status was evaluated at protocol-specified timepoints. ECGs were conducted at baseline and at the EOT visit. Additional ECGs were to be conducted if clinically indicated. A complete eye examination was performed at baseline by a qualified ophthalmologist or optometrist. The slit-lamp examinations were conducted at Cycle 2 Day 22 and Cycle 6 Day 22 on all eligible enrolled subjects. The IDMC was responsible for evaluating whether protocol-required slit lamp examinations conducted at Cycle 2 Day 22 and Cycle 6 Day 22 were necessary or could be discontinued. On evaluation of the Cycle 2 Day 22 slit-lamp data from 43 subjects of the first 60 enrolled, the IDMC recommended this exam could be discontinued. At EOT, slit lamp examinations were performed ≥ 4 weeks from last dose for all subjects who experienced corneal AEs during the study.

Adverse events were classified by system organ class (SOC) and PT using the Medical Dictionary for Regulatory Activities (MedDRA, version 20.0) and AEs were graded using the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE version 4.03). Subjects with multiple episodes were counted only once per event; subjects with multiple events coded to the same PT were only counted once for that PT (and SOC).

In all AE (and medical history) tables by SOC and PT, the following sorting were used: PTs were first sorted by SOC in alphabetic order (ascending), and within each SOC, PTs were then sorted by descending frequency. In the event that the frequencies for multiple PTs were numerically equal, the PTs were presented in alphabetical order. The all enfortumab vedotin group was used for sorting the frequency of the PT.

If toxicity was present on day 1 of any cycle and required enfortumab vedotin dosing to be held, then the start of the cycle may have been delayed. If toxicity was present on days 8 or 15 of any cycle and required the dose to be held > 2 days, the dose(s) was sequentially skipped, rather than delayed. Individual AEs associated with more than one type of dose modification (ie, dose interrupted, dose reduced and/or dose discontinued) are summarized under the dose modification that was most recently employed.

Astellas and Seattle Genetics identified AEs of interest (AEOI) for enfortumab vedotin to determine and further characterize the safety profile of enfortumab vedotin. The AEOI categories were generated based on 1) the potential or theoretical risk based on the nonclinical pharmacology and/or toxicology of enfortumab vedotin; and 2) observed findings in the clinical and laboratory data. The AEOIs for enfortumab vedotin are rash, peripheral neuropathy, hyperglycemia, extravasation site reaction, infusion-related reactions (IRRs, both local and systemic IRRs), anemia, neutropenia (including neutropenic infections), GI disorders (grouped into two categories: diarrhea, nausea and vomiting and all other), ocular toxicity (corneal disorders) and ATAs.

AEOI were assessed based on composite terms where applicable, to ensure reported rates of similar terms reflected the overall incidence of similar events. While composite terms were used, individual PTs were also reported and reviewed. The summarization of AEOI was based on standardized MedDRA queries, where possible. If a standardized MedDRA query was not available, then search strategies using a comprehensive list of PTs utilizing High Level Terms (MedDRA, Version 20.0) or customized MedDRA queries (CMQs)/sponsor-specific queries (SSQ) were applied. Though there was no search strategy specified for ATAs, subjects who were confirmed positive for ATAs were evaluated for relevant TEAEs.

The protocols defined AEs and serious events, as well as the reporting procedures. The safety reporting period for all AEs and SAEs was from Study Day 1 (predose) through the EOT visit or 30 days after the last study treatment, whichever was later. However, all study protocol-related AEs were to be recorded from the time of informed consent. All SAEs that occurred after the safety reporting period and were considered study treatment-related in the opinion of the investigator were also to be reported to the study sponsor.

SAEs were followed until significant changes returned to baseline, the event stabilized (recovering/resolving) or was no longer considered clinically significant by the investigator, or the subject died or withdrew consent. All other non-serious AEs were followed through the safety reporting period.

The FDA's Assessment:
The FDA generally agrees with the applicant's assessment. The categorization of ocular events is discussed in the Ocular Toxicity section (8.2.5.11).

Routine Clinical Tests

Data:
N/A, please see The Applicant's Position.

The Applicant's Position:
Laboratory results were graded using NCI-CTCAE (version 4.03), when applicable. Laboratory parameters that had criteria available for both low and high values (i.e., hypo- and hyper-) were summarized for both criteria. The same subject could have been counted for both criteria if the subject had different laboratory values meeting each criterion. Shift tables of NCI-CTCAE grade change from baseline to worst postbaseline grade were generated. The number and percentage of subjects with Grade 3 or 4 laboratory test results were summarized by safety analysis group and laboratory parameter. Treatment-emergent NCI-CTCAE Grade 3 or 4 laboratory results were defined as a subject's worst/highest postbaseline (during treatment period) NCI-CTCAE Grade 3 or 4 for a laboratory parameter that was higher than the subject's baseline. If a baseline grade was missing, any postbaseline Grade of 3 or 4 was considered treatment-emergent. When determining the worst postbaseline value for a subject, both scheduled and unscheduled laboratory results were included.

The baseline value was considered the last non-missing measurement taken prior to initial study drug administration.

There were minor differences in laboratory parameter collection between studies (e.g., lipase and amylase were only collected in Study EV-201). Of note, fasting glucose was not required for the clinical studies; therefore, treatment-emergent Grade 1 to 2 hyperglycemia (glucose high) could not be determined.

The FDA's Assessment:
The FDA agrees with the applicant's assessment. FDA acknowledges that CTCAE Grade 2 is defined as fasting glucose >160-250 mg/dL. In USPI labeling, Section 6, the footnote to Table 4 still reports the proportion of patients with glucose values >160 -250 mg/dL, and notes that these results were not from fasting laboratory evaluations.

8.2.4. Safety Results

Deaths

Data:
Overall, in Study EV-201, 9 subjects (5.9%) experienced a TEAE leading to death; 3 cases were attributed to transitional cell carcinoma and transitional cell carcinoma metastatic. In Cohort 1, 7 subjects (5.6%) died due to a TEAE; none were considered drug-related. Additionally, 1 subject in Study EV-201 Cohort 1 died of interstitial lung disease that was considered related to study drug; the event did not meet the definition of a TEAE because it occurred > 30 days after the last dose of enfortumab vedotin. In Cohort 2, two subjects (7.4%) died due to a TEAE; neither event was considered drug related.

In the overall enfortumab vedotin 1.25 mg/kg safety analysis group, 19 subjects (6.1%) experienced a TEAE leading to death (EV-101: 9, EV-102: 1 and EV-201: 9); 5 were related to the underlying malignancy: the 3 cases from EV-201 of transitional cell carcinoma and, from the other studies, 1 subject each with TEAEs of malignant bowel obstruction and disease progression. Four of these TEAEs were considered drug-related, all of which occurred in Study EV-101 (multiple organ dysfunction syndrome, diabetic ketoacidosis, urinary tract obstruction, and respiratory failure). Each case of drug-related TEAE leading to death was confounded by multiple factors including medical history, concomitant medications, comorbidities and underlying disease, as described below.

Narrative summaries for the 5 subjects with drug-related AEs leading to death are provided in this section. Table 75 describes all deaths by safety analysis subgroups.

Table 75: Treatment-emergent Adverse Events Leading to Death by System Organ Class and Preferred Term

MedDRA (v20.0) System Organ Class Preferred term, n (%)	EV-201 Cohort 1 1.25 mg/kg[a] (n = 125)	EV-201 Cohort 2 1.25 mg/kg (n = 27)	EV-201 All Cohorts[a] 1.25 mg/kg (n = 152)	Enfortumab Vedotin 1.25 mg/kg[a] (n = 310)	All Enfortumab Vedotin[a] (n = 379)
Overall	**7 (5.6)**	**2 (7.4)**	**9 (5.9)**	**19 (6.1)**	**22 (5.8)**
Cardiac Disorders	**1 (0.8)**	**0**	**1 (0.7)**	**2 (0.6)**	**3 (0.8)**
Cardiac arrest	0	0	0	1 (0.3)	2 (0.5)
Cardiac disorder	1 (0.8)	0	1 (0.7)	1 (0.3)	1 (0.3)

MedDRA (v20.0) System Organ Class Preferred term, n (%)	EV-201 Cohort 1 1.25 mg/kg[a] (n = 125)	EV-201 Cohort 2 1.25 mg/kg (n = 27)	EV-201 All Cohorts[a] 1.25 mg/kg (n = 152)	Enfortumab Vedotin 1.25 mg/kg[a] (n = 310)	All Enfortumab Vedotin[a] (n = 379)
Gastrointestinal Disorders	**0**	**0**	**0**	**1 (0.3)**	**1 (0.3)**
Malignant bowel obstruction	0	0	0	1 (0.3)	1 (0.3)
General Disorders and Administration Site Conditions	**0**	**0**	**0**	**2 (0.6)**	**2 (0.5)**
Disease progression	0	0	0	1 (0.3)	1 (0.3)
Multiple organ dysfunction syndrome	0	0	0	1 (0.3)	1 (0.3)
Infections and Infestations	**1 (0.8)**	**1 (3.7)**	**2 (1.3)**	**3 (1.0)**	**4 (1.1)**
Sepsis	1 (0.8)	1 (3.7)	2 (1.3)	3 (1.0)	3 (0.8)
Pneumonia	0	0	0	0	1 (0.3)
Metabolism and Nutrition Disorders	**0**	**0**	**0**	**1 (0.3)**	**1 (0.3)**
Diabetic ketoacidosis	0	0	0	1 (0.3)	1 (0.3)
Neoplasms Benign, Malignant and Unspecified (Includes Cysts and Polyps)	**3 (2.4)**	**0**	**3 (2.0)**	**3 (1.0)**	**3 (0.8)**
Transitional cell carcinoma metastatic	2 (1.6)	0	2 (1.3)	2 (0.6)	2 (0.5)
Transitional cell carcinoma	1 (0.8)	0	1 (0.7)	1 (0.3)	1 (0.3)
Renal and Urinary Disorders	**0**	**1 (3.7)**	**1 (0.7)**	**2 (0.6)**	**3 (0.8)**
Acute kidney injury	0	1 (3.7)	1 (0.7)	1 (0.3)	2 (0.5)
Urinary tract obstruction	0	0	0	1 (0.3)	1 (0.3)
Respiratory, Thoracic and Mediastinal Disorders	**2 (1.6)**	**0**	**2 (1.3)**	**5 (1.6)**	**5 (1.3)**
Acute respiratory failure	1 (0.8)	0	1 (0.7)	2 (0.6)	2 (0.5)
Dyspnoea	0	0	0	1 (0.3)	1 (0.3)
Pneumonia aspiration	1 (0.8)	0	1 (0.7)	1 (0.3)	1 (0.3)
Respiratory failure	0	0	0	1 (0.3)	1 (0.3)

Events are sorted in alphabetical order by system organ class and descending by the number of subjects in the all enfortumab vedotin group by preferred term. In case of ties, alphabetical order by preferred term is applied.

AE: adverse event; TEAE: treatment-emergent adverse event.

a One subject from Study EV-201 had a drug-related AE leading to death (interstitial lung disease) that occurred > 30 days after the last dose of enfortumab vedotin, and therefore did not meet the definition of a TEAE leading to death. This subject is not represented in the table above.

Source: ISS Supplemental Table 12.6.1.2.9

- **Multiple organ dysfunction syndrome**: **Subject** (b) (6) (Study EV-101) was an 81-year-old white male with metastatic UC who had a medical history of arrhythmia (atrial flutter) and hypercholesterolemia and who started enfortumab vedotin on (b) (6) (b) (6) (day 1). The subject received a total of 4 doses of enfortumab vedotin and received the last dose on (b) (6) (day 39). On day 46 (after 4 doses of study drug), the subject had Grade 3 rash maculo-papular and was subsequently started on prednisone 60 mg daily. He developed Grade 3 hyperglycemia, Grade 3 hemolysis, pancytopenia and worsening acidosis. On day 49, the subject became tachycardic and was in atrial fibrillation. He required pressor support for hypotension. Blood culture grew coagulase negative staphylococcus bacteremia and urine culture was positive for candida albicans. The subject died on day 53, with the cause of multi-organ failure, considered by the investigator to be possibly drug-related. Sponsor agreed with the Investigator's assessment with no comment.

- **Diabetic ketoacidosis**: **Subject** (b) (6) (Study EV-101) was a 63 year-old white male with metastatic UC who had a medical history of type 1 and type 2 diabetes, obesity, coronary artery disease and stage 3 chronic kidney disease, with elevated glucose levels at screening and baseline. The subject was hospitalized for small bowel obstruction and urinary tract infection (UTI) with positive culture from his nephrostomy tube after the first dose of enfortumab vedotin, and discharged on home IV antibiotics. After 3 doses of study drug, on (b) (6) he developed hyperglycemia with ketoacidosis that was largely refractory to insulin therapy. The subject developed neutropenic fever and acute renal failure and was treated with broad spectrum antibiotics. Metabolic acidosis worsened with compensatory hyperventilation resulting in respiratory failure that required intubation and vasopressor support. On (b) (6) the subject died. The investigator considered the cause of death to be diabetic ketoacidosis, possibly related to study drug (based primarily on the occurrence of the event after initiation of enfortumab vedotin), but indicated that the ketoacidosis could have been triggered by UTI. The causal relationship to study drug for these events was assessed by the Sponsor as possible and was based primarily on the occurrence after initiation of study drug.

- **Urinary tract obstruction**: **Subject** (b) (6) (Study EV-101) was a 71-year-old white male with metastatic UC who received a total of 3 doses of enfortumab vedotin (last dose on day 15). On day 18, the subject was admitted to the hospital for Grade 4 sepsis and Grade 3 UTI. The subject also experienced urinary retention with increased blood

clots in his urine, which required placement of a Foley catheter. Cystoscopy results on an unspecified date revealed a urinary obstruction, likely caused by tumor necrosis. On day 21, the subject underwent a transurethral resection of bladder tumor and ureteral stent exchange, with findings of diffuse clots. After the procedure, he had significant left hydronephrosis and developed Grade 3 acute kidney injury. The subject was experiencing overall clinical deterioration with worsening renal insufficiency but was discharged home per his wishes on day 26. At that time, he continued to have urinary clots and retention issues. On day 27, the subject died at home, with the cause of death listed as urinary tract obstruction. The investigator reported that there was not enough information about the subject's death at home to exclude a role with study drug, and indicated that the urinary obstruction was likely caused by tumor necrosis. Given the the subject's UC (involving bladder cancer), as well as the history of hematuria from his intact primary and left hydronephrosis, the sponsor considers this event was likely related to the subject's underlying malignancy, and not the study drug.

- **Respiratory failure**: **Subject** (b) (6) (Study EV-101) was a 64-year-old white female with metastatic UC and a history of laryngeal carcinoma status post radiation who received a total of 2 doses of enfortumab vedotin. The subject was admitted to the hospital for dehydration secondary to vomiting on day 12 and was discharged on day 14. On day 19, the subject developed worsening shortness of breath and dyspnea on exertion, and was hospitalized on day 21 for septic shock with hypoxic respiratory failure, secondary to hospital-acquired pneumonia and aspiration pneumonia. On the same day, the subject died with the cause of death assessed as respiratory failure. The event of respiratory failure was considered by the investigator as possibly related to study drug, based on temporal relationship. The Sponsor agreed with the Investigator's assessment with no comment.

- **Interstitial lung disease**: **Subject** (b) (6) (Study EV-201) was a 55-year-old Asian (Japanese) male with metastatic UC and a history of diabetes, prolonged use of systemic high-dose corticosteroids and smoking (former smoker) who received the cycle 4 day 15 dose of study drug on day 108. On day 120, the subject complained of exertional respiratory discomfort and on day 121 had acute respiratory failure diagnosed as interstitial pneumonia (suspected drug-induced interstitial pneumonia). Beta-D-glucan, a diagnostic marker for fungal infection, was elevated. The subject was treated with IV steroids, Bactramin IV, and broad-spectrum antibiotics. The subject died on day 142 due to interstitial pneumonia. The event of respiratory failure was considered by the investigator as possibly related to study drug; however, the investigator also considered the definitive cause of interstitial pneumonia not yet identified at the time of the subject's death. The Sponsor considers the case not consistent with interstitial lung disease related to enfortumab vedotin due to a more plausible alternative diagnosis of *Pneumocystis jiroveci* pneumonia or invasive fungal

infection.

The Applicant's Position:

TEAEs leading to death were infrequent and typical of an elderly subject population with underlying malignancy and comorbidities. Most TEAEs leading to death were considered not related to enfortumab vedotin therapy. Of the 19 deaths in the 1.25 mg/kg enfortumab vedotin safety group, 5 of these were directly attributed to underlying disease or process of the underlying disease (transitional cell carcinoma [3], disease progression and malignant bowel obstruction [1 each]). Of the remaining 14 deaths sepsis was the only TEAE leading to death observed in > 2 subjects. Few related deaths occurred: 4 deaths in the EV-101 and 1 death in EV-201 (outside of the safety reporting period) which were considered related to enfortumab vedotin treatment by the investigators. Each case of drug-related AEs leading to death was confounded by multiple factors including medical history, concomitant medications, comorbidities and underlying disease.

The FDA's Assessment:

The applicant provided narrative summaries of deaths that were considered to be due to drug-**related** adverse events. In a single-arm study, all deaths within 30 days of enfortumab treatment are relevant and attribution of causality is difficult to establish.

Additional deaths that occurred in EV-201 within 30 days due to adverse event were

1) **"Acute respiratory failure"**: SUBJECTID (b) (6) (EV-201): 67-year-old woman with history of sleep apnea and asthma, extensive lung metastases, received 6 weeks of enfortumab, and then presented with dyspnea and bilateral pulmonary edema. The differential diagnosis from the pulmonary consultant began with anti-neoplastic therapy-induced **pneumonitis**. She was hospitalized, for one week which was complicated by aspiration pneumonia leading to respiratory failure.
2) **"Pneumonia aspiration"**: SUBJECTID (b) (6) (EV-201) was a 77-year-old man with history of scleroderma who initially suffered a thoracic compression fracture on day 4. He received palliative radiotherapy to T7-T8 for two weeks. He resumed enfortumab until day 116, and then presented with dyspnea and cough due to aspiration pneumonia, which led to sepsis and hypotension. Both the scleroderma and radiation may have contributed to the aspiration pneumonia.
3) **"Cardiac disorder":** SUBJECTID (b) (6) (EV-201) was a 61-year-old man with history of hypothyroidism and chronic kidney disease (baseline creatinine clearance 50 mL/min), widely metastatic cancer to lung, liver, and bone, received 2 weeks of enfortumab therapy. On the day of his second dose, his hemoglobin was 6.7 g/dL. He received 2 units packed red blood cells in addition to enfortumab on day 8. On day 15, the patient's daughter informed the study site that the patient died. This occurred outside of a healthcare setting, and the patient's daughter believed the cause of death to be cardiac in nature.
4) **"Sepsis":** SUBJECTID (b) (6) (EV-201) was a 75-year-old woman who discontinued

therapy on day 71 due to progression of disease. On day 76, she had redness and swelling of the left leg. He was diagnosed with cellulitis and deep vein thrombus of the left leg at the same time. Her absolute lymphocyte count was 400 cells/mm^3 while her absolute neutrophil count was high (14,200 cells/mm^3). The patient appeared septic as evidenced by lactic acidosis, leukocytosis and tachycardia, and was treated with antibiotics, but died within 3 days due to sepsis and acute renal failure.

These 4 fatal adverse reactions were mentioned in section 6 of product labeling, which enumerates fatal adverse reactions that occurred in patients treated on cohort 1 of EV-201.

For the narratives that the applicant lists above, the FDA generally agrees with the applicant's assessment, with the following clarifications

1) SUBJECTID (b) (6) (EV-101): cause of death was suspected drug-induced hemolytic anemia which led to multi-organ failure.
2) SUBJECTID (b) (6) (EV-101): baseline hemoglobin a1c was not assessed. The patient was insulin-dependent at baseline, and also taking a sulfonylurea. Baseline BMI was 39, weight 121 kg. He enrolled prior to the protocol amendment that instituted the dose cap of 125 mg. His dose was 151 mg.
3) SUBJECTID (b) (6) (EV-101): cause of death was likely aspiration pneumonia in the context of prior neck radiation.
4) SUBJECTID (b) (6) (EV-201): cause of death was likely Pneumocystis pneumonia which may have been steroid-related. The patient had no history of underlying immunodeficiency. He did have history of diabetes mellitus, not requiring medication at baseline. His absolute lymphocyte count was about 500 cells/mm^3 at baseline and fluctuated 500-800 cells/mm^3 throughout treatment without a clear trend. His absolute neutrophil count was 1800-2700 cells/mm^3 prior to high-dose steroids. From day 38 to 52, he was treated with 1 mg/kg systemic steroid for a grade 3 rash. Subsequently, he received a steroid taper over several weeks. Signs of subacute pneumonia became apparent about 1 month later. The event did not meet the definition of a TEAE because it occurred > 30 days after the last dose of enfortumab vedotin and was thus not included in section 6 of product labeling that lists the fatal adverse events that occurred to patients in cohort 1 of EV-201.

Other relevant death narratives are summarized below:

5) SUBJECTID (b) (6) (EV-101) was a 54-year-old man with history of penile cellulitis one month prior to enrollment. He received 1 dose of enfortumab at the lower dose (0.75 mg/kg) and then had recurrence of penile cellulitis complicated by *C. difficile* colitis and then acute tubular necrosis. His baseline absolute lymphocyte count was 800 cells/mm^3 and decreased to 400 cells/mm^3 with the single dose of enfortumab. He died on day 16 due to acute kidney injury.
6) SUBJECTID (b) (6) (EV-201, Cohort 2) was a 75-year-old woman with recent history of

productive cough and bronchitis treated with azithromycin prior to enrollment. She received 2 doses of enfortumab. On day 16, she presented with hypoxemia. She was found to have worsening cytopenias (WBC 380 cells/mm^3, ANC 350 cells/mm^3, ALC <30 mm^3), and **invasive fungal pneumonia** confirmed by Fungitell®, which was her cause of death.

7) SUBJECTID [redacted] (b) (6) (EV-201, Cohort 2) was a 75-year-old man with upper tract primary mUC metastatic to the liver and a pelvic mass. He had no diabetes mellitus at baseline (hemoglobin a1c 5.3) but he did have chronic kidney disease (baseline creatinine 1.7). After 2 doses (day 8), he developed diarrhea followed by lactic acidosis, ketoacidosis and shock of unclear etiology. He died on day 15. No autopsy was done and mechanism was unclear.

Most of the deaths that were not due to progression could be attributed to either infection or a constellation of severe unexplained metabolic derangements/acidosis. See Section 8.2.7 for a summary of deaths due to infection or metabolic acidosis according to age (<65 years vs. ≥ 65 years).

Serious Adverse Events

Data:
In Study EV-201 overall, 43.4% of subjects experienced at least 1 SAE regardless of causality. The most common SAEs (occurring in ≥ 3% of subjects) reported in Cohort 1 included UTI, cellulitis, febrile neutropenia, sepsis, acute kidney injury and dyspnea. The only SAEs reported in > 1 subject in Cohort 2 were acute kidney injury and diarrhea (2 subjects, each). The most common drug-related SAEs (occurring in ≥ 2% of subjects) reported in Cohort 1 included febrile neutropenia, fatigue, nausea and vomiting (Table 76).

In the enfortumab vedotin 1.25 mg/kg safety analysis group, 42.3% of subjects experienced at least one SAE regardless of causality. Consistent with the EV-201 data, the most common SAEs (occurring in ≥ 3% of subjects) were acute kidney injury, UTI and sepsis. In the enfortumab vedotin 1.25 mg/kg safety analysis group, 17.1% of subjects experienced at least 1 drug-related SAE. Consistent with Study EV-201 Cohort 1, a common drug-related SAE was vomiting. In addition, drug-related serious hyperglycemia was reported in ≥ 2% of subjects in the enfortumab vedotin 1.25 mg/kg safety analysis group.

Table 76: Drug-related Serious Treatment-emergent Adverse Events (≥ 1% of Total Subjects†) by System Organ Class and Preferred Term

Category/Statistic, n (%)	EV-201 Cohort 1 1.25 mg/kg (n = 125)	EV-201 Cohort 2 1.25 mg/kg (n = 27)	EV-201 All Cohorts 1.25 mg/kg (n = 152)	Enfortumab Vedotin 1.25 mg/kg (n = 310)	All Enfortumab Vedotin (n = 379)
Overall	**24 (19.2)**	**6 (22.2)**	**30 (19.7)**	**53 (17.1)**	**63 (16.6)**
Blood and Lymphatic System Disorders	**7 (5.6)**	**2 (7.4)**	**9 (5.9)**	**11 (3.5)**	**13 (3.4)**
Febrile Neutropenia	5 (4.0)	1 (3.7)	6 (3.9)	6 (1.9)	6 (1.6)
Neutropenia	2 (1.6)	1 (3.7)	3 (2.0)	4 (1.3)	4 (1.1)
Gastrointestinal Disorders	**8 (6.4)**	**1 (3.7)**	**9 (5.9)**	**13 (4.2)**	**14 (3.7)**
Vomiting	3 (2.4)	1 (3.7)	4 (2.6)	7 (2.3)	7 (1.8)
Nausea	3 (2.4)	1 (3.7)	4 (2.6)	5 (1.6)	5 (1.3)
Infections and Infestations	**2 (1.6)**	**1 (3.7)**	**3 (2.0)**	**10 (3.2)**	**11 (2.9)**
Pneumonia	0	1 (3.7)	1 (0.7)	3 (1.0)	4 (1.1)
Metabolism and Nutrition Disorders	**3 (2.4)**	**1 (3.7)**	**4 (2.6)**	**12 (3.9)**	**13 (3.4)**
Hyperglycemia	1 (0.8)	0	1 (0.7)	7 (2.3)	7 (1.8)
Decreased appetite	0	1 (3.7)	1 (0.7)	3 (1.0)	4 (1.1)
Renal and Urinary Disorders	**(0.8)**	**1 (3.7)**	**2 (1.3)**	**6 (1.9)**	**8 (2.1)**
Acute kidney injury	1 (0.8)	1 (3.7)	2 (1.3)	5 (1.6)	6 (1.6)

Events are sorted in alphabetical order by system organ class and descending by the number of subjects with any event in the all enfortumab vedotin group by preferred term. In case of ties, alphabetical order by preferred term is applied.

Drug-related treatment-emergent adverse events have a reasonable possibility that the event may have been caused by the study drug as assessed by the investigator. If relationship was missing, then it was considered drug-related.

† All table cutoff values are referenced to the all enfortumab vedotin group.

Source: ISS Supplemental Table 12.6.1.4.8

The Applicant's Position:

The overall incidence of SAEs was similar across these safety analysis groups, and the events and rates observed in EV-201 Cohort 1 are representative of the overall safety profile. Two of the most common serious events reported, UTIs and acute kidney injury, are commonly observed in this patient population and were generally not drug-related. The most common drug-related SAEs were predominately GI (vomiting and nausea), hematologic (febrile neutropenia and neutropenia) and metabolic (hyperglycemia). The majority of SAEs of vomiting and hyperglycemia were drug-related. The sponsor continues to closely monitor these AEOIs. Further vomiting and nausea are considered identified risks of enfortumab vedotin.

The FDA's Assessment:

FDA disagrees with the applicant's approach to assessment of serious adverse events. The applicant chose to include only the drug-related treatment-emergent adverse events (TEAEs) in the table above. Furthermore, the applicant's "overall" rate of serious adverse events reported in the table above reflects only the total number of patients who experienced one of the most common serious drug-related TEAEs (the events included in the table, which occurred in at least 1% of patients), rather than the total number of patients who experienced any serious TEAE.

Additionally, in drug labeling, FDA reports all serious TEAEs regardless of attribution to drug, given that causality is difficult to establish in a single-arm trial. Serious adverse reactions occurred in 58 (46%) of patients in EV-201, which is conveyed in the package insert and noted by the applicant in table 75.

The most common (≥3%) serious adverse TEAEs were urinary tract infection (6%), cellulitis (5%), febrile neutropenia (4%), diarrhea (4%), sepsis (3%), and acute kidney injury (3%). See table below.

Table 77: Treatment-emergent Serious Adverse Events, Any Grade (≥ 2%), by Preferred Term

	EV-201 Cohort 1 N=125		All 1.25 mg/kg N=310	
	N	%	N	%
Any Serious TEAE	**58**	**46%**	**129**	**42%**
Urinary tract infection[a]	7	6%	16	5%
Cellulitis	6	5%	7	2%
Diarrhea[b]	5	4%	9	3%
Febrile neutropenia	5	4%	6	2%
Sepsis	4	3%	12	4%
Acute kidney injury	4	3%	11	4%

	EV-201 Cohort 1 N=125		All 1.25 mg/kg N=310	
	N	%	N	%
Dyspnea	4	3%	7	2%
Pneumonia/lung infection	3	2%	10	3%
Nausea/vomiting	3	2%	8	3%
Rash[c]	3	2%	8	3%
Fatigue/asthenia	3	2%	5	2%
Abdominal pain	3	2%	7	2%
Hyperglycemia/DKA	2	2%	8	3%

Note: italicized terms are grouped terms. Abbreviations: DM, diabetes mellitus; DKA, diabetic ketoacidosis

[a]Includes: urinary tract infection, urinary tract infection bacterial, urinary tract infection pseudomonal, urinary tract infection staphylococcal
[b]Includes: colitis, diarrhea, enterocolitis
[c]Includes: dermatitis bullous, drug eruption, eczema, rash maculo-papular, rash vesicular, Stevens-Johnson syndrome (final diagnosis symmetrical drug-related intertriginous and flexural exanthema [SDRIFE]; see 8.2.5.1)

Dropouts and/or Discontinuations Due to Adverse Effects

Data:
TEAEs and drug-related TEAEs that led to treatment discontinuation in > 1 subject overall are presented here. Peripheral sensory neuropathy was the most common reason for discontinuation, and accounted for more than a third of all discontinuations.

In Study EV-201, 25 subjects (16.4%) experienced TEAEs that led to treatment discontinuation and 18 subjects (11.8%) experienced drug-related events that led to treatment discontinuation. The most common TEAE leading to treatment discontinuation in Cohort 1 was peripheral sensory neuropathy (8 subjects [6.4%]); which was considered drug-related in all cases. In Cohort 1, the median time from the first dose of study drug to treatment discontinuation due to a TEAE was 3.8 months (range, 0.3 to 12.2). In Cohort 2, the most common TEAE leading to treatment discontinuation was acute kidney injury (2 subjects [7.4%]); 1 of these events was considered drug-related. No other TEAE or drug-related TEAE led to treatment discontinuation in > 1 subject in either cohort. In Cohort 2, the median time from the first dose of study drug to treatment discontinuation due to a TEAE was 2.6 months (range, 1.3 to 5.0).

In the enfortumab vedotin 1.25 mg/kg safety analysis group, 60 subjects (19.4%) experienced TEAEs that led to treatment discontinuation and 33 subjects (10.6%) experienced drug-related events that led to treatment discontinuation. Consistent with the Study EV-201 data, the most

common TEAE leading to treatment discontinuation was peripheral sensory neuropathy (13 subjects [4.2%]). Other common TEAEs leading to treatment discontinuation were fatigue and sepsis (3 subjects each).

The Applicant's Position:

The overall incidence of TEAEs and drug-related TEAEs leading to treatment discontinuation was similar across the safety analysis groups and drug-related TEAEs were infrequent. The events and rates observed in EV-201 Cohort 1 are representative of the overall safety profile. Discontinuations due to drug-related TEAEs were infrequent with peripheral sensory neuropathy being the most common reason. These data indicate that enfortumab vedotin is tolerable.

The FDA's Assessment:

FDA generally agrees with the applicant's assessment. The similarity of TEAE incidence across safety analysis groups cannot be interpreted due to small numbers. FDA's independent assessment of safety including the 30-day safety update included 3 additional patients who discontinued enfortumab due to neuropathy. Discontinuations for grade 3 peripheral sensory neuropathy was required per protocol. The second most common reason for discontinuation was rash (see table below).

Table 78: Treatment-emergent Adverse Events Leading to Discontinuation In At Least 2 Patients, Any Grade, by Preferred Term

	EV-201 Cohort 1 N=125		Enfortumab vedotin All 1.25 mg/kg N=310	
	N	%	N	%
All Discontinuations	**20**	**16%**	**60**	**19%**
Neuropathy[a]	8	6%	14	5%
Rash[b]	2	2%	5	2%
Fatigue/asthenia	2	2%	4	1%
Bowel obstruction[c]	1	1%	3	1%
Hyperglycemia/DKA	1	1%	2	1%
Respiratory failure[d]	1	1%	3	1%
Dyspnea/hypoxia[e]	0	0	4	1%
Transaminitis[f]	0	0	3	4%

	EV-201 Cohort 1 N=125		Enfortumab vedotin All 1.25 mg/kg N=310	
	N	%	N	%
Hypercalcemia			2	0.4%

Note: italicized terms are grouped terms. Abbreviation: DKA, diabetic ketoacidosis

[a]Includes: peripheral sensory neuropathy, peripheral motor neuropathy
[b]Includes: dermatitis bullous, drug eruption, rash erythematous, rash maculo-papular, Stevens-Johnson syndrome (final diagnosis symmetrical drug-related intertriginous and flexural exanthema [SDRIFE]; see 8.2.5.1)
[c]Includes large intestinal obstruction, malignant bowel obstruction, small intestinal obstruction
[d]Includes: respiratory failure, acute respiratory failure
[e]Includes: dyspnea, dyspnea exertional, hypoxia
[f]Includes: aspartate aminotransferase increased, liver function test increased

Dose Interruption/Reduction Due to Adverse Effects

Data:
In Study EV-201 Cohort 1, 80 subjects (64.0%) experienced TEAEs that led to dose interruption, and 60 subjects (48.0%) experienced drug-related events that led to dose interruption. The TEAEs that led to dose interruption in ≥5% of subjects each in Cohort 1 or in Cohort 2 were peripheral sensory neuropathy and fatigue; most of these events were drug-related. Other common TEAEs that led to dose interruption in > 3 subjects in Cohort 1 were hyperglycemia, rash maculopapular, acute kidney injury, lipase increased and neutropenia. There were no other TEAEs leading to dose interruption reported in >1 subject in Cohort 2.

In the enfortumab vedotin 1.25 mg/kg safety analysis group, 187 subjects (60.3%) experienced TEAEs that led to dose interruption and 145 subjects (46.8%) experienced drug-related events that led to dose interruption. The most common TEAEs that led to dose interruption were consistent with Study EV-201 Cohort 1 including peripheral sensory neuropathy and fatigue.

In Study EV-201 overall, 50 subjects (32.9%) experienced a TEAE that led to dose reduction, and 47 subjects (30.9%) experienced drug-related events that led to dose reduction. TEAEs leading to dose reduction in ≥ 5% of subjects in either Cohort 1 or Cohort 2 were peripheral sensory neuropathy and rash maculo-papular; all events were drug-related. Other events leading to dose reduction in ≥2 subjects in Cohort 1 included fatigue, neutropenia, hyperuricemia, peripheral motor neuropathy, rash erythematous and weight decreased. There were no other TEAEs leading to dose reduction reported in > 1 subject in Cohort 2.

In the enfortumab vedotin 1.25 mg/kg safety analysis group, 98 subjects (31.6%) experienced TEAEs that led to dose reduction and 94 subjects (30.3%) experienced drug-related events that

led to dose reduction. The most common TEAEs leading to dose reduction were consistent with EV-201 Cohort 1 and included peripheral sensory neuropathy, fatigue and rash maculo-papular.

The Applicant's Position:

Most subjects received treatment as intended. Dose reductions were required due to TEAEs in approximately one-third of subjects and were used to manage toxicities, such as peripheral neuropathy and rash. The overall incidence of TEAEs and drug-related TEAEs leading to dose interruption or reduction in EV-201 Cohort 1 are representative of the overall safety profile. Differences in event rates of some common TEAEs that led to dose reduction and dose interruption in Study EV-201 Cohort 2 compared to the other groups are likely due to the smaller number of subjects enrolled in this cohort.

The FDA's Assessment:

FDA generally agrees with the applicant's assessment. Minor differences due to broader grouping of terms can be noted in the below table. For example, greater than 5% of patients in FDA's analysis of rash in Cohort 1 required dose interruption, which is more than the sponsor identified.

In labeling, the proportion of patients who required dose reduction is reported based on Cohort 1 only, which was 34%, rather than the 32.9% reported by the applicant above, reflecting dose reductions in Cohorts 1 and 2 combined.

Table 79: Treatment-emergent Adverse Events Leading to Dose Interruption or Reduction, Any Grade (≥2%), by Preferred Term

	EV-201, Cohort 1 (N=125)			
	Dose interruption		Dose reduction	
	N	%	N	%
Any TEAE	**80**	**64%**	**43**	**34%**
Neuropathy[a]	22	18%	15	12%
Rash[b]	11	9%	10	8%
Fatigue	7	6%	5	4%
Hyperglycemia	5	4%	8	3%
Neutropenia[c]	5	4%	4	3%
Amylase or lipase increased	5	4%	1	0.8%
Acute kidney injury	4	3%	0	0
Abdominal pain[d]	4	3%	0	0

	EV-201, Cohort 1 (N=125)			
	Dose interruption		Dose reduction	
	N	%	N	%
Transaminitis[e]	3	2%	1	0.8%
Anemia	3	2%	1	0.8%
Urinary tract infection	3	2%	0	0

[a]Includes peripheral sensory neuropathy, peripheral motor neuropathy, muscular weakness, hypoaesthesia, neuralgia
[b]Includes dermatitis exfoliative, pruritus, pruritus generalized, rash maculopapular, rash erythematous, rash generalized, rash papular, rash pruritic, rash pustular, rash vesicular skin exfoliation
[c]Includes neutropenia, febrile neutropenia
[d]Includes: abdominal pain, abdominal pain lower, abdominal pain upper
[e]Includes: alanine aminotransferase increased, aspartate aminotransferase increased

Significant Adverse Events

Data:

For the purposes of this section, severe TEAEs are considered to be significant. A total of 109 (71.7%) subjects in Study EV-201 overall experienced at least 1 ≥ Grade 3 TEAE (Table 80). The most common ≥ Grade 3 events (occurring in > 5% of subjects) reported in both Cohort 1 and Cohort 2 included anemia, neutropenia and fatigue. In Cohort 1, ≥ Grade 3 events of hyperglycemia and hyponatremia also occurred frequently. The incidence of ≥ Grade 3 TEAEs was generally similar across the safety analysis groups, and the events and rates observed in Study EV-201 Cohort 1 are representative of the overall safety profile.

Table 80: Treatment-emergent Adverse Events NCI-CTCAE ≥ Grade 3 (≥ 3% of Total Subjects[a]) by System Organ Class and Preferred Term

MedDRA (v20.0) System Organ Class Preferred term, n (%)	EV-201 Cohort 1 1.25 mg/kg (n = 125)	EV-201 Cohort 2 1.25 mg/kg (n = 27)	EV-201 All Cohorts 1.25 mg/kg (n = 152)	Enfortumab Vedotin 1.25 mg/kg (n = 310)	All Enfortumab Vedotin (n = 379)
Overall	**91 (72.8)**	**18 (66.7)**	**109 (71.7)**	**198 (63.9)**	**237 (62.5)**
Blood and Lymphatic System Disorders	**31 (24.8)**	**6 (22.2)**	**37 (24.3)**	**55 (17.7)**	**67 (17.7)**
Anemia	17 (13.6)	2 (7.4)	19 (12.5)	30 (9.7)	37 (9.8)
Neutropenia	11 (8.8)	4 (14.8)	15 (9.9)	21 (6.8)	22 (5.8)
General Disorders and Administration Site Conditions	**14 (11.2)**	**3 (11.1)**	**17 (11.2)**	**32 (10.3)**	**35 (9.2)**

MedDRA (v20.0) System Organ Class Preferred term, n (%)	**EV-201 Cohort 1 1.25 mg/kg (n = 125)**	**EV-201 Cohort 2 1.25 mg/kg (n = 27)**	**EV-201 All Cohorts 1.25 mg/kg (n = 152)**	**Enfortumab Vedotin 1.25 mg/kg (n = 310)**	**All Enfortumab Vedotin (n = 379)**
Fatigue	7 (5.6)	2 (7.4)	9 (5.9)	16 (5.2)	18 (4.7)
Infections and Infestations	**22 (17.6)**	**4 (14.8)**	**26 (17.1)**	**53 (17.1)**	**68 (17.9)**
Urinary tract infections	6 (4.8)	2 (7.4)	8 (5.3)	16 (5.2)	20 (5.3)
Sepsis	4 (3.2)	1 (3.7)	5 (3.3)	12 (3.9)	15 (4.0)
Metabolism and Nutrition Disorders	**30 (24.0)**	**6 (22.2)**	**36 (23.7)**	**65 (21.0)**	**83 (21.9)**
Hyperglycemia	9 (7.2)	1 (3.7)	10 (6.6)	19 (6.1)	24 (6.3)
Hyponatremia	7 (5.6)	1 (3.7)	8 (5.3)	19 (6.1)	20 (5.3)
Hypophosphatemia	4 (3.2)	1 (3.7)	5 (3.3)	10 (3.2)	15 (4.0)
Renal and Urinary Disorders	**10 (8.0)**	**3 (11.1)**	**13 (8.6)**	**19 (6.1)**	**27 (7.1)**
Acute kidney injury	4 (3.2)	2 (7.4)	6 (3.9)	8 (2.6)	12 (3.2)
Skin and Subcutaneous Tissue Disorders	**16 (12.8)**	**4 (14.8)**	**20 (13.2)**	**32 (10.3)**	**34 (9.0)**
Rash maculo-papular	5 (4.0)	1 (3.7)	6 (3.9)	10 (3.2)	12 (3.2)

Events are sorted in alphabetical order by system organ class and descending order by the number of subjects in the all enfortumab vedotin group by preferred term.

NCI-CTCAE: National Cancer Institute-Common Terminology Criteria for Adverse Events.

a All table cutoff values are referenced to the all enfortumab vedotin group.

The Applicant's Position:

Anemia and neutropenia were among the more frequent severe TEAEs. These events are discussed in more detail in Sections 8.2.5.6 and 8.2.5.7. Severe hyperglycemia was also frequently observed. Hyperglycemia events are discussed in more detail in Section 8.2.5.3.

Of the other frequently observed severe TEAEs, fatigue is common in the general cancer population and hyponatremia is a well-described metabolic complication in subjects with urinary diversions. Few serious cases of either of these events occurred in the safety analysis groups.

In addition, the sponsor considers the identified risks of rash, peripheral neuropathy, extravasation site reactions, nausea, vomiting, and diarrhea to be causally associated with enfortumab vedotin and significant as described in Sections 8.2.5.1, 8.2.5.2, 8.2.5.4, and 8.2.5.9.

The FDA's Assessment:

The applicant defined "significant adverse events" as "any grade 3-5 TEAE." FDA's independent

analyses agree with the applicant's numbers in the above table. FDA's approach is to separate grade 3-4 from grade 5 TEAEs in labeling. Please see analysis of grade 3-4 events below and separate analyses of deaths above.

Treatment Emergent Adverse Events and Adverse Reactions

Data:
All 152 subjects in Study EV-201 experienced at least one TEAE. The most common events (occurring in ≥ 30% of subjects) reported in both Cohort 1 and Cohort 2 included fatigue, alopecia, anemia, and diarrhea. Other common events occurring in Cohort 1 included decreased appetite, nausea, peripheral sensory neuropathy, dysgeusia, and weight decreased. Other common events occurring in Cohort 2 only included dry eye and edema peripheral.

Nearly all subjects (99.7%) in the enfortumab vedotin 1.25 mg/kg safety analysis group experienced at least 1 TEAE. Consistent with the EV-201 data, the most common events were fatigue, decreased appetite, alopecia, nausea, diarrhea, dysgeusia and peripheral sensory neuropathy.

TEAEs that have been determined by the sponsor to be associated with enfortumab vedotin, based on the totality of the data, are considered to be adverse drug reactions (ADRs). The identified ADRs are: nausea, diarrhea, vomiting, fatigue, decreased appetite, dysgeusia, alopecia, dry skin, pruritus, peripheral neuropathy, rash and extravasation site reactions.

The Applicant's Position:
The overall incidence of TEAEs was similar across these safety analysis groups, and the events and rates observed in EV-201 Cohort 1 are representative of the overall safety profile. Differences were observed between Cohort 1 and 2, however these are likely due to small sample size and baseline characteristics.

Overall, enfortumab vedotin has a manageable safety profile in adult subjects with locally advanced or metastatic UC.

The FDA's Assessment:
FDA's independent analyses generally agree with the applicant's assessment. Below are the most common grade 3-4 treatment-emergent adverse events (TEAEs) identified in FDA's analysis of the 90-day safety update. Anemia, neutropenia, hyperglycemia, and fatigue were still among the most common grade 3-4 TEAEs in FDA's analysis, but the incidence is higher compared to the applicant's table above because the FDA's analysis uses pooled terms whereas the applicant's analysis reflects single preferred terms (PTs). For the same reason, diarrhea and peripheral neuropathy not included in the applicant's table but they are among the most common grade 3-4 TEAEs when including closely related terms.

Table 82. Treatment-emergent Adverse Events, Any Grade, 3 (≥ 10% of Patients) by System Organ Class and Preferred Term

	Cohort 1, N=125		All 1.25 mg/kg, N=310	
	N	%	N	%
Any grade TEAE	125	100%	309	100%
General disorders and administration site conditions				
Fatigue/asthenia	70	56%	171	55%
Peripheral edema[a]	30	24%	65	21%
Dizziness	20	16%	43	14%
Pyrexia	17	14%	45	15%
Nervous system disorders				
Peripheral neuropathy[b]	70	56%	151	49%
Dysgeusia	52	42%	119	38%
Insomnia	17	14%	42	14%
Metabolism and nutrition disorders				
Decreased appetite	65	52%	150	48%
Weight loss[c]	41	33%	85	27%
Hyperglycemia/DM/DKA	20	16%	46	15%
Skin and subcutaneous tissue disorders				
Rash[d]	65	52%	166	54%
Alopecia	63	50%	147	47%
Pruritus[e]	33	26%	94	30%
Dry skin	33	26%	77	25%
Gastrointestinal disorders				
Nausea	56	45%	128	41%
Diarrhea[f]	52	42%	123	40%
Vomiting	23	18%	71	23%
Abdominal pain[g]	30	24%	70	23%
Constipation	35	28%	84	27%
Eye disorders				
Dry eye[h]	50	40%	112	36%
Vision blurred[i]	20	16%	42	14%
Blood and lymphatic system disorders				

See next page

	Cohort 1, N=125		All 1.25 mg/kg, N=310	
	N	%	N	%
Anemia/iron deficiency anemia	39	31%	87	28%
Neutropenia[j]	21	17%	41	13%
Respiratory, thoracic, and mediastinal disorders				
Cough[k]	24	19%	51	16%
Dyspnea	20	16%	50	16%
Infections and infestations				
Urinary tract infection[l]	23	18%	69	21%
Investigations				
Abnormal liver tests[m]	21	17%	76	25%
Amylase or lipase increased	20	16%	not evaluated	
Hyponatremia	17	14%	39	13%
Hypokalemia	16	13%	38	12%
Hypophosphatemia	8	6%	34	11%
Musculoskeletal and connective tissue disorders				
Back pain	20	16%	42	14%
Arthralgia	10	8%	35	11%
Renal and urinary disorders				
Acute kidney injury[n]	17	14%	50	16%
Hematuria	12	10%	34	11%

Note: italicized terms are grouped terms. Abbreviations: DM, diabetes mellitus; DKA, diabetic ketoacidosis

[a]Includes: peripheral edema, lymphedema, genital swelling, peripheral swelling, swelling
[b]Includes: hypoesthesia, gait disturbance, muscular weakness, neuralgia, paresthesia, peripheral motor neuropathy, peripheral sensory neuropathy and peripheral sensorimotor neuropathy
[c]Includes: weight decreased, abnormal loss of weight, failure to thrive, adult failure to thrive
[d]Includes: dermatitis acneiform, dermatitis bullous, dermatitis contact, dermatitis exfoliative, drug eruption, eczema, erythema, erythema multiforme, exfoliative rash, palmar-plantar erythrodysesthesia syndrome, photosensitivity reaction, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pustular, rash pruritic, rash vesicular, skin exfoliation, stasis dermatitis, Stevens-Johnson syndrome (final diagnosis symmetrical drug-related intertriginous and flexural exanthema [SDRIFE]; see 8.2.5.1), urticaria
[e]Includes: pruritus and pruritus generalized
[f]Includes: colitis, diarrhea, enterocolitis, autoimmune colitis, Clostridium difficile colitis
[g]Includes: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper
[h]Includes: blepharitis, conjunctivitis, dry eye, eye irritation, keratitis, keratopathy, lacrimation increased, limbal stem cell deficiency, Meibomian gland dysfunction, ocular discomfort, punctate keratitis, tear break up time decreased
[i]Includes: vision blurred, visual acuity reduced, visual impairment

[j]Includes: neutropenia, febrile neutropenia, neutrophil count decreased
[k]Includes: cough, productive cough
[l]Includes urinary tract infection, Escherichia urinary tract infection, Urinary tract infection bacterial, Urinary tract infection enterococcal, Urinary tract infection pseudomonal, Urinary tract infection staphylococcal
[m]Includes aspartate aminotransferase increased, alanine aminotransferase increased, liver function test abnormal, liver function test increased, gamma-glutamyltransferase increased, transaminases increased
[n]Includes: acute kidney injury, blood creatinine increased, creatinine renal clearance decreased

Table 81: Treatment-emergent Adverse Events, Grade 3-4 (≥ 2%), by Preferred Term

	Cohort 1, N=125		All 1.25 mg/kg, N=310	
	N	**%**	**N**	**%**
Any grade 3-4 TEAE	**85**	**68%**	**179**	**58%**
Blood and lymphatic system disorders				
Anemia	17	14%	30	10%
Neutropenia[a]	17	14%	31	10%
Skin and subcutaneous tissue disorders				
Rash[b]	15	12%	30	10%
Metabolism and nutrition disorders				
Hyperglycemia/DM/DKA	10	8%	19	6%
Decreased appetite	3	2%	8	3%
General disorders and administration site conditions				
Fatigue/asthenia	8	6%	19	6%
Gastrointestinal disorders				
Diarrhea[c]	8	6%	15	5%
Nausea	4	3%	9	3%
Abdominal pain[d]	4	3%	7	2%
Vomiting	3	2%	7	2%
Investigations				
Amylase/lipase increased	7	6%	not evaluated	
Abnormal liver tests[e]	4	3%	8	3%
Infections and infestations				
Urinary tract infection[f]	6	5%	19	6%
Cellulitis/skin infection	5	4%	7	2%

	Cohort 1, N=125		All 1.25 mg/kg, N=310	
	N	%	N	%
Pneumonia/lung infection	3	2%	12	4%
Sepsis	3	2%	9	3%
Nervous system disorders				
Neuropathy[g]	5	4%	7	2%
Renal and urinary disorders				
Acute kidney injury[h]	4	3%	9	3%

Note: italicized terms are grouped terms. Abbreviations: DM, diabetes mellitus; DKA, diabetic ketoacidosis

[a]Includes: neutropenia, febrile neutropenia, neutrophil count decreased
[b]Includes: dermatitis bullous, dermatitis exfoliative, drug eruption, eczema, palmar-plantar erythrodysesthesia syndrome, rash erythematous, rash generalized, rash maculo-papular, rash pustular, rash vesicular, skin exfoliation, Stevens-Johnson syndrome (final diagnosis symmetrical drug-related intertriginous and flexural exanthema (SDRIFE); see 8.2.5.1)
[c]Includes: colitis, diarrhea, enterocolitis, autoimmune colitis, Clostridium difficile colitis
[d]Includes: abdominal pain, abdominal pain lower, abdominal pain upper
[e]Includes: aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased
[f]Includes: urinary tract infection, Urinary tract infection bacterial, Urinary tract infection pseudomonal
[g]Includes: hypoesthesia, muscular weakness, peripheral motor neuropathy, peripheral sensory neuropathy
[h]Includes: acute kidney injury, blood creatinine increased, creatinine renal clearance decreased

Laboratory Findings

Data:

Treatment-emergent hematology laboratory abnormalities:

Anemia and neutropenia are potential risks associated with enfortumab vedotin and details of these TEAEs are discussed in Sections 8.2.5.6 and 8.2.5.7. Laboratory data inherent to these TEAEs are discussed here with focus on the pivotal study data.

In EV-201, treatment-emergent hematology laboratory abnormalities were predominately Grades 1–2. In Cohort 1, low hemoglobin and low lymphocytes were the only Grade 3 abnormalities reported for >5% of subjects (12 subjects [10%] and 10 subjects [8%], respectively). The only Grade 4 hematology laboratory abnormalities were low lymphocytes in 2 subjects (2%) and low neutrophils in 1 subject (1%). In addition, the number of subjects who experienced shifts to Grade 3 or 4 in hematology laboratory parameters from baseline to postbaseline study visit was low. Similar patterns were observed in Cohort 2 and in the enfortumab vedotin 1.25 mg/kg group.

Treatment emergent chemistry laboratory abnormalities:
The number of subjects who experienced shifts in chemistry laboratory parameters to Grade 3 or 4 at any postbaseline study visit are summarized for each parameter collected. Of note, fasting glucose was not required for the clinical studies; therefore, treatment-emergent Grade 1 to 2 hyperglycemia, based on laboratory values (glucose-high), could not be determined.

In Study EV-201 Cohort 1, Grade 3 or 4 chemistry abnormalities reported for > 5% of subjects were low phosphate, high glucose, high lipase, low sodium and high urate. In Cohort 2, Grade 3 or 4 chemistry abnormalities reported for > 5% of subjects were low sodium, high urate, high glucose, and low phosphate.

In the enfortumab vedotin 1.25 mg/kg group, rates were similar to EV-201 Cohort 1. Grade 3 or 4 chemistry abnormalities reported for > 5% of subjects were low phosphate, low sodium, high glucose, and high urate.

Amylase and lipase were routinely measured only in study EV-201 and elevated lipase and amylase were infrequently observed, most were asymptomatic. There were no reported cases of treatment-emergent pancreatitis in Study EV-201 and the observed amylase and lipase elevations had no clinical sequelae; however, 1 subject in the Study EV-101 had an SAE of pancreatitis that was not considered drug-related and was attributed to underlying advanced malignancy involving the pancreas.

Overall, in the all enfortumab vedotin safety analysis group, 4 subjects (1.1%) experienced combined liver transaminase levels > 3 × ULN and total bilirubin > 2 × ULN (2 subjects in EV-101, 1 subject in EV-102, and 1 subject in EV-201 Cohort 1). None of the subjects with laboratory assessments meeting these laboratory criteria were considered to have drug-induced liver injury and alternative etiologies were identified in each case.

The Applicant's Position
Hematology laboratory abnormalities observed on trial were common as expected in this population; however, the number of subjects who experienced shifts to Grade 3 or 4 in hematology laboratory parameters from baseline to postbaseline study visits was low. Anemia and neutropenia are potential risks associated with enfortumab vedotin and details of these TEAEs are discussed in Sections 8.2.5.6 and 8.2.5.7.

Chemistry laboratory abnormalities observed on trial were common. The majority of subjects had some degree of renal insufficiency; therefore, shifts in laboratory parameters, such as low phosphate and sodium and high urate are likely a result of underlying disease. Elevated glucose was frequently observed but fasting for laboratories was not required per protocol.

Hyperglycemia is an AEOI and is discussed in detail in Section 8.2.5.3.

Overall, enfortumab vedotin is not considered to have clinically meaningful adverse effects on hepatic liver function or a potential for drug-induced liver injury.

The FDA's Assessment:

FDA agrees that chemistry laboratory abnormalities observed on trial were common. The most common treatment-emergent laboratory (grade 1-4) abnormality was elevated AST (see table below): 65% in Cohort 1 and 61% of all those who received 1.25 mg/kg. Elevated ALT and decreased albumin were also common. However, most of these were grades 1-2. Less than 3% were grades 3-4.

In FDA labeling, only grade 2-4 laboratory abnormalities were included. Since this patient population has received prior chemotherapy and immunotherapy, laboratory abnormalities are expected. Many grade 1 laboratory abnormalities are not clinically relevant. For the same reason, only the more common laboratory abnormalities (grade 2-4 in at least 10% of patients, or grade 3-4 in at least 5% of patients) were included in the label. The bolded rows in the table below are the laboratory abnormalities included in the label. See Appendix for analysis of grade 2-4 laboratory abnormalities occurring in 5% or more of patients.

Table 84. Laboratory Abnormalities Reported in ≥ 25% of Patients

	Cohort 1, N=125		All 1.25 mg/kg, N=310	
	N	%	N	%
AST increased	78	65%	185	61%
Glucose increased*	**68**	**56%**	**166**	**55%**
Lymphocytes decreased	**55**	**45%**	**102**	**34%**
Sodium decreased	**53**	**43%**	**123**	**40%**
Hemoglobin decreased	**51**	**42%**	**129**	**42%**
Creatinine increased	**46**	**38%**	**95**	**31%**
Albumin decreased	38	31%	98	32%
ALT increased	34	28%	105	34%
Leukocytes decreased	**33**	**27%**	**110**	**36%**
Urate increased	**32**	**27%**	**79**	**27%**
Phosphate decreased	**30**	**25%**	**88**	**29%**

**not fasting*

Table 85. Grade 3-4 Laboratory Abnormalities Reported in ≥ 2% of Patients

	Cohort 1, N=125		All 1.25 mg/kg, N=310	
	N	%	N	%
Lymphocytes decreased	12	10%	37	12%
Phosphate decreased	12	10%	31	10%
Hemoglobin decreased	12	10%	24	8%
Lipase increased	11	9%	not evaluated	
Glucose increased	10	8%	25	8%
Sodium decreased	10	8%	29	10%
Urate increased	8	7%	23	8%
Neutrophils decreased	6	5%	18	6%
Leukocytes decreased	5	4%	9	3%

Note that magnesium was only monitored in EV-101 and not in EV-201. The rates of all grade and ≥ grade 3 hypermagnesemia were 5% (8/160) and 0.6% (1/160), respectively.

FDA sent an information request questioning the etiology of the hypophosphatemia. The applicant reiterated that hypophosphatemia is a relatively common laboratory abnormality and is often an incidental finding [Imel, 2012]. The applicant noted that the rate of hypophosphatemia was comparable to pembrolizumab (14%, grades 3-4) as previously published in KEYNOTE-045.

An accurate summary of the proportion of patients requiring phosphate supplementation cannot be estimated because of lack of complete concomitant medication usage data. Only EV-201 differentiated between previous and concomitant medications. Of the 156 patients enrolled in EV-201, 13 patients required phosphate supplementation. These 13 patients were all treated in 7 sites representing a total of 34 (22%) patients of EV-201 enrollment, which suggests that the proportion of patients requiring phosphate supplementation may have been as high as 38% (13 of 34). Lack of documentation is suspected because 3 of the 4 highest-enrolling sites did not report any phosphate supplementation, which accounted for 40 patients (26%) of EV-201.

FDA also sent an information request questioning the need to monitor lipase. The applicant responded that there were no reported AEs of pancreatitis in EV-201. Two patients in EV-201 Cohort 2 reported PTs of lipase increase." Both patients had elevated lipase at baseline and one experienced a complicated clinical course with infections of their ileal conduit, bacteremia, and Klebsiella pneumonia requiring antibiotic therapy. Neither reported any clinical sequelae from

their hyperlipasemia. The applicant does not recommend routine lipase monitoring for patients. Based on review of this information, FDA agrees.

Vital Signs

Data:
Vital sign measurements, including heart rate, diastolic and systolic blood pressure, and temperature, were listed by subject and visit. Routine vital signs data were collected and presented by subject. Any clinically significant changes were captured as AEs.

The Applicant's Position:
Enfortumab vedotin did not appear to have clinically meaningful adverse effects on subject vital signs during any clinical study.

The FDA's Assessment:
FDA agrees with the applicant's assessment.

Electrocardiograms (ECGs)

Data:
In Study EV-201, ECGs were conducted at baseline and at the EOT visit. Additional ECGs were conducted if clinically indicated. Routine 12-lead ECGs were performed after the subject had been in a supine position for at least 5 minutes. The ECG assessments were performed prior to obtaining the pharmacokinetic and biomarker samples when possible. ECG status (normal, abnormal clinically significant, or abnormal not clinically significant) was summarized for each scheduled and unscheduled ECG, and shifts from baseline were tabulated. In Study EV-101 and EV-102 measurements were taken more frequently (at Screening, Day 1, Day 3 (Study EV-102 only), Day 15 (Study EV-102 only], Day 17 (Study EV-102 only) and at the safety follow-up visit).

Abnormal/clinically significant ECG interpretations by the investigator were reported in Study EV-201 Cohort 1 at baseline in 1 out of 125 subjects (0.8%). No subjects in Study EV-201 Cohort 2 had abnormal/clinically significant ECG interpretations reported at baseline.

No subjects in Study EV-201 Cohort 1 had abnormal/clinically significant ECG interpretations reported postbaseline. A postbaseline clinically significant ECG interpretation by the investigator in Study EV-201 Cohort 2 was reported at EOT/safety follow-up in 1 subject. This subject was a 49-year old female who had prolonged QT that was non-serious and not considered related to study drug. The event occurred coincident with Grade 3 hypokalemia (also non-serious). All other assessments at EOT/safety follow-up were interpreted as normal.

Clinically significant ECG interpretations by the investigator were reported in the enfortumab vedotin 1.25 mg/kg group at baseline in 2 subjects (0.6%). Postbaseline clinically significant ECG interpretations by the investigator were reported at EOT/safety follow-up in 1 subject (0.7%); the subject in Cohort 2, described above.

The Applicant's Position:
Overall, the incidence of changes in 12-lead ECGs was low and similar across the safety analysis groups.

The FDA's Assessment:
FDA agrees with the applicant's assessment. The molecular size of enfortumab vedotin suggests a low likelihood of direct interaction with cardiac ion channels.

QT

Data:
Study EV-102 evaluated the effect of enfortumab vedotin on the duration of cardiac ventricular repolarization. This analysis was conducted on the ECG data from 17 subjects with locally advanced or metastatic UC, and reported in (Study 7465-PK-0001). The purpose of this analysis was to characterize the relationship between ADC and MMAE concentrations and QTcF and to assess the potential for QT prolongation.

The relationship between ADC and MMAE concentrations and change in QTcF intervals from baseline (ΔQTcF) was explored using linear effect mixed effect models after enfortumab vedotin intravenous infusion. The slope estimates were determined to be 0.143 msec/(µg/mL) with 90% CI (CI; -0.300, 0.587) for ADC and -2.40 msec/(ng/mL) with 90% CI (-6.28, 1.48) for MMAE. Because the 90% CIs of the slope estimates included zero, the results suggest that changes from baseline QTcF interval were independent of ADC or MMAE concentration over the observed range in subjects who received enfortumab vedotin. Enfortumab vedotin does not appear to have adverse effects on ventricular repolarization and does not result in a clinically meaningful prolongation of the QTc interval.

The Applicant's Position:
At the recommended dose of 1.25 mg/kg, enfortumab vedotin had no large QTc prolongation, (>20 msec).

The FDA's Assessment:
The Division of Cardiovascular and Renal Products QT Interdisciplinary Review Team reviewed the data. FDA agrees with the applicant's assessment.

Immunogenicity

Data:
There is potential for an immunogenic response with any antibody therapy. Please see Section 8.2.5.12, Antitherapeutic antibodies for further details. In the overall integrated safety population, 4 subjects were found to be transiently positive for ATA and 1 subject was found to be persistently positive for ATA. None of these subjects experienced IRRs and the TEAEs that were reported were consistent with the overall safety profile.

The Applicant's Position:
Immunogenicity associated with enfortumab vedotin is infrequent. Based on the available data, there is no indication of a safety risk associated with immunogenicity (Section 8.2.5.12).

The FDA's Assessment:
FDA agrees with the applicant's assessment.

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1. Rash

Data:
Nectin-4 is expressed in the skin, and rash events are commonly associated with enfortumab vedotin treatment. The most common TEAEs were maculo-papular rash, stomatitis, and erythematous rash (Table 82). In Study EV-201 overall, study drug was reduced in 10 subjects (6.6%), interrupted in 13 subjects (8.6%), and discontinued in 2 subjects due to rash (drug eruption and Steven-Johnson syndrome, both Cohort 1).

For both cohorts, the majority of treatment-emergent rash events occurred within the first treatment cycle. The majority of events in both cohorts were considered related to study treatment and were Grade 1 or 2 in severity. Of the 64 subjects in Cohort 1 who experienced rash, 46 (72%) had complete resolution of all events and an additional 14 subjects (22%) had some resolution or improvement as of last study follow-up. The median time to resolution for both cohorts was < 1 month. Thus, the majority of rash events did not require dose modifications and most subject were able to continue treatment despite experiencing rash.

In the enfortumab vedotin 1.25 mg/kg group, the rates of rash treatment-emergent events were similar to EV-201 with 52.6% experiencing any rash event, and the most common event being rash maculo-papular. The majority of events were considered related to study treatment and were Grade 1 or 2 in severity.

The incidence and severity of rash was similar across safety analysis groups.

Table 82: Overview of Rash Treatment-emergent Adverse Events – Integrated Safety Populations

MedDRA (v20.0) Category, n (%)	EV-201 Cohort 1 1.25 mg/kg (n = 125)	EV-201 Cohort 2 1.25 mg/kg (n = 27)	EV-201 All Cohorts 1.25 mg/kg (n = 152)	Enfortumab Vedotin 1.25 mg/kg (n = 310)	All Enfortumab Vedotin (n = 379)
Any rashes or SCAR events	**64 (51.2)**	**17 (63.0)**	**81 (53.3)**	**163 (52.6)**	**192 (50.7)**
Any rashes	**59 (47.2)**	**17 (63.0)**	**76 (50.0)**	**149 (48.1)**	**172 (45.4)**
Any SCAR	**32 (25.6)**	**4 (14.8)**	**36 (23.7)**	**67 (21.6)**	**82 (21.6)**
TEAE by PT (≥ 5%†)					
Rash maculo-papular	28 (22.4)	8 (29.6)	36 (23.7)	79 (25.5)	87 (23.0)
Stomatitis	10 (8.0)	0	10 (6.6)	21 (6.8)	28 (7.4)
Rash erythematous	15 (12.0)	2 (7.4)	17 (11.2)	22 (7.1)	23 (6.1)
Rash	1 (0.8)	0	1 (0.7)	13 (4.2)	22 (5.8)
Skin exfoliation	7 (5.6)	2 (7.4)	9 (5.9)	16 (5.2)	21 (5.5)
Serious rashes or SCAR events	**4 (3.2)**	**1 (3.7)**	**5 (3.3)**	**9 (2.9)**	**9 (2.4)**
Rashes or SCAR events leading to withdrawal of study drug	**2 (1.6)**	**0**	**2 (1.3)**	**5 (1.6)**	**5 (1.3)**

† All table cutoff values are referenced to the all enfortumab vedotin group
Events are sorted by descending number of subjects in the "all enfortumab vedotin" group
Sources: ISS Supplemental Table 12.6.1.5.3.1 to 12.6.1.5.3.6

One serious rash event was reported as Stevens-Johnson Syndrome. Complete details of the reported event are provided in the narratives for EV-201. This case was reviewed by 3 independent, consulting dermatologists (reports included with the narrative). Based on these expert evaluations, the sponsor concluded that the details of this case were most consistent with a primarily intertriginous drug eruption (symmetrical drug-related intertriginous and flexural exanthema) or a variant of toxic erythema of chemotherapy.

The Applicant's Position:

The majority of rash events were low grade, did not require dose modifications and most subjects were able to continue treatment despite experiencing rash. The majority of subjects who experienced rash had complete resolution of all events.

The FDA's Assessment:

FDA generally agrees with the applicant's assessment. The minor disagreements listed below did not meaningfully impact the overall clinical assessment.

FDA's grouped term of "rash" included dermatitis acneiform; dermatitis bullous; dermatitis

contact; dermatitis exfoliative; erythema; erythema multiforme; exfoliative rash; palmar-plantar erythrodysaesthesia syndrome; photosensitivity reaction; rash; rash erythematous; rash generalised; rash macular; rash maculo-papular; rash papular; rash pruritic; rash pustular; rash vesicular; skin exfoliation; stasis dermatitis; Stevens-Johnson syndrome; urticaria. The underlined terms are Preferred Terms not included in the applicant's pooled term of "rash." The applicant included 4 Preferred Terms that the FDA excluded from its grouped term of "rash": blister, blood blister, conjunctivitis, and intertrigo. FDA's definition resulted in an increase in all-grade rash in from 51 to 52% and in grade 3-4 rash from 12 to 13% in Cohort 1. Most events occurred during cycle 1.

Twenty-six percent (26%) of patients had maculopapular rash and 30% had pruritus. Grade 3-4 skin reactions occurred in 10% of patients and included symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), bullous dermatitis, exfoliative dermatitis, and palmar-plantar erythrodysesthesia.

The final assessment of the event that was reported as Stevens-Johnson Syndrome (SJS), according to the consulting dermatologists, was symmetrical drug-related intertriginous and flexural exanthema (SDRIFE). The key reasons for this conclusion include 1) absence of mucosal involvement in this patient; 2) biopsy showed "a vacuolar interface dermatitis with maturation disarray of keratinocytes and a sparse perivascular lympho-eosinophilic infiltrate, which was interpreted to be consistent with a drug eruption" rather than necrosis or apoptotic keratinocytes; and 3) clinical and histologic similarities in this case with other reported and unreported cases, which have not been thought to be consistent with SJS/toxic epidermal necrolysis. Therefore, the label does not include Stevens-Johnson syndrome. The consulting reports suggest that the skin reaction was a result of direct toxicity of nectin-4-directed MMAE. They note that Nectin-4 expression in the skin may contribute to the cutaneous toxicity, but that rash is a common adverse reaction involving other antibody-drug conjugates that incorporate MMAE, occurring in 31% of patients treated with brentuximab vedotin [USPI, cHL], 44% of patients treated with glemutumumab vedotin [Ott, 2019], and 13-31% of patients treated with polatuzumab vedotin, suggesting that MMAE may also have a role in skin reactions.

The protocol did not specify supportive care measures to manage skin reactions. It stated: "Topical corticosteroids have been used along with antihistamines for pruritus as needed."

The Enfortumab Vedotin USPI includes Skin Reactions as a Warning and Precaution, and includes general instructions for managing skin reactions, including the use of topical corticosteroids and antihistamines.

8.2.5.2. Peripheral Neuropathy

Data:
Peripheral neuropathy is often associated with drugs that affect microtubules and is associated with other MMAE ADCs [Donaghy, 2016]. Overall, peripheral neuropathy occurred commonly, at low grades with no ≥ Grade 4 events (Table 83). Events were predominantly sensory in nature and were manageable with dose modifications. Subjects with baseline peripheral neuropathy had a similar rate of treatment-emergent peripheral neuropathy as subjects without prior history. In Cohort 1, peripheral neuropathy events resulted in dose reductions for 15 subjects (12%) and dose interruptions for 22 subjects (18%). With a shorter duration of treatment on Cohort 2, dose modifications were not observed. In both cohorts, treatment discontinuations were observed in ~6% of subjects.

For both cohorts, the majority of treatment-emergent events occurred within the first 4 months of starting treatment. Of the 70 Cohort 1 subjects who experienced any event of peripheral neuropathy, 14 (20%) had complete resolution of all events and an additional 19 subjects (27%) had some resolution or improvement. At the time of this analysis, subjects in Cohort 2 had shorter treatment duration, which allowed observation of time to onset but not resolution.

In the enfortumab vedotin 1.25 mg/kg group, the rates of treatment-emergent events were similar to EV-201, with 49% experiencing any peripheral neuropathy event. The most common event was peripheral sensory neuropathy. Most events were Grade 1 or 2; there were no ≥ Grade 4 events and the majority were considered related to study treatment. SAEs of peripheral neuropathy were infrequent. The study drug was discontinued in 14 subjects (4.5%), reduced in 34 subjects (11%) and interrupted in 42 subjects (13.5%).

The incidence and severity of peripheral neuropathy was similar across the safety analysis groups.

Table 83: Overview of Peripheral Neuropathy Treatment-emergent Adverse Events – Integrated Safety Populations

MedDRA (v20.0) Category, n (%)	EV-201 Cohort 1 1.25 mg/kg (n = 125)	EV-201 Cohort 2 1.25 mg/kg (n = 27)	EV-201 All Cohorts 1.25 mg/kg (n = 152)	Enfortumab Vedotin 1.25 mg/kg (n = 310)	All Enfortumab Vedotin (n = 379)
Any peripheral neuropathy event	**70 (56.0)**	**11 (40.7)**	**81 (53.3)**	**152 (49.0)**	**182 (48.0)**
TEAE by PT (≥ 5%†)					
Peripheral sensory neuropathy	54 (43.2)	7 (25.9)	61 (40.1)	117 (37.7)	134 (35.4)
Grade 1	22.1 (17.6)	5 (18.5)	27 (17.8)	49 (15.8)	60 (15.8)
Grade 2	30 (24.0)	2 (7.4)	32 (21.1)	65 (21.0)	71 (18.7)
Grade 3	2 (1.6)	0	2 (1.3)	3 (1.0)	3 (0.8)
Muscular weakness	12 (9.6)	2 (7.4)	14 (9.2)	28 (9.0)	29 (7.7)

Grade 1	6 (4.8)	2 (7.4)	8 (5.3)	21 (6.8)	22 (5.8)
Grade 2	5 (4.0)	0	5 (3.3)	6 (1.9)	6 (1.6)
Grade 3	1 (0.8)	0	1 (0.7)	1 (0.3)	1 (0.3)
Gait disturbance	8 (6.4)	2 (7.4)	10 (6.6)	20 (6.5)	21 (5.5)
Grade 1	5 (4.0)	2 (7.4)	7 (4.6)	15 (4.8)	16 (4.2)
Grade 2	3 (2.4)	0	3 (2.0)	5 (1.6)	5 (1.3)
Serious TEAE	**1 (0.8)**	**1 (3.7)**	**2 (1.3)**	**2 (0.6)**	**2 (0.5)**
TEAE leading to withdrawal of study drug	**8 (6.4)**	**1 (3.7)**	**9 (5.9)**	**14 (4.5)**	**16 (4.2)**

Subjects are counted once under maximum NCI-CTCAE grade. Highest non-missing grade is considered as the maximum NCI-CTCAE grade. A missing NCI-CTCAE grade is considered the maximum NCI-CTCAE grade when all grades for the subject are missing.

Events are sorted by descending number of subjects in the "all enfortumab vedotin" group.

Drug-related treatment-emergent adverse events have a reasonable possibility that the event may have been caused by the study drug as assessed by the investigator. If relationship was missing, then it was considered drug-related.

NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; PT: preferred term; TEAE: treatment-emergent adverse event.

†All table cutoff values are referenced to the all enfortumab vedotin group.

Sources: ISS Supplemental Table 12.6.1.5.1.1 to 12.6.1.5.1.6

The Applicant's Position:

Peripheral neuropathy events were predominantly sensory in nature and were manageable with dose modifications. Though there were few treatment discontinuations, the most common TEAE overall leading to treatment discontinuation was peripheral sensory neuropathy. Subjects with baseline peripheral neuropathy had a similar rate of treatment-emergent peripheral neuropathy as subjects without prior history.

The FDA's Assessment:

The pooled definition of peripheral neuropathy was based on the SMQ. This reviewer notes that gait disturbance and muscular weakness are nonspecific terms which may emerge due to cancer cachexia or generalized illnesses rather than treatment-emergent toxicity to the peripheral nervous system. However, exclusion of gait disturbance and muscular weakness does not significantly impact the rates of pooled peripheral neuropathy: any grade neuropathy would decrease from 56% to 52%, and grade 3-4 neuropathy would decrease from 4% to 3%, because most of the gait disturbance events occurred in the patients who developed neuropathy. Since other reviews have used the SMQ strategy for defining peripheral neuropathy, we agree with using this pooled/grouped term. See polatuzumab vedotin review (June 2019).

The statement that there were no ≥ Grade 4 events is misleading because the protocol specified that grade 3 peripheral neuropathy should result in permanent discontinuation of drug. Any grade 4 events would have counted as protocol violations.

Peripheral neuropathy appears to be a cumulative exposure-related phenomenon. In EV-201, the median time to onset of any grade neuropathy was 2.4 months (range, <0.1 to 7.9) and to Grade ≥2 was 3.8 months (range, 0.6 to 9.2). No patients with grade ≥2 events experienced complete resolution of all neuropathy. Of the patients with grade 1 neuropathy, 11 patients experienced resolution. Six of the resolutions occurred after discontinuation of therapy, as late as two months later.

The Enfortumab Vedotin USPI includes Peripheral Neuropathy as a Warning and Precaution.

8.2.5.3. Hyperglycemia

Data:

Hyperglycemia occurred in ~15% of subjects treated with enfortumab vedotin. Most events were low grade (Grade 1 or 2 [58%]) with few SAEs (Table 84). There was a higher incidence of treatment-emergent hyperglycemia reported in obese subjects and subjects who had pre-existing hyperglycemia or diabetes. In Cohort 1, 104 subjects (83%) had a baseline body mass index (BMI) < 30 (non-obese) and 21 (17%) subjects had a baseline BMI ≥ 30 (obese). A higher percentage of obese subjects (33%) developed treatment-emergent hyperglycemia as compared to non-obese subjects (13%). In Cohort 2, all but 1 treated subject was non-obese; the 1 obese subject developed treatment-emergent hyperglycemia. The majority of events resolved and did not require long-term anti-hyperglycemic agents. Of the subjects who experienced hyperglycemia 75% (15/20) in Cohort 1 and 100% (all 4) of subjects in Cohort 2 had complete resolution or improvement. Of the 5 subjects in Cohort 1 with no resolution or improvement, 4 had pre-existing diabetes.

In the enfortumab vedotin 1.25 mg/kg group, the rates of treatment-emergent events of hyperglycemia were similar to EV-201. The majority of events were Grade 1 or 2 (58%) and were considered related to study treatment (58%). SAEs of hyperglycemia were infrequent. The study drug was discontinued in 2 subjects (0.6%) and interrupted in 10 subjects (3.2%).

The incidence and severity of hyperglycemia was similar across the safety analysis groups.

Table 84: Overview of Hyperglycemia Treatment-emergent Adverse Events – Integrated Safety Populations

MedDRA (v20.0) Category, n (%)	EV-201 Cohort 1 1.25 mg/kg (n = 125)	EV-201 Cohort 2 1.25 mg/kg (n = 27)	EV-201 All Cohorts 1.25 mg/kg (n = 152)	Enfortumab Vedotin 1.25 mg/kg (n = 310)	All Enfortumab Vedotin (n = 379)
Hyperglycemia event	**20 (16.0)**	**4 (14.8)**	**24 (15.8)**	**48 (15.5)**	**56 (14.8)**
Hyperglycemia	19 (15.2)	4 (14.8)	23 (15.1)	45 (14.5)	53 (14.0)
Grade 1	4 (3.2)	2 (7.4)	6 (3.9)	15 (4.8)	17 (4.5)
Grade 2	6 (4.8)	1 (3.7)	7 (4.6)	11 (3.5)	12 (3.2)

MedDRA (v20.0) Category, n (%)	EV-201 Cohort 1 1.25 mg/kg (n = 125)	EV-201 Cohort 2 1.25 mg/kg (n = 27)	EV-201 All Cohorts 1.25 mg/kg (n = 152)	Enfortumab Vedotin 1.25 mg/kg (n = 310)	All Enfortumab Vedotin (n = 379)
Grade 3	8 (6.4)	1 (3.7)	9 (5.9)	17 (5.5)	22 (5.8)
Grade 4	1 (0.8)	0	1 (0.7)	2 (0.6)	2 (0.5)
Blood glucose increased	0	0	0	2 (0.6)	2 (0.5)
Grade 1	0	0	0	1 (0.3)	1 (0.3)
Grade 2	0	0	0	1 (0.3)	1 (0.3)
Diabetes mellitus	2 (1.6)	0	2 (1.3)	2 (0.6)	2 (0.5)
Grade 3	2 (1.6)	0	2 (1.3)	2 (0.6)	2 (0.5)
Diabetic ketoacidosis	0	0	0	1 (0.3)	1 (0.3)
Grade 5	0	0	0	1 (0.3)	1 (0.3)
Serious TEAE	**2 (1.6)**	**0**	**2 (1.3)**	**8 (2.6)**	**8 (2.1)**
TEAE leading to withdrawal of study drug	**1 (0.8)**	**0**	**1 (0.7)**	**2 (0.6)**	**2 (0.5)**

Sources: ISS Supplemental Table 12.6.1.5.4.1 to 12.6.1.5.4.6

The Applicant's Position:

The incidence of treatment-emergent hyperglycemia was found to be higher in obese subjects and subjects who had pre-existing hyperglycemia or diabetes suggesting confounding effects of subject characteristics. Most events were low grade with few SAEs.

The FDA's Assessment:

The FDA generally agrees with the applicant's assessments.

FDA sent an information request for more explanation of the mechanism and suggested monitoring and management of hyperglycemia.

- The applicant stated that the mechanism is unclear. FDA disagrees. As with several of the other toxicities, including peripheral neuropathy and cytopenias, hyperglycemia can be attributed to the MMAE payload.
    1. According to the applicant, there is no clear relationship between Nectin-4 and glucose homeostasis. Nectin-4 staining is not strong in the endocrine pancreas, liver, or muscle. Nectin-4 staining is evident in the exocrine pancreas, but the fact that patients with hyperglycemia receiving enfortumab vedotin have high C-peptide levels confirms that off-target effects in pancreatic islet cells is not the cause.
    2. According to the applicant, there is no clear relationship between MMAE exposure or the valine-citrulline linker. Monkeys exposed to 70x higher free MMAE than the clinically recommended dose showed no alterations in glucose levels or histopathological findings in the pancreas. When human cells were exposed to MMAE or the linker in *in vitro* studies, pancreatic cells showed no changes in insulin secretion and skeletal muscle cells showed no changes in

glucose uptake.

- See FDA's assessment of the nonclinical data, last paragraph of section 5.5.5

  Loss in human islet viability was reported at concentrations ≥0.1 ng/mL following 12 hours incubation with MMAE (0.03-fold **lower** than the Cmax reported in human at the clinical recommended dose). A decline in insulin secretion (not dose dependent) from human islets was reported following exposure to MMAE. Following ADC administration, a decline in islet cell viability was reported following 12 hours incubation, but was not concentration-dependent

- The USPI (label) for brentuximab vedotin, which shares the same cytotoxic component, was updated on October 15, 2019, to include a *Warning and Precaution* for hyperglycemia. This occurred after FDA's Pharmacovigilance Division (DPV II) conducted a search of postmarketing safety databases to evaluate the safety signal of hyperglycemia. A summary of the results (below) reveal many similarities with the clinical characteristics of the cases identified in the enfortumab safety population, including clinical sequelae of ketoacidosis in patients without baseline hyperglycemia, and death.

  "DPV II identified 43 postmarketing [FDA Adverse Event Reporting System] and literature cases of hyperglycemia associated with brentuximab vedotin. All cases in our case series reported serious outcomes. Three fatal cases reported a cause of death attributed to hyperglycemia (n=1) or diabetic ketoacidosis (DKA) (n=2). Among 32 cases that reported sufficient clinical information to assess for baseline hyperglycemia, new-onset hyperglycemia occurred in 19 cases and worsening hyperglycemia in 13 cases. Overall, we assessed causality as probable in five cases and possible in the remaining cases. The most common confounding factors were obesity (n=7) and concomitant glucocorticoid use (n=7). Clinical manifestations included DKA or ketoacidosis, which were reported in 11 cases (26%); six of these 11 cases did not have baseline hyperglycemia. The severity of hyperglycemia was assessed as grade 3-5 in 32 cases (74%). Thirty cases (70%), required initiation or dose adjustments of insulin or oral hypoglycemic agents. Among 40 cases that reported a time to onset, the median time to onset was 13 days from initiation of brentuximab vedotin therapy. Notably, among 38 cases that reported the total number of doses administered prior to event onset, hyperglycemia occurred after a single dose of brentuximab vedotin in 28 cases (74%)."

- Additionally, other MMAE-carrying antibody-drug conjugates also are associated with hyperglycemia, in a variety of patient populations.
  - One targeting SLC44A4 and given to 20 patients in the dose expansion cohort of a metastatic castration-resistant prostate cancer trial resulted in two deaths following grade 3 hyperglycemia. (Invest New Drugs. 2019;37(5):1052-1060. doi: 10.1007/s10637-019-00731-5).
  - Another targeting mesothelin given to 54 patients with pancreatic

or ovarian cancer, resulted in two dose-limiting toxicities of grade 3 hyperglycemia (Mol Cancer Ther. 2016;15(3):439-47. doi: 10.1158/1535-7163.MCT-15-0693).

FDA's clarifications include

- The clinical data for enfortumab vedotin shows that patients with higher body weight had higher incidence of hyperglycemia, but it is not clear if this is due to correlation with baseline impaired glucose tolerance or the possibility of higher drug exposure due to weight-based dosing (suggested by PK modeling).
- The risk of hyperglycemia (and its more clinically relevant downstream effects such as diabetic ketoacidosis or progression to long-term insulin-dependence) in patients with baseline uncontrolled diabetes mellitus is unclear at this time.
    1. In Cohort 1, 16% of patients had hyperglycemia as defined by the SMQ, with most events being grade 1-2, complicated by concurrent systemic illness, and reversible with skipping or delaying doses. However, the severity of events related to hyperglycemia may be relatively lower in the trial compared to the risk in the intended patient population due to eligibility criteria. EV-201 excluded patients with baseline hemoglobin a1c ≥8%. The proposed labeling does not limit use to patients with any glycemic control.
    2. The SMQ definition of hyperglycemia is not the most clinically relevant definition of hyperglycemia. It includes "weight decreased," "dehydration," "hyperlipidaemia." Therefore, the label reports a more clinically relevant summary of hyperglycemia, including only "hyperglycemia," "diabetes mellitus," and "diabetic ketoacidosis."
- Hyperglycemia/diabetes mellitus/diabetic ketoacidosis was the third most common grade 3-4 treatment-emergent adverse event (occurring in 6-8% of patients, after only anemia and neutropenia); see below. Two patients had diabetic ketoacidosis with **no** history of diabetes mellitus; one was grade 4 and the other ended in death (SUBJECTID (b) (6) see narratives) but was not thought to be the cause of death. Another patient had DKA resulting in death (SUBJECTID (b) (6) see narratives) in the setting of baseline insulin-dependent diabetes mellitus, BMI 39, weight 121 kg, and an enfortumab dose of 151 mg. All three cases occurred after only 2-3 doses of enfortumab. Of the patients who developed hyperglycemia, 10% progressed to a long-term insulin requirement.

Table 89: Hyperglycemia-Related Treatment-emergent Adverse Events

Grade 3-4	Cohort 1, N=125		All 1.25 mg/kg, N=310	
	N	%	N	%
Hyperglycemia/diabetes mellitus/diabetic ketoacidosis	10	8%	20	6%

The Enfortumab Vedotin USPI includes Hyperglycemia as a Warning and Precaution, and includes the fact that these events occurred in those with and without pre-existing diabetes mellitus, that fatal events occurred, and that patients with baseline hemoglobin A1C ≥8% were excluded from trial enrollment. The USPI also notes that the incidence of Grade 3-4 hyperglycemia increased consistently in patients with higher body mass index and in patients with higher baseline A1C.

8.2.5.4. Extravasation Site Reactions

Data:
In Study EV-201, 3 subjects (2.4%) experienced events of extravasation site reactions; all were in Cohort 1. All events were considered related to study treatment and were Grade 2 (2 subjects) or Grade 3 (1 subject) in severity. Two out of 3 of the subjects had serious extravasation site reactions. Study drug administration was delayed and dose interruptions occurred as a result, but both subjects continued on treatment. Clinical findings and symptoms associated with the events included erythema, edema, and moderate-to-severe pain at both the injection site and a portion of the involved extremity. Initial onset was within 24 hours post-extravasation, with worsening over 4 to 5 days followed by partial improvement and subsequent exacerbation at 7 to 10 days after the event. Additional features such as bullae and superficial desquamation were present. The clinical presentation appeared to resemble or be associated with cellulitis. Both cases resolved after ~50 days.

In the enfortumab vedotin 1.25 mg/kg group, the extravasation site reaction rate (1.3%) was similar to EV-201. All events were Grade 2 or 3 in severity and were considered related to study treatment. Three subjects had serious extravasation site reaction events, including the 2 events described above and an additional event from Study EV-101. Clinical findings and symptoms associated with the event from Study EV-101 included redness, pain and development of an ~4 cm clear blister in the affected area; evaluation determined it was not cellulitis. No events led to dose reduction or treatment discontinuation and all events resolved.

The Applicant's Position:
Enfortumab vedotin is administered intravenously and extravasation may occur. Few subjects experienced extravasation site reactions. Events were Grade 2 or 3 in severity, did not require dose reduction or treatment discontinuation and all resolved. In general, these events were related to venous site access. Extravasation site reactions can be managed by ensuring good venous access prior to administration and monitoring the infusion site during enfortumab vedotin administration.

The FDA's Assessment:

FDA generally agrees with the applicant's assessment.
Narratives were provided for three of the four grade 2-3 extravasation reactions. All three patients had signs and symptoms of cellulitis, and were treated for possible cellulitis. Extravasation site reactions are not noted in association with brentuximab vedotin or polatuzumab vedotin. FDA sent an information request asking the applicant to "Justify whether a central line should or should not be recommend or required for the safe administration." Given the low frequency of extravasation reactions (1%), the applicant stated that "For patients with difficult peripheral venous access or who are at increased risk for extravasation (i.e., limited vein selection, small or fragile veins, local neuropathies, or lymphedema), the need for placement of a central line should be assessed on a patient-by-patient basis and in consideration of the potential risks associated with insertion of a Central Venous Access Device" but given the low incidence (1%) of extravasation reactions, CVADs should not be routinely recommended. The reviewer notes that the 1% quoted in the IR response is from the larger cohort of patients who received 1.25 mg/kg in all cohorts (n=310).

The Enfortumab Vedotin USPI includes Infusion Site Extravasation as a Warning and Precaution.

8.2.5.5. Infusion-related Reactions

Data:
In Study EV-201, 5 subjects (4.0%) in Cohort 1 and 1 subject (3.7%) in Cohort 2 experienced infusion-related reactions other than extravasation site reactions. All events were mild or moderate in severity and considered related to study treatment. There were no serious events of infusion-related reaction other than extravasation site reactions reported and no events resulted in dose modification.

In the enfortumab vedotin 1.25 mg/kg group, the infusion-related reactions other than extravasation site reaction rate (2.3%) were similar to EV-201. All events were mild or moderate and considered related to study treatment. There were no serious events or events that resulted in dose modification.

The incidence and severity of infusion-related reactions was similar across safety analysis groups.

The Applicant's Position:
As enfortumab vedotin is an ADC, there is a risk of a hypersensitivity reaction and/or systemic infusion-related reactions and other local infusion-related reactions with enfortumab vedotin administration (extravasation site reactions). Few subjects experienced infusion-related reactions other than extravasation site reactions. All events were mild or moderate in severity and none resulted in a dose modification.

The FDA's Assessment:

FDA agrees with the applicant's assessment. Of the 4 systemic infusion-related reactions (PT "infusion related reaction"), two were grade 1 and two were grade 2.

8.2.5.6. Anemia

Data:
In Study EV-201, events of anemia were reported for 31.2% of subjects in Cohort 1 and 40.7% of subjects in Cohort 2. The majority of events in both cohorts were considered related to study treatment and were Grade 2 or 3 in severity. There were no ≥ Grade 4 or serious events in either cohort. In Cohort 1, TEAEs of anemia resulted in dose reduction for 1 subject (0.8%) and dose interruptions for 3 subjects (2.4%). In Cohort 2, no events of anemia resulted in dose reduction and 1 subject (3.7%) experienced dose interruption. No event of anemia in either cohort led to treatment discontinuation.

In the enfortumab vedotin 1.25 mg/kg group, the rate of anemia was similar to EV-201 with 27.7% of subjects experiencing an event of anemia. The majority of events were considered related to study treatment and were Grade 2 or 3 in severity. One subject experienced a serious event of anemia. The study drug was reduced in 2 subjects (0.6%) and interrupted in 8 subjects (2.6%) due to events of anemia.

The incidence and severity of anemia was similar across the safety analysis groups.

The Applicant's Position:
Overall, anemia occurred commonly, and the majority of events were considered drug-related. The variability between cohorts is likely due to the smaller number of subjects enrolled in Cohort 2. Most TEAEs of anemia were Grade 2 or 3 in severity, but SAEs were rare. Dose modifications were uncommon, and no events resulted in treatment discontinuation.

The FDA's Assessment:

Anemia and neutropenia were the most common grade 3-4 events. Grade 3-4 anemia occurred in 14% of Cohort 1 and 10% of all patients who received 1.25 mg/kg (33 out of 336 in the 90-day safety update). However, these rates are similar to other trials with different drugs used in similar patient populations. For example, in two immunotherapy trials for cisplatin-refractory metastatic bladder cancer, 13% of patients in both trials treated with a checkpoint inhibitor had grade 3-4 events of "hemoglobin decreased."

Ten percent of patients in Cohort 1 of EV-201 required RBC transfusion during cycle 1 and 7 percent of patients required transfusion during cycle 2. No patients required transfusion during or after cycle 5.

8.2.5.7. Neutropenia

Data:
In Study EV-201, TEAEs of neutropenia were reported for 16.8% of subjects in Cohort 1 and 29.6% of subjects in Cohort 2. The majority of events in both cohorts were considered related to study treatment and were ≥ Grade 3 in severity. In Study EV-201, 9 subjects (5.9%) experienced serious events of neutropenia, all considered drug-related. In Cohort 1, 7 subjects reported SAEs: febrile neutropenia (5 subjects), neutropenia (2 subjects) and neutrophil count decreased (1 subject); no events led to treatment discontinuation. In Cohort 2, 2 subjects reported SAEs: febrile neutropenia and neutropenia (1 subject each), neither led to treatment discontinuation. The majority of subjects who experienced serious events of neutropenia (8/9; 88.9%) had complete resolution of the events by the data cutoff. Overall in Study EV-201, events of neutropenia resulted in dose reduction for 5 subjects (3.3%) and dose interruption for 7 subjects (4.6%).

In the enfortumab vedotin 1.25 mg/kg group, the rate of neutropenia was similar to EV-201 with 13.2% of subjects experiencing an event of neutropenia. The majority of events were considered related to study treatment and were ≥ Grade 3 in severity. Ten subjects (3.2%) experienced SAEs: febrile neutropenia (6 subjects), neutropenia (4 subjects) and neutrophil count decreased (1 subject); all considered drug-related. The study drug was reduced in 5 subjects (1.6%) and interrupted in 9 subjects (2.9%), due to events of neutropenia.

The incidence and severity of neutropenia was similar across the safety analysis groups.

The Applicant's Position:
Overall, neutropenia occurred commonly, and the majority of events were considered drug-related. The variability between cohorts is likely due to the smaller number of subjects enrolled in Cohort 2. Most TEAEs of neutropenia were ≥ Grade 3 in severity, however, dose modifications were uncommon, and no events resulted in treatment discontinuation.

The FDA's Assessment:
Anemia and neutropenia were the most common grade 3-4 events both in EV-201 and in the overall safety population that received 1.25 mg/kg. Grade 3-4 neutropenia (preferred terms neutropenia, neutrophil count decreased, or febrile neutropenia) occurred in 14% of Cohort 1 and 10% of all patients who received 1.25 mg/kg (34 out of 336 in the 90-day safety update). In contrast to anemia, neutropenia is not seen as commonly in other trials evaluating targeted agents or immunotherapy recently approved for similar patient populations (grade 3-4 approximately 1-3%). Nectin-4 RNA expression is present at low levels in granulocytes [Human Protein Atlas, 2015].

During cycle 1, 3% of patients in Cohort 1 received granulocyte colony stimulating factor (gCSF).

The EV-201 protocol did not discuss gCSF use. One percent of patients during cycle 2 and 1% during cycle 3 received gCSF. None received gCSF after cycle 3.

8.2.5.8. Neutropenic Infections

Data:
Due to the potential risk for neutropenia in subjects, as described above, there is a risk of infections in the setting of neutropenia. The incidence of neutropenic infections was infrequent. All cases were heavily confounded by subject and disease factors. A listing of subjects with reported events of both neutropenia and infection identified 32 potential neutropenic infection cases and further review of the listing was performed to assess the individual cases for neutropenic infections based on temporal relationship between the infection and neutropenia and clinical evaluation of the nature, severity and seriousness of the events. This identified 10 potential cases in subjects treated at 1.25 mg/kg enfortumab vedotin, 3 of which were from Study EV-201. In addition, the PT febrile neutropenia was considered to be a neutropenic infection. Subjects who had both a febrile neutropenic event and a potential neutropenic infection event were counted only once in the below summary.

Overall, in Study EV-201, 7 subjects (4.6%) experienced neutropenic infections, 6 of whom were in Cohort 1 and 1 in Cohort 2. Of these, 5 subjects in Cohort 1 and 1 subject in Cohort 2 had febrile neutropenia (4 subjects: Grade 3, 2 subjects: Grade 4). The remaining subject had individual infection terms reported (e.g., pneumonia, UTI) associated with neutropenia.

In the enfortumab vedotin 1.25 mg/kg group, the rate of neutropenic infections was similar to EV-201, with 4.5% of subjects experiencing concurrent events of neutropenia and infection. The most common infections reported in this setting were UTI and pneumonia. Most infections in the setting of neutropenia were heavily confounded by subject and disease factors.

The Applicant's Position:
The incidence of neutropenic infections was infrequent. The rate of neutropenic infections was similar between Study EV-201 and the enfortumab vedotin 1.25 mg/kg group. All cases were heavily confounded by subject and disease factors.

The FDA's Assessment:
FDA agrees that the incidence of neutropenic infections was about 5% in Cohort 1. The applicant did not conduct an analysis of lymphopenic infections. Since lymphocytopenia was more common than neutropenia (see table below summarizing the incidence of grade 3-4 lymphocytes decreased and neutrophils decreased, counting only patients that worsened by one CTCAE grade level from baseline), FDA evaluated the incidence of lymphopenic infections.

Table 90: Grade 3-4 Treatment-Emergent Lymphocytes Decreased and Neutrophils Decreased

Grade 3-4	Cohort 1, N=125		All 1.25 mg/kg, N=310	
	N	%	N	%
Lymphocytes decreased	12	10%	37	12%
Neutrophils decreased	6	5%	18	6%

The proportion of patients with lymphopenic infections was higher than the proportion of patients who had neutropenic infections: 23 (18%) patients in Cohort 1 had lymphopenic infections (absolute lymphocyte count [ALC] < 1000 prior to infection), with 19 events among 16 patients (13%) occurred during periods of grade ≥2 lymphocytopenia (ALC < 800). Additionally, one patient in Cohort 2 had a lymphopenic infection of invasive fungal pneumonia which led to death. The infections in Cohort 1 included 3 cases of herpes zoster (one involving the eye), a fungal skin infection, and Pneumocystis pneumonia. See Appendix for a description of the overall incidence of herpes zoster infections across the combined safety population. Of the five patients with herpes zoster who had laboratory results documented prior to infection, two were Lymphopenic, and one was neutropenic. However, the patients with lymphopenia did not develop progressively worsening lymphopenia with enfortumab treatment. Whether incidence of infections was increase can not be assessed in a single arm trial. The incidence of infection may reflect the heavily treated older population.

8.2.5.9. Diarrhea, Nausea and Vomiting

Data:

Nectin-4 expression has been identified in the esophagus and the stomach (Study ES10-001) and weak staining was observed in the mucosal glands of other GI tract organs including the small intestine, colon and rectum. The GI toxicities of diarrhea, nausea and vomiting, are common events reported with the use of MMAE-ADCs, including enfortumab vedotin. The majority of events were considered treatment related. Most diarrhea, nausea and vomiting events were low grade with few SAEs. Dose modifications were uncommon and no subject discontinued treatment due to a treatment-emergent event of diarrhea, nausea or vomiting.

In Study EV-201, events of diarrhea, nausea and vomiting were reported for 41.6%, 44.8% and 18.4% of subjects in Cohort 1, respectively, and 33.3%, 18.5% and 18.5% of subjects in Cohort 2, respectively. The majority of events in both cohorts were considered related to study treatment and were Grade 1 or 2 severity. In both cohorts, serious events of diarrhea, nausea and vomiting were infrequent. In Cohort 1, diarrhea led to dose reduction for 1 subject and diarrhea

and nausea led to dose interruption for 1 subject. In Cohort 2, diarrhea led to dose interruption for 1 subject; no events led to dose reduction. No event of diarrhea, nausea or vomiting led to treatment discontinuation in either cohort.

In the enfortumab vedotin 1.25 mg/kg group, the rate of diarrhea, nausea and vomiting was similar to EV-201, with 39.7%, 41.3% and 22.9% of subjects experiencing events, respectively. The majority of events were considered related to study treatment and were mild or moderate in severity. Serious events of diarrhea, nausea and vomiting were infrequent (6 subjects, 7 subjects and 8 subjects, respectively). The study drug was reduced due to nausea in 2 subjects (0.6%) and due to diarrhea in 1 subject (0.3%). The study drug was interrupted in 5 subjects (1.6%) due to nausea, 9 subjects (2.9%) due to diarrhea and 3 subjects (1.0%) due to vomiting. No event of diarrhea, nausea or vomiting led to treatment discontinuation.

The incidence and severity of diarrhea, nausea and vomiting was similar across the safety analysis groups.

The Applicant's Position:
GI events of nausea, vomiting and diarrhea were common. However, SAEs for these events were infrequent and no subjects discontinued treatment due to a TEAE of nausea, vomiting and diarrhea.

The FDA's Assessment:
FDA generally agrees with the applicant's assessment. Between cycles 2 and 7, approximately 50% of patients each cycle required antiemetics and approximately 15% of patients each cycle required antidiarrheal medication.

Two patients in EV-201 (described in narratives) and two patients in EV-101 had fatal adverse reactions of aspiration pneumonia. Some of these aspiration events occurred after vomiting.

8.2.5.10. Gastrointestinal Disorders Other Than Diarrhea, Nausea and Vomiting

Data:
In Study EV-201, GI disorder events were reported for 80.8% of subjects in Cohort 1 and 63.0% of subjects in Cohort 2. The majority of events in both cohorts were considered related to study treatment and were Grade 1 or 2 in severity. Serious GI disorder events were reported in 10 subjects (8.0%) in Cohort 1 and 3 subjects (11.1%) in Cohort 2. In Cohort 1, 2 subjects had events of abdominal pain that led to dose interruption and 1 subject had a small intestinal obstruction that led to dose interruption. No subjects in Cohort 2 had an event that led to dose

interruption. No subject in either cohort had a GI disorder event other than diarrhea, nausea or vomiting that resulted in dose reduction or treatment discontinuation.

In the enfortumab vedotin 1.25 mg/kg group, the rate of GI disorder events was similar to EV-201, with 76.8% of subjects experiencing events. The most common event was constipation reported in 27.1% of subjects. The majority of events were considered related to study treatment and were mild or moderate in severity. Serious events were reported in ~10% of subjects. One subject with abdominal pain had an event that led to dose reduction and 3 subjects (1.0%) had an event that led to treatment discontinuation. Including all GI disorders, 27 subjects (8.7%) had events that led to dose interruption.

The incidence and severity of GI disorder events was similar across the safety analysis groups.

The Applicant's Position:
Overall, GI disorders occurred in over 75% of subjects treated with enfortumab vedotin. The most common TEAEs other than diarrhea, nausea and vomiting were constipation and abdominal pain. More than half of the events were considered treatment related. Most GI disorder events were low grade. Nearly 10% of subjects experienced a serious event; however, dose modifications including treatment discontinuation were uncommon.

The FDA's Assessment:
FDA generally agrees with the applicant's assessment. The proportion of patients in Cohort 1 of EV-201 (n=125) with grade 3-4 diarrhea was 7%. The proportion of patients who received 1.25 mg/kg (n=336) with grade 3-4 diarrhea was 5%. The proportion of patients with grade 3-4 nausea or vomiting was 3% in both Cohort 1 of EV-201 as well as the combined 1.25 mg/kg safety population.

Bowel obstructions and fistulas also occurred. The proportion of patients with bowel obstructions or fistulas that led to treatment discontinuation was 1% in both Cohort 1 of EV-201 as well as the combined 1.25 mg/kg safety population. Most, if not all, of these patients had peritoneal carcinomatosis. Two patients with peritoneal metastases in EV-101 had small bowel obstructions that led to death.

8.2.5.11. Ocular Toxicity (Corneal Disorders)

Data:
Ocular toxicities such as keratitis or other corneal epithelial changes have been recognized with several ADCs containing anti-tubulin cytotoxic moieties. MMAE ADCs however, are not typically associated with these events (10). Study EV-201 incorporated serial eye exams; at baseline, Cycle 2 Day 22 and Cycle 6 Day 22. A complete eye examination was performed at baseline by a qualified ophthalmologist or optometrist. The examination was to include, at minimum,

uncorrected, corrected and best corrected visual acuity, slit lamp, tonometry examination, and dilated fundus examination. To evaluate corneal disorders following enfortumab vedotin treatment, the protocol specified that slit lamp examinations were to be conducted on at least the first 60 enrolled subjects (from Cohorts 1 and/or 2) on Cycle 2 Day 22 (±1 week) and Cycle 6 Day 22 (±1 week). The IDMC was responsible for evaluating slit lamp data from the initial enfortumab vedotin-treated subjects to determine whether continued slit lamp examinations were necessary or could be discontinued. The most common corneal disorder TEAE was punctate keratitis. All corneal disorder TEAEs were Grade 1 or 2 in severity and none were serious. No subjects discontinued treatment due to corneal disorder events and dose modifications were uncommon.

Data for subjects in Cohort 1 are detailed below.

- Baseline study slit lamp exams were performed for 123 Cohort 1 subjects. A total of 14 subjects (11%) had corneal findings at baseline.

- Cycle 2 Day 22 slit lamp exams were performed for 88 Cohort 1 subjects. These exams identified treatment-emergent corneal events in 13/88 subjects (15%), 3 of whom had corneal abnormalities at baseline. Events in the majority of subjects (10/13; 77%) were Grade 1 in severity. Treatment-related corneal events were reported for 4/88 subjects (5%) at Cycle 2 Day 22; 1 subject had a Grade 1 event and 3 subjects had Grade 2 events.

- Cycle 6 Day 22 slit lamp exams were performed for 50 subjects. These exams identified treatment-emergent corneal events in 12 subjects (24%), 2 of whom had corneal abnormalities at baseline. Six of the 12 subjects had ongoing corneal events that were previously identified on their Cycle 2 Day 22 slit lamp exam; each of these events remained at the same severity. Overall, events in the majority of subjects (9/12; 75%) were Grade 1 in severity at the Cycle 6 Day 22 exam. Treatment-related corneal events were reported for 6/50 subjects (12%) at Cycle 6 Day 22; 4 subjects had Grade 1 events and 2 subjects had Grade 2 events.

- One dose interruption occurred in a contact lens wearing subject for an event of Grade 2 keratitis and subsequently improved.

- No subjects received systemic steroids for corneal TEAEs.

In Study EV-201 Cohort 2, treatment-emergent corneal disorders were identified for 2 subjects (7%). Events were Grade 1 for 1 subject and Grade 2 for the other subject. No subjects discontinued treatment due to a corneal disorder and there were no serious corneal events. No subjects received systemic or topical steroids for corneal TEAEs. Notably, of 5 subjects who had Cycle 6, Day 22 slit lamp exams, only 1 subject had a corneal event (punctate keratitis); this event was previously identified at Cycle 2, Day 22 and improved from Grade 2 to Grade 1.

The incidence and severity of corneal disorders was similar across the safety analysis groups, with the exception of a higher incidence of corneal disorders in Study EV-201 overall compared with the 1.25 mg/kg group. Corneal exams were mandated to be done more frequently in Study EV-201. In addition, a greater percentage of subjects in Study EV-201 had a medical history of cataract surgery which is a risk factor for the development of corneal abnormalities [Hwang & Smith, 1991]. Though the incidence was higher, the event Grades were similarly low across the safety analysis groups.

The Applicant's Position:
Corneal disorder TEAEs were low grade, none were serious, and no subjects discontinued treatment. Few subjects required treatment to manage corneal disorders and dose modifications were uncommon. Although the sponsor maintains this as a potential risk, the evidence suggests that the events have been mild and not clinically meaningful.

The FDA's Assessment:
FDA disagrees with the applicant's assessment. FDA's ophthalmology consultant made the following comments, focusing on EV-201:

- *Regarding Study 201: of the 152 patients in the study, 78 reported an ocular adverse event. Of the 78 reported ocular adverse events, 5 had bacterial and/or viral infections affecting the ocular structures and 2 had a posterior vitreous detachment highly likely to be associated with advancing age without any dry eye findings.*
- *The blurred vision reported in this study is almost always likely to be related to dry eye disease in the patient. Although there are other potential causes of decreased vision such as cataracts or macular degeneration, of the 5 patients reported to have cataracts, only one reported decreased vision.*
- *Of the 152 patients in the study,* 63 *(41%) had signs or symptoms of dry eye disease (reported as either dry eyes/tearing/keratitis (*58*) or blurring without another cause of blurring (*5*)).*
- *Reporting of ocular adverse events in this trial was inconsistent. There are only a couple of reports of posterior vitreous detachments and cataracts; however, based on the ages of the patients, it is highly likely that there were additional patients with these findings, but not reported.*

Incorporating the entire safety population, this reviewer notes:

1) **Corneal disorders** were common. Similar to the 41% rate of dry eye symptoms in EV-201, dry eye symptoms occurred in 36% of the entire 1.25 mg/kg safety population (n=310).
2) The applicant's assessment above only describes the incidence and severity of corneal disorders, but not **blurred vision**. In the 90-day safety update, 46/336 (14%) of patients who received the 1.25 mg/kg dose had "vision blurred", "visual impairment", or "visual acuity reduced", of which 10 events (3%) were grade 2. Although grade 2 CTCAEs may be considered mild for other adverse events, grade 2 vision changes are defined as "symptomatic; limiting instrumental activities of daily living." This is a problematic grading system for any drug with ocular toxicities. Many clinically relevant and serious ocular toxicities are not necessarily symptomatic. They are serious because they lead to irreversible sequelae, such as vision loss, if untreated over a subacute period of time.

FDA sent two information requests to the applicant regarding this issue.

In response to the first information request, the applicant provided a descriptive summary of PROs in patients each cycle who had no ocular events vs. grade 1 CTCAE ocular event vs. grade 2 event.

- The number of patients who had grade 2 events each cycle was small (2-3), which limits the ability to draw conclusions.
- The median QLQ-C30 **global health status (GHS)** subscale scores for patients who had grade 1 ocular events worsened by 4 points from baseline to cycle 6, whereas the median GHS score associated with grade 0 ocular events improved by 4 points from baseline to cycle 6. A change of 4 points might be considered the minimal clinically important difference [Maringwa, 2011], but this analysis does not follow a cohort of patients longitudinally, and these trends were not consistently found in the other PRO subscales.
- Patients with grade 1 ocular events had median **physical functioning subscale** scores that were, on average, 10 points worse than patients with no ocular events each cycle (range, 4-14–point difference each cycle). See section 8.2.6.

In the second information request, FDA asked the applicant to "address why ocular toxicities are not included as a Warning & Precaution in the proposed labeling. In addition to analyses outlined above, please provide a table with all ocular toxicities, whether corneal or not, throughout your EV development program. This toxicity was not necessarily followed until stabilization or resolution. You should propose protocol changes in ongoing trials (EV-301, (b) (4) (b) (4) etc.) to monitor for ocular changes with greater duration of follow-up and a plan to characterize the natural history of these events and optimal management of this toxicity. Include in your plan the number of patients that

will potentially be affected by the proposed protocol amendment."

The applicant stated that age-related eye disorders are common in the elderly population. The applicant also summarized the frequency of eye disorders in all patients who received EV 1.25 mg/kg (n=336) as below:

Table 91: Treatment-Emergent Eye Disorders, Any Grade, Among Patients Who Received 1.25 mg/kg (N=310)

Eye disorders Systems Organ Class: Maximum CTCAE Grade	n (%)
All	**149 (44%)**
Grade 1	110 (35%)
Grade 2	32 (10%)
Grade 3	2 (1%)

For the analysis of grade 2 vision disorders, the applicant provided additional analyses

- The median time to onset for grade 2 vision disorders was 94 days, and median duration 31-38 days (range: 8-78 days), with 3 events still ongoing as of last follow-up.
- Of the 10 patients with grade 2 vision disorders, dosing was interrupted for 2 patients.

The applicant proposed no changes to Study EV-301, stating that the IDMC has not identified any concerns regarding ocular toxicity and therefore the monitoring for ocular toxicity is adequate in EV-301.

FDA added a Warning and Precaution to the applicant's proposed USPI for Ocular Disorders (see Section 11). In accordance with the FDA ophthalmology consultant's analysis, the incidence of dry eye was 36% in the 1.25mg/kg safety population (112 of 310 patients) and 40% in Cohort 1 (50 of 125 patients). Most of these events were documented as either "dry eye" or "lacrimation increased." Increased tearing is frequently a manifestation of the dry eye syndrome.

8.2.5.12. Antitherapeutic Antibodies

Data:

There is potential for an immunogenic response with any antibody therapy. Therefore, serum samples from subjects administered enfortumab vedotin were evaluated for ATA. In Study EV-201, 147 subjects were assessed for ATA and a total of 3 subjects (2.0%) were confirmed to be transiently positive for ATA and 1 subject (0.7%) was confirmed to be persistently positive for ATA. One additional subject in Study EV-102 (Arm A: 1.0 mg/kg dose) was confirmed to be transiently positive for ATA.

The Applicant's Position:
These were the only findings of ATA across the 4 clinical studies included in the integrated safety analyses. Subjects who were confirmed positive for ATA were evaluated for relevant TEAEs. None of these subjects experienced IRRs and the TEAEs that were reported were consistent with the overall safety profile.

The FDA's Assessment:
The FDA generally agrees with the applicant's assessment. The small numbers of patients with ATAs limits the ability to assess the impact of ATA positivity on safety and efficacy.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Data:
N/A

The Applicant's Position:
None of the studies supporting this application collected clinical outcome assessment (COA) data.

The FDA's Assessment:

See 8.1.2, Efficacy Results. The Applicant collected PRO data from two questionnaires, EORTC-QLQ-C30 and EQ-5D. The overall review of the PRO results did not identify a large decrement in symptoms or function that would materially alter the overall favorable risk-benefit determination.

On October 16, FDA sent an information request for data regarding the PRO results from specific items on EORTC-QLQ-C30 to further characterize the impact of some of the most common adverse events (nausea, diarrhea, corneal toxicities, and rash) on quality of life, including global health status, physical functioning, and role functioning subscale.

For consistency across drug applications, FDA's approach is to focus on physical functioning (PF):

- Patients with worse PRO nausea or diarrhea have worse PF. Out of a possible 100 points, patients with no nausea or diarrhea reported median PF scores of 80-87 each cycle, compared to patients with "a little" nausea or diarrhea who reported median PF scores of 67-73. Few patients report "quite a bit" or "very much" nausea or diarrhea.
- Patients with grade 1 or 2 rash had similar PF compared to those with no rash. The number of patients with grade 3 rash was low (about 5 patients each cycle), limiting the

ability to compare PF across groups.

- Patients with grade 1 ocular events had median PF scores that were, on average, 10 points worse than patients with no ocular events each cycle (range, 4-14–point difference each cycle), suggesting that although grade 1 ocular events are, by definition, "asymptomatic," they may either be associated with other events that affect physical function, or that patients are not reporting their ocular symptoms to investigators and providers.

8.2.7. Safety Analyses by Demographic Subgroups

The safety populations were assessed with subgroup analyses for intrinsic and baseline characteristics. In the sections below, data presentation focuses on the enfortumab vedotin 1.25 mg/kg group.

Age

The median age of subjects treated with enfortumab vedotin was > 65 years in all of the safety analysis groups. In the enfortumab vedotin 1.25 mg/kg group, 39.7% (123/310) of subjects were < 65 years and 60.3% (187/310) were ≥ 65 years; 74.2% (230/310) were < 75 years and 25.8% (80/310) were ≥ 75 years. The overall incidence of TEAEs (related, serious, resulting in study discontinuation or dose modification, etc.) was similar between age subgroups, with the exception being a higher incidence of ≥ Grade 3 TEAEs observed in subjects ≥ 75 years compared to those < 75 years (61.3% vs 71.3%).

The only TEAE with a ≥ 10% increase in incidence in subjects ≥ 65 vs < 65 years was constipation (32.1% vs 19.5%). Asthenia occurred more frequently in subjects ≥ 75 compared to those < 75 years (13.8% vs 1.7%, respectively). No individual ≥ Grade 3 event was observed at a higher incidence (≥ 5%) in either elderly subject population. Overall, there were no differences observed between age subgroups that were considered to be clinically meaningful.

Sex

The effect of sex on the safety of enfortumab vedotin was assessed across the safety analysis groups. In the enfortumab vedotin 1.25 mg/kg group, 32.9% (102/310) of subjects were female and 67.1% (208/310) were male, consistent with the general UC population.

In the enfortumab vedotin 1.25 mg/kg group, female and male subjects had a similar overall incidence of TEAEs (related, serious, discontinued, dose reduced, etc.). A ≥ 10% increase in the incidence of alopecia (55.9% vs 43.3%) and pruritus (33.3% vs 20.7%) was observed in females. No other TEAE or ≥ Grade 3 TEAE was reported at a higher frequency (≥ 10%) in male or female subjects. Overall, there were no differences observed between males and females that were considered to be clinically meaningful.

Race

The effect of race (white vs non-white) on the safety of enfortumab vedotin was assessed. In the enfortumab vedotin 1.25 mg/kg safety group, 86.1% of subjects (267/310) were white and 13.5% of subjects (42/310) were non-white. Some TEAEs were higher in the non-white vs white groups (e.g. pruritus) and some TEAEs were higher in the white vs non-white groups (e.g. edema peripheral, fatigue and peripheral sensory neuropathy). These differences are most likely due to the small number of subjects in the non-white subgroup and are not clinically meaningful.

Ethnicity

The effect of ethnicity (non-Hispanic or Latino vs Hispanic or Latino) on the safety of enfortumab vedotin was assessed. In the enfortumab vedotin 1.25 mg/kg group, 96.7% (297/307) of subjects were non-Hispanic or Latino and 2.3% (7/307) were Hispanic or Latino. The number of Hispanic or Latino subjects available for this analysis was small, and there were no differences observed between the subgroups of non-Hispanic or Latino vs Hispanic or Latino that were considered to be clinically meaningful.

Baseline Body Mass Index (BMI)

The effect of BMI on the safety of enfortumab vedotin was assessed for subjects with a baseline BMI < 30 kg/m^2 (non-obese) vs ≥ 30 kg/m^2 (obese). The frequency of obese subjects was similar between the EV-201 group (14.5%) and the enfortumab vedotin 1.25 mg/kg group (18.4%). Obese individuals (both in the general population and in subjects with cancer) are prone to greater morbidity and mortality compared to non-obese individuals, which is reflected in the clinical study results (11, 12).

The incidence of hyperglycemia was greater in the obese subgroup compared to the non-obese subgroup for both the EV-201 and enfortumab vedotin 1.25 mg/kg safety analysis groups. The severity (≥ Grade 3) of hyperglycemia was also greater in the obese subgroup. In Study EV-201, regardless of pre-existing hyperglycemia or diabetes at baseline, the incidences of treatment-emergent hyperglycemia and drug-related hyperglycemia remained higher in the obese subgroup compared to the non-obese subgroup.

Four of the 5 drug-related AEs leading to death occurred in obese subjects. All 4 drug-related deaths in obese subjects occurred on Study EV-101. Three of these events were associated with hyperglycemia, including one event of diabetic ketoacidosis. Each subject had pre-existing comorbidities that placed them at increased risk (full subject narratives are available in the EV-101 and EV-201 CSRs). Subsequent to these events, clinical protocols were amended, instructing investigators to monitor blood glucose levels and ensure appropriate management per institutional standards (particularly in subjects with a prior history of hyperglycemia or diabetes mellitus), to hold dosing for blood glucose ≥ 250 mg/dL, and implement a dose cap for subjects > 100 kg. Since these actions were implemented, there have been no drug-related deaths in obese subjects.

The Applicant's Position:

Overall, there were no safety-related differences observed between subgroups based on age, sex, race, or ethnicity that were considered to be clinically meaningful. A higher incidence of hyperglycemia was observed in obese subjects compared to non-obese subjects, consistent with what is generally observed in the obese population. Protocols now emphasize optimal glucose management and include a dose modification schema for enfortumab vedotin.

Obese individuals are at greater mortality risk as compared to non-obese individuals and 4 of the 5 drug-related AEs leading to death occurred in obese subjects prior to protocol amendments across the program as described above. Following changes to study protocols which were implemented early in the enrollment period for EV-201, no further deaths in obese subjects have occurred.

The FDA's Assessment:

The FDA conducted independent safety analyses, focusing on the 1.25 mg/kg group (n=310), and found additional trends in demographic subgroups:

Age

The overall risk of any grade 3-4 adverse event was comparable across the three age groups, but the risk of certain grade 3-4 adverse events increased modestly with age, including lab abnormalities (creatinine [acute kidney injury], amylase, lipase, glucose elevation) and infections (cellulitis, pneumonia, and sepsis). See table below.

Table 92: Selected Grade 3-4 Treatment-Emergent Adverse Events Occurring More Frequently in ≥75-Year-Olds Than <65-Year-Olds

	Grade 3-4 Treatment-Emergent Adverse Events (AEs)					
	<65y, N=123		≥65-<75y, N=107		≥75y, N=80	
	n	%	n	%	n	%
Acute kidney injury	1	**0.8**	4	**3.7**	4	**5**
Amylase or lipase increased	3	**2.4**	3	**2.8**	4	**5**
Anemia	11	**8.9**	10	**9.3**	9	**11.2**
Cellulitis	2	**1.6**	2	**1.9**	3	**3.8**
Hyperglycemia	10	**8.1**	9	**8.4**	10	**12.5**
Pneumonia	3	**2.4**	5	**4.7**	4	**5**
Rash	9	**7.3**	14	**13.1**	9	**11.2**
Sepsis	3	**2.4**	3	**2.8**	3	**3.8**
Any treatment-emergent AE	72	**58.5**	59	**55.1**	48	**60**

BMI

- The interpretability of the safety analysis by baseline BMI was limited by the relatively small number of patients with BMI ≥30 (n=57).
- The overall risk of any grade 3-4 adverse event was comparable across the three BMI categories, but the risk of certain grade 3-4 adverse events increased with BMI. See table below.
- The safety profile in patients with BMI <25 (n=129) was similar to the safety profile in overweight patients (BMI ≥25-<30, n=124) except in regards to hyperglycemia.
    - The risk of grade 3-4 hyperglycemia increased consistently across BMI categories from 4.7% in those with BMI<25, to 8.9% in those with BMI ≥25-<30, to 21.1% in those with BMI ≥30.
- The risk of death due to TEAE increased with BMI (5.1% for patients with BMI <30, 10.5% for patients with BMI ≥30).
- Whether lowering the dose for patients with BMI ≥30 would improve the safety profile is not clear. See Clinical Pharmacology section regarding the weight-based dosing cap for patients > 100 kg.

Table 93: Selected Grade 3-4 Treatment-Emergent Adverse Events Occurring More Frequently in Patients with BMI ≥ 30 Than Patients with BMI < 30

	Grade 3-4 Treatment-Emergent Adverse Events (AEs)			
	BMI <30, N=253		BMI ≥30, N=57	
	n	%	n	%
Acute kidney injury	5	2	4	7
Amylase or lipase increased	10	4	0	0
Anemia	23	9.1	7	12.3
Hyperglycemia	17	6.7	12	21.1
Neuropathy	4	1.6	3	5.3
Pneumonia	8	3.2	4	7
Urinary tract infection	13	5.1	6	10.5
Any treatment-emergent AE	144	56.9	35	61.4

Baseline renal function

- No significant safety signals were identified when comparing the TEAEs in patients with normal (CrCl ≥ 90 mL/min, n=60) to those with mild insufficiency (CrCl ≥ 60-<90 mL/min, n=125) to those with moderate insufficiency (CrCl ≥ 30-<60 mL/min, n=119). In the 90-

day safety update, 15 patients had been assigned to a 1.25 mg/kg dose across the drug development program. The safety profile was consistent with the safety profile in the overall population. The median duration of therapy (4.6 months) was comparable to the median duration in the overall safety population, but the mean dose intensity was lower (2.7 mg/kg out of an expected 3.75 mg/kg each cycle, compared to 2.93 mg/kg in patients with no/mild/moderate renal insufficiency); i.e., a relative dose intensity of 71% versus 78%.

Baseline hemoglobin A1c

- Not all studies in the development program comprehensively collected baseline hemoglobin A1c data. EV-201 had the most substantial amount of data. Of the 152 patients in the safety population of EV-201, baseline hemoglobin A1c was reported for 144 patients.
    - According to A1c, 38% of patients had impaired fasting glucose (defined as A1c ≥5.7 to <6.5) and 8% had a1c diagnostic of diabetes mellitus (defined as A1c ≥6.5). The majority (55%) of patients had normal baseline A1c (<5.7).
    - Therefore, this analysis is limited by small numbers of patients
- The risk of any grade 3-4 TEAE increased modestly with worse baseline glycemic control, and the risk of specific grade 3-4 TEAEs, including hyperglycemia, neuropathy, and urinary tract infection, also increased with worse baseline glycemic control. See table below.

Table 94: Selected Grade 3-4 Treatment-Emergent Adverse Events Occurring More Frequently in Patients with Hemoglobin A1c ≥ 6.5 Than Hemoglobin A1c < 6.5

Grade 3-4 Treatment-Emergent Adverse Events (AEs) in EV-201 by Baseline Hemoglobin A1c						
	A1c <5.7 [Normal] N=78		**A1c ≥5.7-<6.5 [IFG], N=54**		**A1c ≥6.5 [DM], N=12**	
	n	%	n	%	n	%
Amylase or lipase increased	3	3.8	5	9.3	2	16.7
Decreased appetite or dysgeusia	1	1.3	2	3.7	1	8.3
Hyperglycemia	6	7.7	6	11.1	5	41.7
Neuropathy	1	1.3	4	7.4	1	8.3
Rash	13	16.7	5	9.3	2	16.7
Urinary tract infection	2	2.6	4	7.4	2	16.7
Any TEAE	49	62.8	38	70.4	9	75

Abbreviations: IFG, impaired fasting glucose; DM, diabetes mellitus

Sex and Race

FDA generally agrees with the applicant's assessment of the safety results in males versus females. FDA's analysis focused on grade 3-4 AEs, which identified higher incidences of grade 3-4 cellulitis, pneumonia and sepsis in women versus men, but the absolute differences are small (1-2% vs. 4-7%) and may not be clinically meaningful.

The proportion of patients who were non-white was less than 14% across the 310 patients who received 1.25 mg/kg. This 14% included 29 (9%) Asian patients, 5 (<2%) Black/African American patients, 5 (<2%) "not reportable", 3 (<1%) "Other". Thus, no conclusive statements can be made with these small numbers. However, in FDA's analysis focusing on grade 3-4 AEs, Asian patients had almost 3 times more rash than white patients (24% vs. 8%).

8.2.8. Specific Safety Studies/Clinical Trials

Data:
N/A

The Applicant's Position:
N/A

The FDA's Assessment:
N/A

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Data:
N/A

The Applicant's Position:
N/A

The FDA's Assessment:

By 6/15/19 (90-day safety update), 3 malignant neoplasms were reported in the combined safety population. These three events can be expected to occur in this patient population.

- [redacted] (b) (6) Study EV-102: 63-year-old man with history of treatment with cisplatin and gemcitabine in [redacted] (b) (6) had been taking enfortumab for 1.5 years

when he was diagnosed with treatment-related high-risk myelodysplastic syndrome (MDS) (b) (6) Enfortumab was withdrawn at that time. This transformed to acute myeloid leukemia (AML) (b) (6) The patient died within 2 weeks of AML diagnosis. Given the several years that treatment-related MDS usually requires to develop, and the exposure to an alkylating agent 2 years prior to diagnosis of MDS, the role of enfortumab in contributing to the secondary malignancy is unclear.

- (b) (6) Study EV-201: 76-year-old man was diagnosed with squamous cell carcinoma (SCC) of the skin (L forearm, L shoulder, right wrist) on day 199 of enfortumab. Study drug was held from days 213 to 241, and then resumed after the patient had Mohs surgery with negative margins. The investigator attributed the SCC to UV exposure. Another confounding factor is the patient's smoking history.

- (b) (6) Study EV-201: 81-year-old man with history of smoking had wall thickening of the descending sigmoid colon on screening CT but was still enrolled in EV-201. On day 100, this was seen again on CT and he had biopsy that confirmed colon carcinoma. The stage is not reported. Enfortumab was withdrawn. He had laparoscopic sigmoidectomy.

Human Reproduction and Pregnancy

Data:

N/A

The Applicant's Position:

There are no available human data on enfortumab vedotin use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. Enfortumab vedotin can cause fetal harm based upon findings from animal studies and the drug's mechanism of action. Female subjects of childbearing potential treated with enfortumab vedotin should be advised of the potential risk to the fetus.

The FDA's Assessment:

FDA agrees with the applicant's assessment. There were no pregnancies in the data reported by the applicant.

Pediatrics and Assessment of Effects on Growth

Data:

N/A

The Applicant's Position:

Enfortumab vedotin has been granted a full product-specific waiver for use in pediatric subjects

with metastatic UC, from birth to 18 years (Agreed Initial Pediatric Study Plan, 15 May 2018).

The FDA's Assessment:

FDA agrees with the applicant's assessment. The youngest patient treated in the combined safety population was 24 years old.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound
Data:
N/A

The Applicant's Position:
Neither the effects of overdose of enfortumab vedotin nor an antidote to overdose are known. The potential for enfortumab vedotin drug abuse and dependence is unknown.

The FDA's Assessment:

FDA agrees with the applicant's assessment.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience
Data:
N/A

The Applicant's Position:
Enfortumab vedotin is not currently approved or marketed in any country.

The FDA's Assessment:

Not applicable.

Expectations on Safety in the Postmarket Setting
Data:
In addition to the studies presented in this BLA, the following are ongoing or planned clinical studies of enfortumab vedotin that will contribute to safety in the postmarket setting.
Monotherapy studies:

- Ongoing EV-301 (7465-CL-0301) – An Open-Label, Multinational Randomized Phase 3 Study to Evaluate Enfortumab Vedotin vs Chemotherapy in Subjects with Previously Treated Locally Advanced or Metastatic Urothelial Cancer (EV-301). This is the

confirmatory study if the current BLA is approved under accelerated approval.

- Planned EV-901 (7465-CL-0108) - A Multicenter, Open-label, Expanded Access Treatment Protocol of Enfortumab Vedotin in Subjects with Locally Advanced or Metastatic Urothelial Carcinoma (EV-901).

Combination therapy studies:

- Ongoing EV-103 (SGN22E-002) – A phase 1b, dose escalation and dose expansion of enfortumab vedotin in combination with pembrolizumab and/or chemotherapy to assess safety, tolerability and efficacy.
- Planned MORPHEUS-mUC (WO39613) – A phase 1b/2, randomized umbrella study evaluating efficacy and safety of multiple immunotherapy-based treatment combinations (enfortumab vedotin in combination with atezolizumab and atezolizumab alone). Genentech/Roche is the study sponsor and Study WO39613 is being conducted under Genentech's IND 136,754.

The Applicant's Position:

The Sponsors are seeking accelerated approval of enfortumab vedotin under the provisions in 21 Code of Federal Regulations (CFR) Part 601 Subpart E. Confirmatory trial(s) are therefore required to verify and describe the clinical benefit of enfortumab vedotin in subjects with UC. As discussed with the FDA at the pre-phase 3 meeting held on 09 Nov 2017, the phase 3 EV-301 study is intended to serve as the confirmatory study for enfortumab vedotin.

All safety concerns that have been identified are adequately represented in the safety database for enfortumab vedotin. Additional ongoing and planned clinical studies will contribute additional safety information to further elucidate the safety profile of enfortumab vedotin.

The FDA's Assessment:

The FDA will continue to monitor any post-marketing reports and safety reports that are submitted after approval. However, the FDA generally agrees that the safety of enfortumab was adequately characterized in this submission, except for

- The overall safety profile of enfortumab 1.25 mg/kg in patients between 85 and 100 kg. The applicant proposed a dose cap for patients > 100 kg, but has not prospectively evaluated alternative thresholds in a dose-finding study.
- The impact of enfortumab on eye disorders after > 6 months of therapy,
- The impact of enfortumab on the risk of hyperglycemia and complications related to diabetes mellitus in patients with hemoglobin A1c ≥8%,
- The impact of enfortumab on the risk of acute kidney injury, electrolyte and metabolic disorders in patients with creatinine clearance (CrCL) <30 mL/min. More data will be needed to clarify the mechanism of sudden severe metabolic/renal derangements. Nectin-4 expression is present at low levels in the renal tubules [Human Protein Atlas, 2015].

- The incidence of herpes zoster infections, particularly ophthalmic herpes zoster.

FDA's expectation is that the safety profile will be better characterized with more data from clinical trials, especially randomized trials and the postmarket setting.

8.2.11. Integrated Assessment of Safety

Applicant's Positions:
The integrated safety profile of enfortumab vedotin is based upon a total of 379 subjects with malignant tumors, primarily UC. The pivotal phase 2 study (EV-201) consists of 152 subjects with locally advanced or metastatic UC who had previously received a PD-1/PD-L1 inhibitor and either previously received platinum-based chemotherapy (Cohort 1, n = 125) or had not received prior platinum-based chemotherapy and were cisplatin ineligible at enrollment (Cohort 2, n = 27). Overall, 310 subjects, the majority of whom had UC (89%), were treated at the recommended commercial dose of 1.25 mg/kg.

At 1.25 mg/kg, enfortumab vedotin was tolerable in subjects with metastatic UC, with a manageable safety profile. No clinically meaningful differences were observed between any safety analysis groups, and Study EV-201 Cohort 1 is representative of the overall safety profile of the integrated safety population.

- The most common drug-related TEAEs in Study EV-201 were PTs of alopecia, fatigue, decreased appetite, dysgeusia, peripheral sensory neuropathy and nausea. The majority of TEAEs were grade 1 or 2 in severity.
- Twenty-five (16.4%) subjects in Study EV-201 had TEAEs that led to treatment discontinuation; ~12% of subjects had events leading to discontinuation that were considered drug-related.
- Peripheral sensory neuropathy was the most common drug-related TEAE leading to discontinuation with no other drug-related event leading to discontinuation occurring in > 1 subject in Study EV-201.
- Overall, in the enfortumab vedotin 1.25 mg/kg safety analysis group, 4 (1.3%) drug-related treatment-emergent events leading to death occurred (multiple organ dysfunction syndrome, diabetic ketoacidosis, urinary tract obstruction, and respiratory failure). An additional related death, interstitial lung disease, occurred outside of the safety reporting period.
- Based on the EV 1.25 mg/kg subgroup analyses of TEAEs of demographic and baseline characteristics, no specific safety precautions are warranted.

AEOI assessed and found to be associated with enfortumab vedotin include composite terms of rash, peripheral neuropathy, extravasation site reactions, as well as diarrhea, nausea, and

vomiting:

- Rash is associated with Nectin-4 expression in the skin and was commonly reported in the integrated safety population. Most events were drug-related, mild to moderate in severity and there were few serious events. The most common type of rash was maculo-papular rash. The majority of rash events did not require dose modifications; and few treatment discontinuations occurred. The majority of subjects had complete resolution of all events.
- Extravasation site reactions are a risk associated with intravenous administration. Few events of infusion site extravasation occurred; however, the majority reported were serious. All subjects with these reactions recovered completely and there were no discontinuations due to these events.
- Peripheral neuropathy, primarily sensory neuropathy, occurred commonly and was observed at similar frequency in subjects with or without baseline peripheral neuropathy. The majority of events were mild to moderate with few severe cases. The time to onset was within the first month of initiating therapy and most events returned to baseline. Most subjects were managed with dose modifications with few discontinuations due to neuropathy. At 4%, peripheral sensory neuropathy was the most common reason for subjects to discontinue treatment.
- Diarrhea, nausea and vomiting occurred frequently but were generally mild to moderate in severity. There were some serious cases but no treatment discontinuations due to diarrhea, nausea or vomiting.

AEOI assessed and found to be potentially associated with enfortumab vedotin include hyperglycemia, infusion-related reactions (other than extravasation site reactions), anemia and neutropenia, GI disorders (other than diarrhea, vomiting and nausea), corneal disorders and ATAs:

- Hyperglycemia was mostly mild to moderate in severity with few serious cases. There was a higher incidence of treatment-emergent hyperglycemia reported in obese subjects and in subjects with pre-existing hyperglycemia or diabetes. Most events resolved and subjects without pre-existing hyperglycemia or diabetes requiring treatment did not require ongoing anti-diabetic medications.
- Infusion-related reactions occurred infrequently and did not result in treatment discontinuation.
- Events of anemia and neutropenia were reported in ~30% and 15% of subjects treated with enfortumab vedotin, respectively. Very few events were considered serious and no subjects discontinued treatment due to events of anemia or neutropenia. Infections in the setting of neutropenia were infrequent in clinical studies and generally not considered drug-related.
- GI disorders occurred in over 75% of subjects treated with enfortumab vedotin. The

most common TEAEs other than diarrhea, nausea and vomiting were constipation and abdominal pain. Most GI disorder events were low grade. Nearly 10% of subjects experienced a serious event of GI disorder; however, dose modifications including treatment discontinuation were uncommon.

- Corneal disorders were thoroughly evaluated in clinical studies. There do not appear to be clinically meaningful corneal effects associated with enfortumab vedotin treatment.
- In the overall integrated safety population, 4 subjects were found to be transiently positive for ATA and 1 subject was found to be persistently positive for ATA. There was no clinically meaningful impact on safety in these 5 subjects.

Enfortumab vedotin was tolerable at the proposed dose and frequency in a predominantly elderly patient population with numerous comorbidities. The safety profile is well-characterized and manageable.

The FDA's Assessment:

Enfortumab's safety profile is acceptable in this setting. The safety profile is not yet well-characterized in all areas. As stated in the "Expectations on Safety in the Postmarket Setting" section above, FDA's expectation is that the safety profile will be better characterized with more data from clinical trials and the postmarket setting. Below are FDA's additions, caveats and clarifications of the applicant's statements regarding specific adverse events.

"Based on the EV 1.25 mg/kg subgroup analyses of TEAEs of demographic and baseline characteristics, no specific safety precautions are warranted."

- Additionally monitoring may be warranted in patients ≥ age 65, poorly controlled diabetes or requirement for systemic steroid therapy, and BMI ≥ 30. The amount of data for patients with CrCL < 30 mL/min is limited. Given the similarity in AE profiles between all antibody-drug conjugates incorporating MMAE, and the finding that "the frequency of ≥Grade 3 adverse reactions and deaths was greater in patients with severe renal impairment" in studies with brentuximab vedotin (USPI), dose reduction could be considered in patients with CrCL < 30 mL/min, although no specific increase in risk was identified in the 15 patients in the combined safety set as of yet.

"Peripheral neuropathy… time to onset was within the first month of initiating therapy and most events returned to baseline. Most subjects were managed with dose modifications with few discontinuations due to neuropathy."

- Peripheral neuropathy appears to be a cumulative exposure-related event. FDA disagrees with the general statement that most events returned to baseline. In patients with no baseline neuropathy, grade 2 events did not return to grade 0. In the patients with grade 1 treatment-emergent neuropathy that resolved, discontinuation of therapy (for progression of disease, a different adverse event, or any other reason) occurred prior to resolution of symptoms.

"There do not appear to be clinically meaningful corneal effects associated with enfortumab vedotin treatment."

- As stated in the Ocular Toxicity section, corneal effects were not evaluated for sufficiently long duration of follow-up to make this statement.

"Hyperglycemia was mostly mild to moderate in severity with few serious cases."

- Grade 3-4 hyperglycemia/diabetes mellitus/diabetic ketoacidosis was the third most common grade 3-4 treatment-emergent adverse event (occurring in 6-8% of patients, after only anemia and neutropenia). Among the 12 patients with baseline hemoglobin A1c ≥6.5, 41% had grade 3-4 treatment-emergent hyperglycemia. Two patients had diabetic ketoacidosis with no history of diabetes mellitus; one was grade 4 and the other ended in death but was not thought to be the cause of death. Another patient had DKA in the setting of baseline insulin-dependent diabetes mellitus. All three cases occurred after only 2-3 doses of enfortumab. Of the patients who developed hyperglycemia, 10% progressed to a long-term insulin requirement.

"Events of anemia and neutropenia… Very few events were considered serious and no subjects discontinued treatment due to events of anemia or neutropenia. Infections in the setting of neutropenia were infrequent in clinical studies."

- Anemia and neutropenia were the most common grade 3-4 events, each occurring in 10-14% of patients. Grade 3-4 anemia occurs at similar rates in other trials with similar patient populations. Grade 3-4 lymphopenia was not frequently reported by investigators, but according to lab data, grade 3-4 decrease in lymphocytes was more common than grade 3-4 decrease in neutrophils. Lymphopenic infections were more common than neutropenic infections (18% versus 5% in Cohort 1), which included 3 cases of herpes zoster, a fungal skin infection, and Pneumocystis pneumonia.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

The Applicant submitted a BLA for Enfortumab vedotin for the treatment of patients with locally advanced or metastatic urothelial cancer based on results from study EV-201 cohort 1. These patients have received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and have received a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting. The estimate of confirmed ORR per blinded independent central review based on RECIST v1.1 was 44% (95% CI: 35%, 53%) with 12% of patients achieving a CR and 32% of patients achieving a PR. The median estimate of

response duration was 7.6 months (95% CI: 6.3, not estimable). We reiterate that no inferential procedures can be used to evaluate results from this single arm study. Instead, the efficacy evaluation was based on the magnitude of response rate and adequate duration of response. Additionally, although progression-free survival and overall survival results were summarized in the clinical study report, we noted that time-to-event endpoints are uninterpretable in a single arm study without a comparator arm. There are no major statistical issues identified for study EV-201 cohort 1.

8.4. Conclusions and Recommendations

The FDA's Assessment:

The review team recommends accelerated approval for enfortumab vedotin. Enfortumab vedotin is a Nectin-4-directed antibody and microtubule inhibitor (b) (4)

This accelerated approval is based on tumor response rate and duration of response. Continued approval for this indication is contingent upon verification and description of overall survival benefit in the confirmatory EV-301 trial.

X X

X X

X X

X	X
Primary Statistical Reviewer	Statistical Team Leader
X	X
X	X
X	X
X	X
Primary Clinical Reviewer	Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

This BLA was not presented to an advisory committee because the benefit-risk profile demonstrated for enfortumab is clearly favorable for its proposed use. No controversial issues were identified that would necessitate an advisory committee meeting.

10 Pediatrics

The Applicant's Position:

Enfortumab vedotin was granted a full product-specific waiver by the FDA on 15 May 2018 for the treatment of pediatric patients (birth to 18 years) with locally advanced or metastatic UC who have disease progression during or following treatment with an immune CPI. This waiver was based on the absence of an unmet medical need in this population and a population too small to feasibly study.

The FDA's Assessment:

FDA agrees with the applicant's assessment.

11 Labeling Recommendations

Data:
This is an original application. Please see annotated label in Module 1.14.1.2 for proposed labeling.

The Applicant's Position:
N/A

The FDA's Assessment:

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
Highlights of Prescribing Information	Indications: (b) (4)	"PADCEV is a Nectin-4-directed antibody and microtubule inhibitor conjugate." The mechanism of the cytotoxic component is clinically relevant and should be included in the description of the Drug Product Class because many of the adverse reactions (peripheral neuropathy, hyperglycemia, and cytopenias) are attributed to MMAE. Added "Avoid use in moderate or severe hepatic impairment" in Dosage & Administration, because of postmarketing study for other ADCs with MMAE, including one where 3 of 6 patients with moderate or severe hepatic impairment died.
Dosage and Administration Dose Modifications (2.2)	Order of Adverse Reactions (b) (4)	Adverse Reactions reordered to reflect clinical relevance: Hyperglycemia, followed by Peripheral Neuropathy, followed by Ocular Disorders (added by FDA), followed by Skin Reactions, followed by Other Non-hematologic toxicity and Hematologic toxicity (latter two both added by FDA).

Summary of Significant Labeling Changes (High level changes and not direct quotations)	(b) (4)	
Dosage and Administration Instructions for Preparation and Administration (2.3)		Added "PADCEV is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]" Revised reconstituted vial and prepared infusion storage conditions to 4 hours based on microbial data supporting storage up to only 4 hours.
Dosage Forms and Strengths (3)		Revised to include correct dosage form ("For Injection") and annotate that PADCEV is provide in a single-dose vial "for reconstitution".
Warnings and Precautions (5)		Changed order to (5.1) Hyperglycemia, (5.2) Peripheral Neuropathy, (5.3) Ocular Disorders, (5.4) Skin Reactions, (5.5) Infusion Site Extravasation, (5.6) Embryo-Fetal Toxicity to reflect the relative clinical significance of the adverse reactions (ARs).
Warnings and Precautions (5.1) Hyperglycemia		Revised to focus this information on severe sequelae and risk factors related to PADCEV hyperglycemia ARs: "Hyperglycemia occurred in patients treated with PADCEV, including death, and diabetic ketoacidosis (DKA) in those with and without pre-existing diabetes mellitus. The incidence of Grade 3-4 hyperglycemia increased consistently in patients with higher body mass index and in patients with higher baseline A1C. In EV-201, 8% of patients developed Grade 3-4 hyperglycemia. In this trial, patients

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
		with baseline hemoglobin A1C ≥8% were excluded."
Warnings and Precautions (5.2) Peripheral Neuropathy		Added [redacted (b) (4)] To be consistent with the EV-201 study protocol and inform appropriate patient management, added "Permanently discontinue PADCEV in patients that develop Grade ≥3 peripheral neuropathy."
Warnings and Precautions (5.3) Ocular Disorders	This section was not in the proposed label. When FDA proposed a section, the applicant wrote, [redacted (b) (4)]	Added "Ocular disorders occurred in 46% of the 310 patients treated with PADCEV. The majority of these events involved the cornea and included keratitis, blurred vision, limbal stem cell deficiency and other events associated with dry eyes." Added a statement to describe the incidence of dry eyes (36%) and blurred vision (14%); and the median time to onset for symptomatic ocular disorders. Added consideration of prophylactic artificial tears and referring patients to ophthalmology for any ocular complaints.
Warnings and Precautions (5.4) Skin Reactions	"Skin reactions occurred in [redacted (b) (4)]% of the 310 patients treated with PADCEV in clinical trials." [redacted (b) (4)]	Increased from [redacted (b) (4)] to 54% after re-defining pooled term. Deleted [redacted (b) (4)] and added "(26%) had maculopapular rash and 30% had pruritus." Added specific types of grade 3 skin reactions. Added. "Permanently discontinue PADCEV in patients that develop Grade 4 or recurrent Grade 3 skin reactions."

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Warnings and Precautions (5.5) Infusion Site Extravasations	(b) (4)	Added details on frequency, clinical presentation, and natural history of extravasation reactions.
Warnings and Precautions (5.6) Embryo-Fetal Toxicity	(b) (4)	Deleted the Applicant's proposed sentence.
	(b) (4)	Revised the second sentence to "… administration of enfortumab vedotin to pregnant rats during the period of organogenesis caused maternal toxicity, embryo-fetal lethality, structural malformations and skeletal anomalies at maternal exposures approximately similar to the clinical exposures at the recommended human dose of 1.25 mg/kg." Added "Advise patients of the potential risk to the fetus," and "Advise male patients with female partners of reproductive potential to use effective contraception during treatment with PADCEV and for 4 months after the last dose".
Adverse Reactions (6)		Clarified that the data in the Warnings and Precautions section reflect exposure to PADCEV in the 310 patients who received 1.25 mg/kg across 3 trials. Added exposure duration data. Added fatal adverse reactions.
	(b) (4)	Table 3: added "Any adverse reactions" and revised diarrhea and fatigue proportions to reflect pooled terms. Re-ordered rows to be in descending order of frequency. Changed (b) (4)

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
		(b) (4) to "symmetrical drug-related intertriginous and flexural exanthema (SDRIFE)," based on independent dermatologic consultation and assessment of the events. For other clinically significant adverse reactions, added "herpes zoster (3%)."
Use in Specific Populations Pregnancy (8.1)	(b) (4)	Deleted (b) (4) Added "Based on the mechanism of action and findings in animals, PADCEV can cause fetal harm…" Added more detail to the animal study results: "maternal toxicity, embryo-fetal lethality, structural malformations and skeletal anomalies at maternal exposures approximately similar to the exposures at the recommended human dose of 1.25 mg/kg."
Lactation (8.2)	(b) (4)	Revised to advise lactating women not to breastfeed during treatment with PADCEV and for at least 3 weeks after the last dose.
Females and Males of Reproductive Potential (8.3)	Advise females of reproductive potential to use effective contraception during PADCEV treatment and for at least (b) (4) months after last do e. Advise male patients with female partners of reproductive potential to use effective contraception during	Changed (b) (4) to 2 months for females. Changed to 4 months for males.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
	treatment and for at least (b) (4) months after last dose	
Geriatric Use (8.5)	(b) (4)	Deleted this sentence.
Hepatic Impairment (8.6)	(b) (4)	Revised to "Avoid the use of PADCEV in patients with moderate or severe hepatic impairment" Added "in another ADC that contains MMAE, the frequency of ≥Grade 3 adverse reactions and deaths was greater in patients with moderate or severe hepatic impairment compared to patients with normal hepatic function."
(b) (4)		Deleted this section.
Description (11)		Added more detail: "PADCEV is supplied as a 20 mg per vial and a 30 mg per vial… (2.3 mL and 3.3 mL, respectively)"
Clinical Pharmacology (12) Pharmacodynamics (12.2)		Added "In an exposure-response analysis, higher enfortumab vedotin exposure was associated with higher incidence of some adverse reactions (e.g., Grade ≥2 peripheral neuropathy, Grade ≥3 hyperglycemia) and a lower exposure was associated with lower efficacy."

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Pharmacokinetics (12.3)	[redacted] (b) (4)	Added a table with exposure parameters of ADC and unconjugated MMAE after cycle 1. Added "The effect of end stage renal disease with or without dialysis or moderate/severe hepatic impairment or liver transplantation on the pharmacokinetics of ADC or unconjugated MMAE is unknown." Reorganized Drug Interaction Studies Section: "Strong CYP3A4 Inhibitors," "Strong CYP3A4 Inducers," "Sensitive CYP3A4 Substrates."
Clinical Studies (14)	[redacted] (b) (4)	Added clinically significant patient exclusion criteria for the EV-201 trial. Deleted [redacted] (b) (4) Added descriptive statistics on histology, proportion of patients who had received prior PD-1 vs. PD-L1 inhibitor vs. both, proportion of patients who had received prior cisplatin vs. carboplatin vs. both. Deleted references to [redacted] (b) (4) Deleted [redacted] (b) (4)
Patient Counseling Information (17)		Reordered the counseling topics to reflect clinical relevance. Added "ocular disorders" counseling subsection.

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
		Added "Advise pregnant women and females of reproductive potential of the potential risk to the fetus." Made changes on time period to avoid lactation and reproduction to be consistent with section 8 as above. Added Infertility section: "Advise males of reproductive potential that PADCEV may impair fertility."

APPEARS THIS WAY ON ORIGINAL

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

DRISK and DO1 agreed that no REMS was required based on review of the safety results of this application.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

PMR 3765-1. Submit the final report and datasets for the final analysis of overall survival (OS) for the confirmatory clinical trial EV-301 entitled; "An Open-Label, Randomized Phase 3 Study to Evaluate Enfortumab Vedotin vs Chemotherapy in Subjects with Previously Treated Locally Advanced or Metastatic Urothelial Cancer," to provide additional long-term efficacy data that will inform product labeling.

14 Division Director (DHOT) (NME ONLY)

X X

X X

15 Division Director (OCP)

X X

X X

16 Division Director (OB)

X X

X X

17 Division Director (Clinical)

X X

X X

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X X

X X

19 Appendices

19.1. References

The Applicant's References:

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1. NCCN. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for T-Cell Lymphomas Version 2.2019. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed January 8, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. 2019.
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The FDA's References:

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19.2. Financial Disclosure

The Applicant's Position:
All financial disclosures and additional processes to minimize bias are described in Section 8.1.2.

The FDA's Assessment:
See Financial Disclosure section in Section 8.1.2.

Covered Clinical Study (Name and/or Number):* EV-101 and EV-201

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: EV-101: 27 investigators; EV-201: 44 investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 0 Sponsor of covered study: Seattle Genetics, Inc.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: NA	Yes ☐	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

19.3. Nonclinical Pharmacology/Toxicology

Data:
All data presented in Section 5, Nonclinical Pharmacology/Toxicology.

The Applicant's Position:
N/A

The FDA's Assessment:
N/A

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Summary of Bioanalytical Method Validation and Performance

ADC
The bioanalytical methods for measuring ADC serum concentrations are shown in **Table 85**. ADC serum concentrations were measured using a validated sandwich enzyme-linked immunosorbent assays (ELISAs). The ADC was captured on an ELISA plate by immobilized anti-MMAE/F antibody (SG15.22) and detected with biotinylated anti-AGS-22M6 antibody (M22-id6-1a21.1) and streptavidin-conjugated horseradish peroxidase. Tetramethylbenzidine was used as a substrate for color development. The methods met the acceptance criteria specified in the method validation plans for selectivity, within-run and between-run accuracy, and precision for the measurement of ADC in clinical study samples. The lower limit of quantitation (LLOQ) was 80 and 25 ng/mL, depending on the method.

Table 85. Method for measuring ADC serum concentrations

Study No.	AR4854	7465-ME-0002
Matrix	Serum	Serum
Analyte	Enfortumab vedotin	Enfortumab vedotin
Analytical instrument and detection method	ELISA	ELISA
Minimum required dilution	1:40	1:40
Validation results		
Lower limit of quantitation [ng/mL]	80.0	25.0
Amount of matrix used [µL]	5	15.0
Concentration range [ng/mL]	80.0 – 640.0	25.0 – 1000
Within-run accuracy [%RE]	−10.0 – 23.3	−11.4 – 9.10
Between-run accuracy [%RE]	0.0 – 10.0	−5.40 – 3.70
Within-run precision [%CV]	0.0 – 20.0	0.700 – 12.9
Between-run precision [%CV]	7.7 – 13.3	4.30 – 7.70
Dilution Integrity Accuracy Precision [%CV]	16667-fold 94.0% - 104.0%† NA	1667-fold -2.53%RE – 0.267%RE‡ 0.848 – 2.81
Short-term stability	24 hours at room temperature	25 hours at room temperature
Long-term stability	684 days at −70 ± 10°C	1 day at −25 ± 5°C 45 days at −80 ± 10°C
Freeze-thaw stability	7 freeze-thaw cycles at −70 ± 10°C	6 freeze-thaw cycles at −80 ± 10°C
Hook effect	NA	No effect up to 125000 ng/mL
Test facility	(b) (4)	
Clinical study in which the method was used	[Study AGS-22M6E-11-1], [Study EV-101], [Study EV-102]	[Study EV-201]

Source: Table 3 from Applicant's Summary of Biopharmaceutic Studies and Analytical Methods

MMAE

The bioanalytical methods for measuring free MMAE plasma concentrations are shown in **Table 86**. Free MMAE plasma concentrations were measured using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) with internal standard (D_8-MMAE) methods. The LLOQ was 10 pg/mL. These methods met the acceptance criteria specified in the method validation plans for selectivity, within-run and between-run accuracy, and precision for the measurement of MMAE in clinical study samples.

Table 86. Methods for measuring free MMAE plasma concentrations

Study No.	8245676	7465-ME-0001
Matrix	Sodium citrate plasma	Sodium citrate plasma
Analyte	MMAE-d_8	Free MMAE
Analytical instrument and detection method	LC-MS/MS	LC-MS/MS
Sample preparation technique	SPE	SLE
Validation results		
Lower limit of quantitation [pg/mL]	10.0	10.0
Amount of matrix used [mL]	0.150	0.025
Concentration range [pg/mL]	10.0 – 2500	10.0 – 2000
Within-run accuracy [%RE]	–0.5 – 11.0	–2.3 – 3.5
Between-run accuracy [%RE]	1.0 – 5.0	–0.1 – 2.0
Within-run precision [%CV]	1.3 – 8.1	1.0 – 7.2
Between-run precision [%CV]	2.5 – 7.9	2.6 – 6.1
Dilution Integrity Accuracy [%RE] Precision [%CV]	10-fold 4.5 5.1	2.5 and 4-fold –1.9 – 0.9 2.6 – 4.9
Short-term stability	6 hours on wet ice in the presence of enfortumab vedotin	24 hours on ice
Long-term stability	1245 days at –10°C to –30°C and –60°C to –80°C in the presence of enfortumab vedotin	4 days at –20°C and –70°C
Freeze-thaw stability	5 freeze-thaw cycles at –10 to –30°C and –60 to –80°C in the presence of enfortumab vedotin	5 freeze-thaw cycles at –20°C and –70°C
Whole blood stability	2 hours† at room temperature in the presence of enfortumab vedotin and on wet ice	2 hours each at room temperature and on ice
Test facility	(b) (4)	
Clinical study in which the method was used	[Study AGS-22M6E-11-1], [Study EV-101], [Study EV-102]	[Study EV-201]

Source: Table 4 from Applicant's Summary of Biopharmaceutic Studies and Analytical Methods

Total Antibody

The bioanalytical methods for measuring total antibody (TAb) serum concentrations are shown in **Table 87**. TAb serum concentrations were measured using validated sandwich ELISA. TAb was captured on an ELISA plate by immobilized anti-AGS-22M6 antibody (M22-id6-1a21.1) and detected with biotinylated anti-AGS-22M6 antibody (M22-id6-1a34.1) and streptavidin-conjugated horseradish peroxidase. Tetramethylbenzidine was used as a substrate for color development. These methods met the acceptance criteria specified in the method validation plans for selectivity, within-run and between-run accuracy, and precision for the measurement of TAb. The LLOQ was 80 and 25 ng/mL, depending on the method.

Table 87. Methods for measuring total antibody serum concentrations

Study No.	AR4855	7465-ME-0003
Matrix	Serum	Serum
Analyte	Enfortumab vedotin TAb	Enfortumab vedotin TAb
Analytical instrument and detection method	ELISA	ELISA
Minimum required dilution	1:40	1:40
Validation results		
Lower limit of quantitation [ng/mL]	80.0	25.0
Amount of matrix used [µL]	5	15.0
Concentration range [ng/mL]	80.0 – 640.0	25.0 – 1000
Within-run accuracy [%RE]	−8.1 – 31.7§	−11.7 – 32.2§
Between-run accuracy [%RE]	5.6 – 15.0	−5.90 – 9.40
Within-run precision [%CV]	0.0 – 12.4	0.9 – 14.4
Between-run precision [%CV]	6.9 – 9.4	4.50 – 13.9
Dilution Integrity Accuracy Precision [%CV]	16667-fold 96.0% – 106.5%† NA	1667-fold −8.00%RE – −2.80%RE‡ 2.55 – 5.66
Short-term stability	24 hours at room temperature	26 hours at room temperature
Long-term stability	714 days at −70 ± 10°C	13 days at −25 ± 5°C 50 days at −80 ± 10°C
Freeze-thaw stability	7 freeze-thaw cycles at −70 ± 10°C	5 freeze-thaw cycles at −80 ± 10°C
Test facility	(b) (4)	
Clinical study in which the method was used	[Study AGS-22M6E-11-1], [Study EV-101], [Study EV-102]	[Study EV-201]

Source: Table 5 from Applicant's Summary of Biopharmaceutic Studies and Analytical Methods

19.4.1. Population PK Analyses

The Applicant submitted a population PK report entitled "*Population Pharmacokinetic Modeling of Enfortumab Vedotin in Subjects with Locally Advanced or Metastatic Urothelial Cancer*" with objective to characterize the PK profile of enfortumab vedotin and unconjugated MMAE in subjects from clinical studies AGS-22M6E-11-1, EV-101, EV-102 and EV-201. The impact of pre-defined covariate effect on the PK of enfortumab vedotin and unconjugated MMAE was also investigated. The reviewer was able to repeat and verity the population PK analyses with the submitted data and codes. The results of the Applicant's population PK analyses are acceptable.

Data: A total of 7330 enfortumab vedotin and 7337 MMAE concentration records representing 369 subjects from 4 clinical studies (AGS-22M6E-11-1, EV-101, EV-102 and EV-201) and based on data cutoff of January 3, 2019 were included in the sequential modeling of enfortumab vedotin and unconjugated MMAE.

Population PK Modeling for Enfortumab Vedotin: The PK of enfortumab vedotin following IV infusion administration was adequately described by a three-compartment model with first-

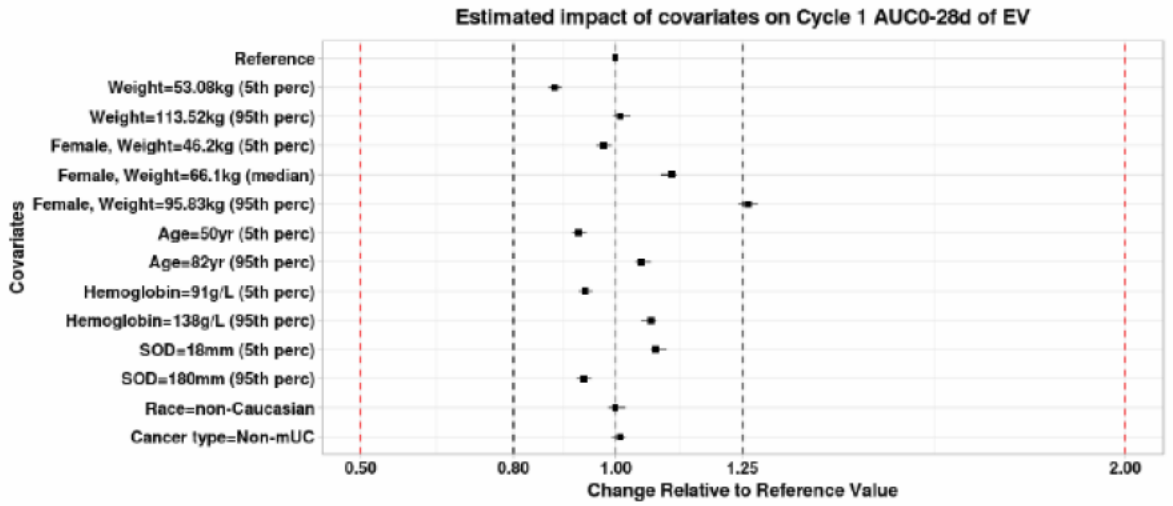
order elimination. Enfortumab vedotin CL_A was estimated to be 0.104 L/h and total volume of distribution at steady state (sum of volume of distribution in central and peripheral compartments) to be 10.9 L. Enfortumab vedotin clearance and volume parameters increased with increasing body weight. The population parameter estimates and bootstrap median with 95%CI are summarized in **Table 88**. The impact of covariates on enfortumab exposures is demonstrated in **Figure 17**.

Table 88: **Parameter estimates of base and final population PK models for enfortumab vedotin**

Parameter [Unit]	*Base Model* Parameter Estimate (%RSE or shrinkage[a])	*Final Model* Parameter Estimate (%RSE or Shrinkage[a])	*Final Model* Bootstrap Estimate Median (95%CI[b])
CL_A [L/h]	0.0992 (1.5)	0.104 (1.5)	0.104 (0.101, 0.107)
V1 [L]	3.52 (1.4)	3.75 (1.7)	3.75 (3.62, 3.87)
Q2 [L/h]	0.00220 (16)	0.00249 (8.4)	0.00248 (0.00210, 0.00292)
V2 [L]	2.49 (18)	4.67 (18)	4.54 (2.98, 5.89)
Q3 [L/h]	0.0378 (3.6)	0.0372 (3.1)	0.0373 (0.0352, 0.0399)
V3 [L]	2.68 (3.5)	2.88 (3.3)	2.88 (2.70, 3.08)
Covariate Effects[c]			
Weight ~ CL_A, Q2, Q3	0.761 (8.9)	0.656 (12)	0.649 (0.496, 0.800)
Weight ~ V1, V2, V3	0.710 (10)	0.592 (13)	0.590 (0.444, 0.741)
Age ~ CL_A	--	-0.267 (27)	-0.268 (-0.419, -0.128)
Hemoglobin ~ CL_A	--	-0.322 (26)	-0.320 (-0.488, -0.159)
Gender(female)~ CL_A	--	-0.146 (15)	-0.146 (-0.191, -0.099)
SOD ~ CL_A	--	0.0645 (28)	0.0652 (0.0310, 0.0972)
Gender(female)~V1	--	-0.149 (18)	-0.149 (-0.196, -0.0942)
SOD ~ V1		0.0672 (30)	0.0676 (0.0268, 0.103)
Cancer type (non-mUC)~ V3	--	-0.226 (19)	-0.229 (-0.301, -0.147)
Inter-individual variability (CV%)			
ω_{CLA}	22.6 (3.5)	19.7 (4.7)	19.5 (18.0, 21.0)
ω_{V1}	25.5 (6.1)	23.6 (7.8)	23.4 (20.9, 25.8)
ω_{V3}	42.8 (12)	40.5 (12.3)	40.4 (36.1, 44.9)
Residual variability			
Proportional error (CV%)	24.3 (2.8)	26.5 (1.9)	26.4 (25.5, 27.4)
Additive error [µg/mL] (SD)	0.0224 (21)	--	--

Source: Table 6 on page 51 of Applicant's population PK Report

Figure 17: Estimated impact of covariates on enfortumab vedotin exposures



Source: Adapted from Figure 9 on page 68 of Applicant's population PK Report

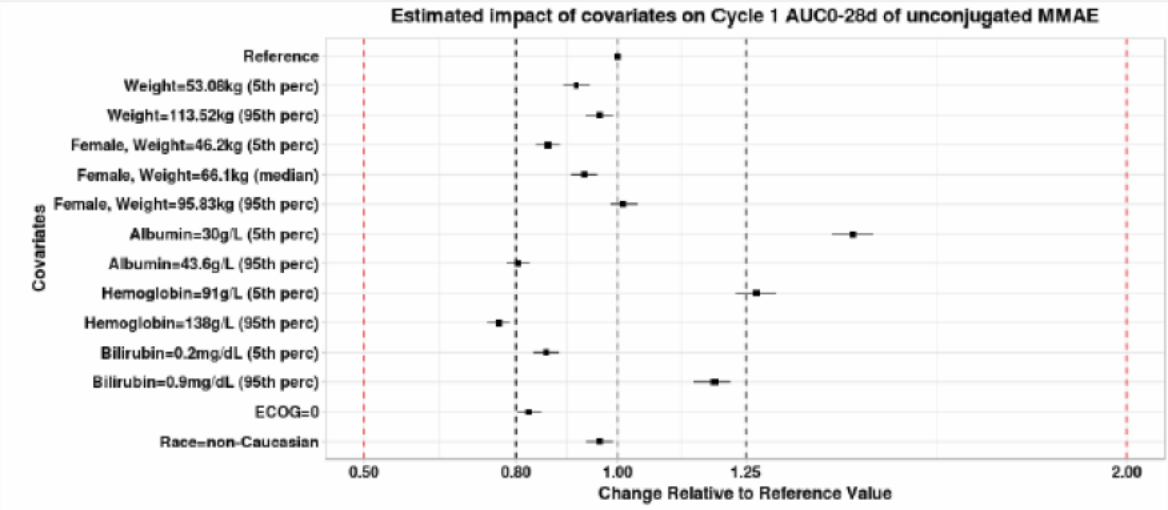
Population PK Modeling for Unconjugated MMAE: The final model for MMAE was a two-compartment model with first-order elimination, exponentially decreasing conversion rate from enfortumab vedotin to MMAE. The population parameter estimates and bootstrap median with 95%CI are summarized in **Table 89**. The impact of covariates on unconjugated MMAE exposures are shown in **Figure 18**.

Table 89: Parameter estimates of base and final population PK models for unconjugated MMAE

Parameter [Unit]	*Base Model* Parameter Estimate (%RSE/Shrinkage[a])	*Final Model* Parameter Estimate (%RSE/Shrinkage[a])	*Final Model* Bootstrap Estimate Median (95%CI[b])
CL_M [L/h]	2.83 (3.1)	2.72 (3.0)	2.74 (2.55, 2.88)
V_M [L]	96.9 (2.9)	99.6 (3.0)	99.3 (94.0,105)
Q_M [L/h]	14.8 (5.8)	15.2 (6.3)	15.2 (13.4, 17.4)
V_{MP} [L]	140 (4.0)	118 (4.2)	118 (107, 130)
DAR0 [Unitless]	3.8 Fixed	3.8 Fixed	3.8 Fixed
BETA [1/h]	0.000521 (11)	0.000519 (10)	0.000530 (0.000444, 0.000737)
Covariate Effects[c]			
WT ~ CL_M, Q_M	0.75 Fixed	0.75 Fixed	0.75 Fixed
WT ~ V_M, V_{MP}	1 Fixed	1 Fixed	1 Fixed
Albumin ~CL_M	--	1.59 (16)	1.58 (1.11, 2.10)
ECOG ~ CL_M	--	0.232 (26)	0.232 (0.116, 0.363)
Hemoglobin ~ CL_M	--	1.21 (18)	1.22 (0.809, 1.609)
Bilirubin ~ CL_M	--	-0.238 (22)	-0.235 (-0.340, -0.140)
Albumin ~ V_M	--	1.71 (15)	1.71 (1.21, 2.23)
Albumin ~ V_{MP}	--	1.52 (21)	1.51 (0.922, 2.19)
Hemoglobin ~ V_{MP}	--	1.77 (17)	1.78 (1.22, 2.35)
Race (Non-Caucasian)	--	0.642 (22)	0.649 (0.336, 1.01)
Gender (female) ~ V_{MP}	--	0.473 (21)	0.468 (0.280, 0.715)
Inter-individual variability (CV%)			
ω_{CLM}	54.5 (3.2)	43.6 (3.8)	43.4 (39.4, 47.1)
ω_{VM}	55.9 (8.0)	52.0 (8.3)	51.8 (46.7, 56.5)
ω_{VMP}	70.3 (14)	54.3 (18)	53.7 (46.7, 60.6)
Residual variability (CV%)			
Proportional error	32.1 (2.2)	32.2 (2.2)	32.1 (30.7, 33.5)

Source: Table 8 on page 64 of Applicant's population PK report

Figure 18: Estimated impact of covariates on unconjugated MMAE exposures



Source: Adapted from Figure 10 on page 69 of Applicant's population PK report

19.4.2. Exposure-Response Analyses

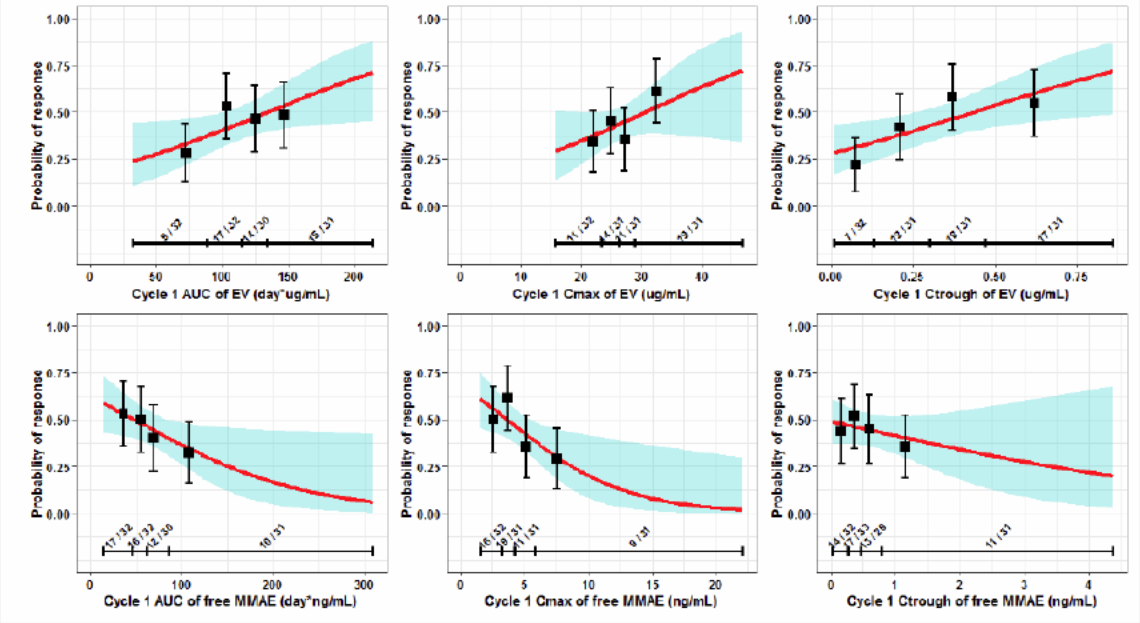
The Applicant submitted a report entitled "Exposure-Response Analysis of Enfortumab Vedotin" with objectives to characterize the relationship of enfortumab vedotin and free MMAE exposure with efficacy and safety endpoints. The Applicant's results are summarized below. The reviewer was able to repeat and verity the analyses with the submitted data and codes. The results of the Applicant's exposure-response analyses are acceptable.

Exposure-Response Relationship for Efficacy
Data: The relationships between enfortumab vedotin and free MMAE exposures and efficacy endpoints were evaluated mainly in metastatic UC subjects enrolled in EV-101 Part C and EV-201 Cohort 1.

Method: The efficacy endpoints evaluated in ER analyses included best overall response (BOR), duration of response (DOR) and progression free survival (PFS) as well as overall survival (OS). For efficacy endpoints, univariate logistic regression modeling was used to evaluate the relationship of BOR and exposures of enfortumab vedotin and free MMAE as a continuous variable. Univariate Cox proportional hazard modeling was used to evaluate the relationship of DOR, PFS and OS and exposures of enfortumab vedotin and free MMAE as continuous variables

Results: The relationships between efficacy endpoints and exposure metrics of enfortumab vedotin and free MMAE and BOR are demonstrated in **Figure 19**.

Figure 19: The relationship between Cycle 1 exposures of enfortumab vedotin (top 3 panels) and free MMAE and BOR using logistic regression model for EV-201 Cohort 1



Source: Figure 2 on page 42 of Applicant's Exposure-Response report

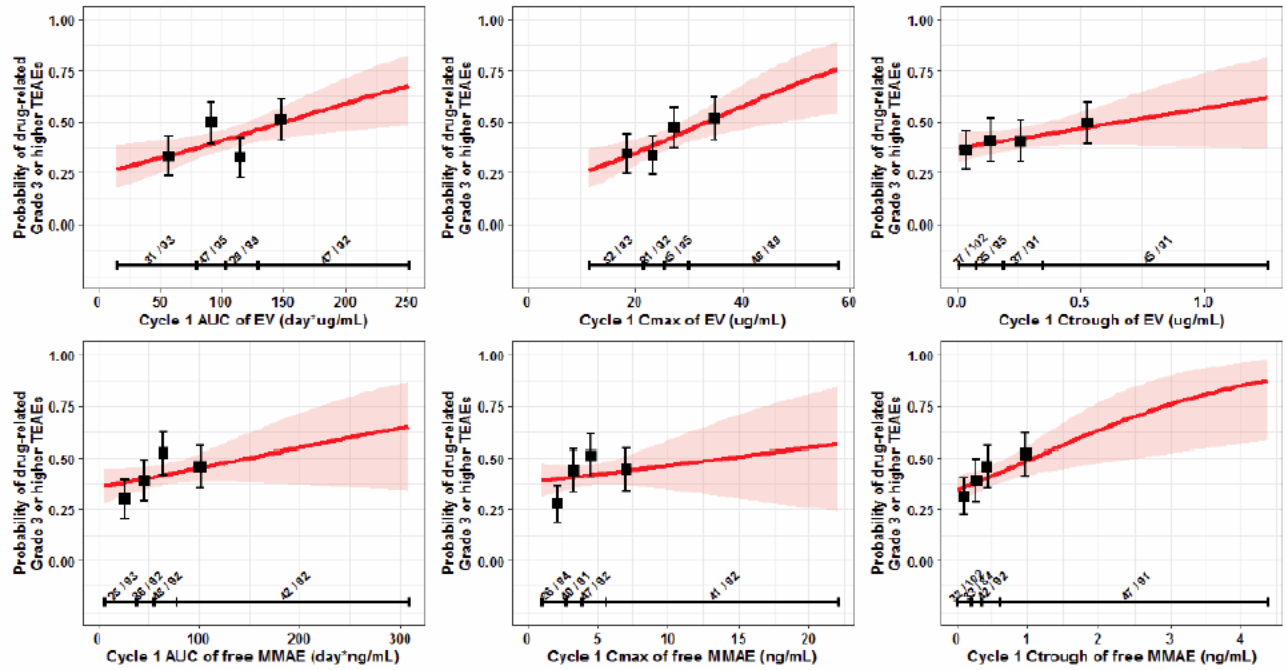
Exposure-Response Relationship for Safety

The exposure-safety analysis evaluated safety data pooled from 4 studies including AGS-22M6E-11-1, EV-102, EV-101 and EV-201.

The primary safety endpoints focused on all drug-related Grade 3 or higher treatment-emergent adverse events (TEAEs), dose adjustment due to TEAEs and those TEAEs of special interest (AESI). Univariate logistic regression modeling was used to evaluate the relationship of all safety endpoints and exposures of enfortumab vedotin and free MMAE.

The relationship between Cycle 1 exposures of enfortumab vedotin and free MMAE and probability of drug-related Grade 3 or higher TEAEs is demonstrated in **Figure 20**.

Figure 20: The relationship between Cycle 1 exposures of enfortumab vedotin (top 3 panels) and free MMAE (bottom 3 panels) and probability of drug-related Grade 3 or higher TEAEs using logistic regression model for the all EV population



Solid black squares represent the proportion of subjects with events grouped by quartiles of enfortumab vedotin (EV) or free MMAE exposure metrics and plotted at the median for the groups with the error bars represent 95%CI. Red solid curves and shaded area represent predicted values and 95%CI of model predicted incident rate, respectively. The exposure range in each quartile is denoted by the horizontal black line along with the number of subjects with adverse event/ total number of subjects in each quartile.

Source: Figure 6 on page 55 of Applicant's Exposure-Response report

19.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:

Overall, herpes zoster was reported in 6 patients out of 405 by June 15, 2018 (the 90-day safety update), half of which were grade 3 events and one was ophthalmic. Four of these 6 patients were in Cohort 1 of EV-201; this was added to section 6 of product labeling. The median exposure to therapy prior to event was 109 days. The median age of patients with the event was 63.5 years. Two of the 6 patients received doses lower than 1.25 mg/kg.

FDA's label (section 6, Table 4) reports the laboratory abnormalities that occurred in at least 10% (grade 2-4) or 5% (grade 3-4) of Cohort 1. Section 8.2.4 of this review includes tables with grade 1-4 laboratory abnormalities and grade 3-4 laboratory abnormalities in Cohort 1 or all patients who received 1.25 mg/kg.

Table 90. Grade 2-4 Laboratory Abnormalities Reported in ≥ 5% of Patients

	Cohort 1, N=125		All 1.25 mg/kg, N=310	
	N	%	N	%
Hematology				

Hemoglobin decreased	42	34	94	31
Lymphocytes decreased	39	32	102	34
Leukocytes decreased	17	14	52	17
Neutrophils decreased	17	14	50	17
Chemistry				
Phosphate decreased	72	34	88	29
Glucose increased	33	27*	89	
Creatinine increased	24	20	48	16
Lipase increased	17	14	not evaluated	
Albumin decreased	12	9.8	38	12
Sodium decreased	10	8.2	29	9.5
Alkaline phosphatase increased	8	6.6	17	5.6
Urate increased	8	6.6	23	7.7
AST increased	7	5.8	19	6.3
Potassium decreased	23	19†	41	13

*CTCAE Grade 2 is defined as fasting glucose >160-250 mg/dL. Fasting glucose levels were not measured. However, 19% of patients in EV-201 and 29% of patients who received 1.25 mg/kg across the drug development program had non-fasting glucose >160-250 mg/dL.
†Includes Grade 1 (potassium 3.0-3.5 mmol/L)-Grade 4.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Eias Zahalka	OOD/DHOT	Sections: 5	**Select one:** x Authored ___ Approved
	Signature: Tiffany Ricks signing on behalf of Eias Zahalka Tiffany K. Ricks -S Digitally signed by Tiffany K Ricks -S DN: c=US o=U S Government ou=HHS ou=FDA ou=People 0 9 2342 19200300 100 1 1=2000497170 cn=Tiffany K Ricks -S Date: 2019 12 17 07:56:54 05'00'			
Nonclinical Team Leader	Tiffany Ricks	OOD/DHOT	Sections: 5	**Select one:** x Authored x Approved
	Signature: Tiffany K. Ricks -S Digitally signed by Tiffany K Ricks -S DN: c US o U S Government ou HHS ou FDA ou People 0 9 2342 19200300 100 1 1 2000497170 cn Tiffany K Ricks -S Date: 2019 12 17 07:57:21 05 00			
Nonclinical Team Division Director (NME only)	John Leighton	OOD/DHOT	Sections: 5	**Select one:** ___ Authored x Approved
	Signature: John K. Leighton -S Digitally signed by John K. Leighton -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300085260, cn=John K. Leighton -S Date: 2019.12.17 08:00:14 -05'00'			
Clinical Pharmacology Reviewer	Vicky Hsu	OCP/DCPI	Sections: 6, 19.4	**Select one:** x Authored ___ Approved
	Signature: Vicky Hsu -S Digitally signed by Vicky Hsu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Vicky Hsu -S, 0.9.2342.19200300.100.1.1=2000996657 Date: 2019.12.16 21:54:48 -05'00'			
Pharmacometrics Reviewer	Fang Li	OCP/DPM	Sections: 6, 19.4	**Select one:** X Authored ___ Approved
	Signature: Fang Li -S Digitally signed by Fang Li -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Fang Li -S, 0.9.2342.19200300.100.1.1=1300430137 Date: 2019.12.16 20:14:56 -05'00'			
Genomics Reviewer	Sarah Dorff	OCP/DTPM	Sections: 6	**Select one:** X Authored __ Approved
	Signature: Sarah E. Dorff -S Digitally signed by Sarah E. Dorff -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Sarah E. Dorff -S, 0.9.2342.19200300.100.1.1=2001211253 Date: 2019.12.17 10:16:01 -05'00'			

Pharmacometrics Team Leader	Jingyu Yu	OCP/DPM	Sections: 6, 19.4	**Select one:** _X__ Authored _X_ Approved
	Jingyu Yu -S Digitally signed by Jingyu Yu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jingyu Yu -S, 0.9.2342.19200300.100.1.1=2000794699 Date: 2019.12.17 10:00:50 -05'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED /APPROVED
Genomics Team Leader	Rosane Charlab Orbach	OCP/DTPM	Sections: 6	**Select one:** X Authored _X__ Approved
	Signature: Rosane Charlaborbach -S Digitally signed by Rosane Charlaborbach -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300436672, cn=Rosane Charlaborbach -S Date: 2019.12.17 11:20:52 -05'00'			
Clinical Pharmacology Team Leader	Pengfei Song	OCP/DCPII	Sections: 6, 19.4	**Select one:** X Authored X Approved
	Signature: Pengfei Song -S Digitally signed by Pengfei Song -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Pengfei Song -S, 0.9.2342.19200300.100.1.1=2000464900 Date: 2019.12.16 20:06:34 -05'00'			
Clinical Pharmacology Division Director	Nam Atiqur Rahman	OCP/DCPII	Sections: 6, 19.4	**Select one:** ___ Authored X Approved
	Signature: Nam A. Rahman -S Digitally signed by Nam A. Rahman -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Nam A. Rahman -S, 0.9.2342.19200300.100.1.1=1300072597 Date: 2019.12.17 16:57:51 -05'00'			
Statistical Reviewer	Lijun Zhang	OB/DBV	Sections: 7, 8, 11	**Select one:** x Authored ___ Approved
	Signature: Lijun Zhang -S Digitally signed by Lijun Zhang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lijun Zhang -S, 0.9.2342.19200300.100.1.1=2000472119 Date: 2019.12.16 19:23:22 -05'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Statistical Team Leader	Shenghui Tang	OB/DBV	Sections: 7, 8, 11	**Select one:** __X__ Authored __X__ Approved
	Signature: Shenghui Tang -S Digitally signed by Shenghui Tang -S Date: 2019.12.17 11:41:35 -05'00'			
Division Director (OB)	Rajeshwari Sridhara	OB/DBV	Sections: 7, 8, 11, 16	**Select one:** ___ Authored __X__ Approved
	Signature: Rajeshwari Sridhara -S Digitally signed by Rajeshwari Sridhara -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300150474, cn=Rajeshwari Sridhara -S Date: 2019.12.17 12:48:47 -05'00'			
Safety Analyst	Yutao Gong	OND/OOD	Section: 8	**Select one:** __x__ Authored ___ Approved
	Signature: Yutao Gong -S Digitally signed by Yutao Gong -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yutao Gong -S, 0.9.2342.19200300.100.1.1=2002364938 Date: 2019.12.17 10:19:12 -05'00'			
Clinical Reviewer	Elaine Chang	OOD/DO1	Sections: 2-4, 8-13, 19	**Select one:** __x__ Authored __x__ Approved
	Signature: Elaine Chang -S Digitally signed by Elaine Chang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Elaine Chang -S, 0.9.2342.19200300.100.1.1=2002602609 Date: 2019.12.17 11:16:10 -05'00'			
Associate Director for Labeling	William Pierce	OOD	Sections: 11 Labeling Recommendations, Prescribing Information	**Select one:** __x__ Authored __x__ Approved
	Signature: William F. Pierce -S5 Digitally signed by William F. Pierce -S5 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300235575, cn=William F. Pierce -S5 Date: 2019.12.17 15:32:46 -05'00'			
Cross-Disciplinary Team Leader (CDTL)	Chana Weinstock	OOD/DO1	Sections: Section 1, 8-13 ALL	**Select one:** __x__ Authored __x__ Approved
	Signature: Chana Weinstock -S Digitally signed by Chana Weinstock -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001659606, cn=Chana Weinstock -S Date: 2019.12.17 19:16:04 -05'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Deputy Division Director (Clinical)	Amna Ibrahim	OOD/DO1	Sections: ALL	**Select one:** ___ Authored _x_ Approved
	Signature: Amna Ibrahim -S Digitally signed by Amna Ibrahim -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Amna Ibrahim -S, 0.9.2342.19200300.100.1.1=1300150984 Date: 2019.12.18 11:27:24 -05'00'			
Office Deputy Director	Marc Theoret	OOD	Sections: ALL	**Select one:** ___ Authored _X_ Approved
	Signature:			

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RAJESH VENUGOPAL
12/18/2019 03:23:36 PM

DANIEL L SUZMAN on behalf of CHANA WEINSTOCK
12/18/2019 03:56:17 PM

MARC R THEORET
12/18/2019 04:02:19 PM