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APPLICATION NUMBER:

761208Orig1s000

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	Biologics License Application (BLA), 351 (a)
Application Number(s)	761208
Priority or Standard	Priority
Submit Date(s)	February 10, 2021
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Division/Office	DO1/OOD/OND/CDER
Review Completion Date	<i>Electronic Stamp Date</i>
Established Name	Tisotumab vedotin-tftv
(Proposed) Trade Name	Tivdak
Pharmacologic Class	Antibody-drug conjugate
Applicant	Seagen Inc.
Formulation(s)	40 mg lyophilized cake or powder
Dosing Regimen	2 mg/kg (up to maximum of 200 mg) IV every 3 weeks
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	<i>Accelerated Approval</i>
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy

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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

Glossary

1Q3W	once every 3 weeks
³ H	tritium
3Q4W	three doses every 4 weeks
⁸⁹ Zr	zirconium 89
%CV	percent coefficient of variance
ADA	antidrug antibody, antidrug antibodies
ADC	antibody drug conjugate
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AESI	adverse event of special interest
ALT	alanine transaminase
APTT	activated partial thromboplastin time
AST	aspartate transaminase
AUC	area under the concentration-time curve
BCRP	Breast Cancer Resistance Protein
BCVA	Best corrected visual acuity
BMI	body mass index
BSEP	bile salt export pump
C _{ave}	average serum concentration
CFR	Code of Federal Regulations
CI	confidence interval
C _{ave}	average serum concentration
CL	linear clearance
CL/F	apparent clearance
C _{max}	maximum serum concentration
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
COA	clinical outcome assessment
CR	complete response
CRO	contract research organization
CrCl	creatinine clearance
CRT	clinical review template
CTCAE	Common Terminology Criteria for Adverse Event
cTF	circulating tissue factor
CYP	cytochrome P450 enzyme
DCR	disease control rate
DDI	drug-drug interaction
DILI	drug-induced liver injuries
DLT	drug-limiting toxicity
DMC	data monitoring committee

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DOR	duration of response
Δ QTcF	Delta QTcF
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EORTC	European Organisation for Research and Treatment of Cancer
FAS	Full Analysis Set
FXa	activated factor X
GCP	good clinical practice
GLP	good laboratory practice
hERG	human ether-a-go-go-related gene
HNSTD	highest non-severely toxic dose
HRQOL	health related quality of life
IgG1	immunoglobulin G1
IHC	immunohistochemistry
IMP	investigational medical product
INR	international normalized ratio
IPD	important protocol deviation
iPSP	Initial Pediatric Study Plan
IRC	independent review committee
IRR	infusion related reaction
ISS	integrated summary of safety
LLOQ	lower limit of quantification
LPS	lipopolysaccharide
MDR1	multidrug resistance mutation 1
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	monomethyl auristatin E
MRP2	Multidrug Resistance Protein2
N/A	not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NME	new molecular entity
NOAEL	No adverse effect level
NSCLC	non-small cell lung cancer
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCE	oncology center of excellence
OCT	organic cation transporter
OCP	division director
OMP	ocular mitigation plan

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ORR	objective response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	progressive disease
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetics
PR	partial response
PRO	patient reported outcome
PT	prothrombin time
QTc	duration of QT interval corrected for heart rate
QTcF	corrected QT interval by Fredericia
RECIST	response evaluation criteria in solid tumors
REMS	risk evaluation and mitigation strategy
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SCCHN	Squamous cell carcinoma of the head and neck
SD	stable disease
SMQ	standardized MedDRA query
SOC	system organ class
STD	standard deviation
TAb	total antibody
TEAE	treatment emergent adverse event
TEG	thromboelastography
TF	tissue factor
TGA	thrombin generation assay
TK	toxicokinetic
T _{max}	time of maximum serum concentration
TTR	time to response
ULN	upper limit of normal
US	United States
vc	valine-citrulline
vcMMAE	valine-citrulline monomethyl auristatin E
Vd	volume of distribution
Vd/F	apparent volume of distribution

1 Executive Summary

1.1 Product Introduction

Tisotumab vedotin-tftv is a tissue factor (TF)-directed antibody drug conjugate (ADC). It contains a human anti-TF IgG1 kappa antibody, a protease-cleavable valine-citrulline linker, and a monomethyl auristatin E (MMAE) payload which is a microtubule-disrupting agent. Tisotumab vedotin is not approved for any indication worldwide.

The Applicant proposed the following indication for BLA 761208:

(b) (4)

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

The recommended indication for accelerated approval is:

Tivdak is indicated for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy.

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

The recommended dose of tisotumab vedotin is 2 mg/kg (up to a maximum of 200 mg for patients ≥ 100 kg) given IV over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.

1.2 Conclusions on the Substantial Evidence of Effectiveness

The review team recommends accelerated approval of tisotumab vedotin

(b) (4)

in accordance with 21 Code of Federal Regulations (CFR) Part 601.41, Subpart E for Biological Products Licensing Regulations. This recommendation is primarily based on data from GCT1015-04 (innovaTV 204, NCT03438396), a single arm, international trial in 101 patients with recurrent or metastatic cervical cancer who had received ≤ 2 prior lines of systemic treatment in the metastatic setting, including doublet chemotherapy, with bevacizumab if eligible. Sixty-nine percent of patients had received bevacizumab as part of prior systemic therapy.

The major efficacy outcomes measures were confirmed overall response rate (ORR) as assessed by an independent review committee (IRC) according to RECIST v1.1, and DOR. Confirmed ORR was 23.8% (95% CI: 15.9%, 33.3%). Median DOR was 8.3 months (95% CI: 4.2, NR). These results

represent an advantage compared to available therapies and are reasonably likely to predict clinical benefit in the indicated patient population.

Available therapies in this treatment setting include single agent chemotherapies with ORRs ranging from 5-21% and median DORs ranging from 2-4 months. One important caveat in interpreting these ORRs/DORs is that these data are from small trials conducted prior to establishment of a chemotherapy doublet with bevacizumab as standard-of-care first-line treatment for patients in the U.S. The efficacy of these chemotherapy agents (as measured by ORR and DOR) in the current era of second-line or later treatment for cervical cancer following first-line treatment with a chemotherapy doublet and bevacizumab is unknown. However, the review team expects that the efficacy of several of the available single agent chemotherapies would be less in the current treatment landscape, after bevacizumab-containing doublet chemotherapy.

As a result, the review team concludes that tisotumab vedotin represents a new treatment option for patients with recurrent or metastatic cervical cancer who have received ≤ 2 prior lines of systemic treatment in the metastatic setting, including doublet chemotherapy, with bevacizumab if eligible. This patient population has a significant unmet medical need for better therapies.

FDA review team recommends granting accelerated approval to tisotumab vedotin for the following indication:

Tivdax is a tissue factor-directed antibody and microtubule inhibitor conjugate indicated for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy.

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

1.3 Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Cervical cancer is the fourth most common cancer in women worldwide. In the U.S., there will be an estimated 14,480 new cases and 4,290 deaths from cervical cancer in 2021. Almost all cases of cervical cancer are associated with HPV infection. The incidence of cervical cancer in the U.S. has fallen over the past few decades due to the implementation of screening with Pap tests. However, once diagnosed, cervical cancer is a serious and life-threatening condition with an estimated 5-year survival of 66%. If detected at an early stage, cervical cancer is potentially curable. Recurrent cervical cancer that is not amenable to local intervention (surgery and/or radiation) or metastatic cervical cancer is incurable, and treatment is palliative.

For early-stage disease, patients will typically receive surgery or radiation treatment with chemotherapy. For recurrent or metastatic disease, patients in the US will typically receive first-line systemic treatment with a chemotherapy doublet with bevacizumab. For second and later-line therapy, treatment options are limited and include single agent chemotherapies such as docetaxel, gemcitabine, ifosfamide, irinotecan, and others, with modest ORRs of 5%-21% and limited median DORs of 2-4 months. An additional challenge with these treatment options is that their efficacy following first-line treatment with a chemotherapy doublet with bevacizumab is unknown. Patients with tumors that express PD-L1 (CPS $\geq$ 1) may receive pembrolizumab which is under an accelerated approval and thus not considered available therapy, based on an ORR of 14% and a median DOR not reached.

The efficacy and safety assessment for tisotumab vedotin was primarily based on results from GCT1015-04, a single arm, international trial which enrolled 101 patients with recurrent or metastatic cervical cancer. Patients had received $\leq$ 2 prior lines of treatment in the recurrent or metastatic setting, including a chemotherapy doublet, with bevacizumab, if eligible to receive bevacizumab. Patients received tisotumab vedotin 2 mg/kg intravenously every 3 weeks until disease progression or unacceptable toxicity. Tumor assessments occurred every 6 weeks for the first 30 weeks, and every 12 weeks thereafter. The primary endpoint was confirmed ORR assessed by IRC according to RECIST v1.1. DOR was a secondary endpoint.

The age distribution of patients on GCT1015-04 was generally representative of a U.S.-based cervical cancer population, with a median age of 50 years (range: 31 years, 78 years), and 13% of patients $\geq$ 65 years. In terms of disease and treatment characteristics, the patient population was relevant to a U.S. based population with recurrent or metastatic cervical cancer. Enrolled patients included 68% with squamous cell carcinoma and 27% with adenocarcinoma. Seventy percent of patients had received 1 prior line of treatment in the metastatic setting and 30%

had received 2 prior lines of treatment in the metastatic setting. Most patients (69%) had received prior bevacizumab, including 63% who received it in combination with doublet chemotherapy for first-line recurrent or metastatic disease.

Confirmed ORR as per IRC according to RECIST v1.1 was 23.8% (95% CI: 15.9%, 33.3%) in 101 patients treated with tisotumab. Median DOR was 8.3 months (95% CI: 4.2, NR). ORR results were generally consistent across subgroups, except for in patients ≥ 65 years old. No patient ≥ 65 years experienced a tumor response, however FDA notes that only 13 patients ≥ 65 years were enrolled.

The safety profile of tisotumab vedotin generally reflects the TF target as well as the MMAE payload. Fatal adverse reactions occurred in 4% of patients and included septic shock and pneumonitis. Serious adverse reactions occurred in 43% of patients and included ileus (6%), hemorrhage (5%), pneumonia (4%), sepsis (3%), constipation (3%), pyrexia (3%), and peripheral neuropathy (3%). The most common adverse reactions ($\geq 30\%$) in GCT1015-04 included fatigue, nausea, peripheral neuropathy, alopecia, epistaxis, conjunctival adverse reactions, and hemorrhage. Adverse reactions leading to dose discontinuations occurred in 13% of patients and adverse reactions leading to dose reductions occurred in 23% of patients.

Ocular toxicity is an important safety signal associated with tisotumab vedotin and affected 55% of patients enrolled to GCT1015-04, including 6% of patients with ulcerative keratitis, including one patient with a corneal ulcer that perforated and required corneal transplantation. There is a Boxed Warning for ocular toxicity in the tisotumab vedotin USPI to alert providers to the risk of patients developing severe ocular toxicity including corneal ulcers. Patients and providers should adhere to the premedication and required eye care plan outlined in the tisotumab vedotin USPI, and patients should be promptly referred to an eye care professional for any new or worsening ocular symptoms.

Other important safety signals associated with tisotumab vedotin include peripheral neuropathy, hemorrhage, pneumonitis, and embryo-fetal toxicity, which are listed under Warnings and Precautions in the tisotumab vedotin USPI.

Patients with recurrent or metastatic cervical cancer have limited therapeutic options following first-line treatment with a chemotherapy doublet with bevacizumab. Available therapies in this treatment setting include single agent chemotherapies with ORRs ranging from 5-21% and median DORs ranging from 2-4 months. These data are from small trials conducted prior to establishment of a chemotherapy doublet with bevacizumab as standard-of-care first-line treatment for patients in the U.S. Given that all patients who received tisotumab vedotin on GCT1015-04 received first-line doublet chemotherapy and 69% of patients had prior bevacizumab as per U.S. standard of care, the review team considers that the efficacy of tisotumab vedotin demonstrates an improvement compared to available therapies, and these results are reasonably likely to predict clinical benefit. Tisotumab vedotin demonstrated acceptable safety and tolerability in a patient population with a

serious and life-threatening illness and limited therapeutic options. Adverse reactions are manageable through labeling which includes a boxed warning for ocular toxicity, required premedication, dose modifications, and supportive therapy.

Overall, the benefit-risk assessment for tisotumab vedotin is favorable. There is a post-marketing requirement to submit results from ongoing trial SGNTV-003/innovaTV 301, a randomized trial comparing tisotumab vedotin to investigator’s choice chemotherapy in patients with recurrent or metastatic cervical cancer, to provide confirmation of clinical benefit.

Tisotumab vedotin is recommended for accelerated approval for the following indication:

Tivdax is a tissue factor-directed antibody and microtubule inhibitor conjugate indicated for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy.

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Cervical cancer, which is almost always caused by persistent HPV infection, is the fourth most common cancer in women worldwide. • In U.S. women., there are 14,480 new cases and 4,290 cervical cancer-related deaths estimated for 2021. • Metastatic cervical cancer or recurrent cervical cancer which is not amenable to local therapy is not curable.	Recurrent or metastatic cervical cancer is incurable and is a serious and life-threatening condition.
Current Treatment Options	• Recurrent or metastatic cervical cancer is not curable, and treatment is palliative. • For first-line treatment in the recurrent or metastatic setting, guideline-based treatment for women in the U.S. is doublet chemotherapy in combination with bevacizumab, if eligible.	There is an unmet medical need for therapies that improve outcomes for patients with recurrent or metastatic cervical cancer following first-line treatment.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- Following first-line treatment, options for subsequent treatment include single agent chemotherapies with relatively low ORRs. Additionally, the efficacy of these therapies after patients receive current standard-of-care first-line treatment with a chemotherapy doublet and bevacizumab is unknown. - For patients with tumors which express PD-L1 (CPS ≥ 1), pembrolizumab is a treatment option which is under an accelerated approval.	
Benefit	- GCT1015-04 enrolled 101 patients with recurrent or metastatic cervical cancer who had received ≤ 2 prior systemic treatment regimens in the recurrent or metastatic setting including a chemotherapy doublet, with bevacizumab if eligible. - Confirmed ORR as assessed by IRC according to RECIST v1.1 was 23.8% (95% CI: 15.9, 33.3). - Median DOR was 8.3 months (95% CI: 4.2, NR).	Treatment with tisotumab vedotin in GCT1015-04 resulted in a confirmed ORR and DOR which represent an improvement compared to available therapies for patients with recurrent or metastatic cervical cancer following first-line treatment. ORR and DOR results are reasonably likely to predict clinical benefit.
Risk and Risk Management	- In GCT1015-04, the most common ($\geq 30\%$) adverse reactions that occurred in patients treated with tisotumab vedotin were hemorrhage, fatigue, nausea, peripheral neuropathy, alopecia, and conjunctival adverse reactions. The most common Grade ≥ 3 adverse reactions ($\geq 5\%$) were: anemia (9%), peripheral neuropathy (7%), fatigue (7%), and hemorrhage (6%). - Fatal adverse reactions occurred in 4% of patients and included septic shock, pneumonitis, sudden death, and multisystem organ failure, each in 1 patient.	The benefit-risk profile of tisotumab vedotin is acceptable for the indicated patient population with recurrent or metastatic cervical cancer and limited therapeutic options. Safe use of tisotumab vedotin can be managed through labeling, which includes ocular toxicity as a boxed warning and the

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- Ocular toxicity is an important safety signal associated with tisotumab vedotin, experienced by 55% of patients enrolled to GCT1015-04. In GCT1015-04, 4% of patients developed corneal ulcers (Grade 3 keratitis) and 1% of patients developed a corneal ulcer with perforation (Grade 4 keratitis) requiring corneal transplantation. - There is a boxed warning to alert providers to the potential for severe ocular toxicity in patients receiving tisotumab vedotin in the USPI. - Additional important safety signals associated with tisotumab vedotin include peripheral neuropathy, hemorrhage, pneumonitis, and embryo-fetal toxicity which are listed under Warnings and Precautions in the USPI.	inclusion of peripheral neuropathy, hemorrhage, pneumonitis, and embryo-fetal toxicity under Warnings and Precautions.

1.4 Patient Experience Data

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

X	The patient experience data that was submitted as part of the application, include: two PROs to assess HRQOL: EORTC-QLQ-C30 and EORTC-QLQ-CX24. Patients completed these measures at baseline, Cycle 2 (D1), Cycle 4 (D1), and treatment discontinuation.	Section where discussed, if applicable
	☐ Clinical outcome assessment (COA) data, such as	N/A
	☒ Patient reported outcome (PRO)	Section 8.1.2 Study Results
	☐ Observer reported outcome (ObsRO)	N/A
	☒ Clinician reported outcome (ClinRO)	Section 8.1.2 Study Results
	☐ Performance outcome (PerFO)	N/A
	☐ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	N/A

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☐	Patient-focused drug development or other stakeholder meeting summary reports	N/A
☐	Observational survey studies designed to capture patient experience data	N/A
☐	Natural history studies	N/A
☐	Patient preference studies (e.g., submitted studies or scientific publications)	N/A
☐	Other: (Please specify)	N/A
☐	Patient experience data that was not submitted in the application, but was considered in this review.	

X

Gwynn Ison, MD
Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1 Analysis of Condition

The Applicant's Position:

According to National Cancer Institute (NCI) estimates, more than 291,000 patients are living with invasive cervical cancer in the US, and more than 4,290 women in the United States (US) were estimated to have died from the disease last year ([National Cancer Institute \(NCI\) 2020](#)). An estimated 16% of patients with cervical cancer are first diagnosed with metastatic disease ([National Cancer Institute \(NCI\) 2020](#)). For patients diagnosed in stages I through III, the chances of developing recurrent or metastatic disease after first-line treatment increase with disease stage. Almost half of patients with stage I cervical cancer will see their disease progress to become recurrent or metastatic, while for patients with stage III cervical cancer this figure is nearly 65% ([Kantar Health 2020](#)). While uncommon, due to immunization and screening, cervical cancer remains the fourth most common and fourth deadliest cancer in women globally with a 5 year survival rate in the US of 17% ([Bray 2018](#))([National Cancer Institute \(NCI\) 2020](#)). No curative therapy is available for these patients.

The FDA's Assessment:

FDA clarifies that no curative therapy is available for patients with metastatic cervical cancer or for patients with recurrent cervical cancer not amenable to local treatment. Other patients may have curative treatment options. Otherwise, FDA agrees with the Applicant's description of cervical cancer.

2.2 Analysis of Current Treatment Options

First-Line Treatment

For the vast majority of patients with recurrent or metastatic cervical cancer who are not surgical candidates, palliative chemotherapy represents the only treatment option.

In the first-line, treatment of recurrent or metastatic cervical cancer is paclitaxel + cisplatin or paclitaxel + topotecan combined with bevacizumab (if eligible). Current data indicate that approximately half of all US patients with recurrent or metastatic cervical cancer receive bevacizumab as part of a first-line treatment regimen ([Kantar Health](#)).

Treatment in the Second Line and Beyond

Patients with recurrent or metastatic cervical cancer that has progressed on first-line therapy have limited treatment options, and no standard-of-care therapy has been identified in the second-line setting.

Current National Comprehensive Cancer Network (NCCN) guidelines for second-line treatment of recurrent or metastatic cervical cancer include pembrolizumab as a category 2A therapy option supported by a contemporary single-arm trial, and a host of chemotherapy agents as category 2B options supported by historical data developed before the adoption of

chemotherapy doublet + bevacizumab in front line, which is considered the current standard of care (Marth 2017; Abu-Rustum 2020).

The most commonly used agents in the US based on health claims data include pembrolizumab (for patients with tumors positive for programmed cell death ligand 1 [PD-L1]), liposomal doxorubicin, topotecan, vinorelbine, gemcitabine, or irinotecan as single agents (Kantar Health 2020).

The data supporting the NCCN recommended therapies are almost entirely derived from trials conducted prior to the adoption of bevacizumab in combination with chemotherapy as first-line standard-of-care in 2014, or in some cases even prior to the adoption of platinum doublet therapy in the first-line setting in 2009.

An exception is the KEYNOTE-158 trial of pembrolizumab (n=98) which led to accelerated approval in 2018 for the treatment of selected patients with PD-L1+ cervical cancer who have demonstrated disease progression on or after chemotherapy. The median duration of response (DOR) was not reached with median 10.2 months of follow up, and responses were seen in 14% of subjects with PD-L1+ tumors (Chung 2019). Median overall survival (OS) was 11 months in the PD-L1+ subgroup and 9.4 months for the entire trial population (Chung 2019). While patients who respond to pembrolizumab may potentially receive durable benefit, no responses were observed in subjects whose tumors did not express PD-L1, hence the large majority of second-line (and beyond) patients with recurrent or metastatic cervical cancer do not benefit from treatment with pembrolizumab.

Currently-used therapies and the trials supporting their inclusion in NCCN guidelines are described in Table 1. These trials generally had small sample sizes, often included unconfirmed response rates in the objective response rate (ORR) calculation, included adjuvant and neoadjuvant therapy as well as chemotherapy plus radiation as prior lines of therapy, allowed single-agent chemotherapy to be used as the standard-of-care in the front line, and included responses that were not assessed by IRC or by response evaluation criteria in solid tumors (RECIST). The efficacy of the chemotherapy agents is limited, with DORs of 6 months or less, and OS in the range of 6 to 9 months.

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Table 1: Summary of Standard Treatments for Recurrent and Metastatic Cervical Cancer

Product Names	Relevant Indication/Trial Population (N)	Year of Approval And Type of Approval *	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Reference
FDA Approved Treatments [Combine by Pharmacologic Class, if relevant]						
Bevacizumab and similar add on to Chemo(b)	2-3Line persistent or recurrent CC (N=46)	14 Aug 2014	5 mg/kg 1Q3W	• ORR=10.9% (4.4–21.5) • No CRs • RECIST 1.0 • median PFS=3.4 mo • median OS=7.3 mo	Increased hypertension, thromboembolic events, and gastro fistulas	(Monk 2009)
Pembrolizumab (b, C) for PD-L1+ or MSI-H/dMMR tumors	advanced cervical cancer who had PD-L1 expression of at least 1% (second line or more) N=98	Accelerated 2018	200 mg 1Q3W or 400 mg 1Q6W	• PD-L1+ • ORR=14.3% (7.4–24.1) • 2 CRs • RECIST 1.1 per IRC • All subjects • ORR =12.2% (6.5–20.4) • 3 CRs, RECIST 1.1 per IRC • median PFS=2.1 mo • median OS=9.4 mo	Pneumonitis, colitis, hepatitis, hormone gland problems, Kidney disease, skin problems, infusion reactions, transplant rejection	(Chung 2019)
Topotecan ^b (+cisplatin)	1L and 2L squamous r or mCC (N=40)	14 June 2006	1.5 mg/m ² / day x 5 every 21 days	• ORR=12.5% (NR) • 1 CR • Non-RECIST evaluation of response • median PFS=2.1 mo • median OS=6.6 mo	Severe myelosuppression, severe GI and respiratory side effects	(Bookman 2000)
Approved for other indications or NCCN Recommended Regimen (Category 2B)						
Nab-paclitaxel	2L mCC N=35	12 Jun 2018	100 mg 1Q3W	• ORR=28.6% (14.6–46.3) • No CRs • RECIST 1.0 • median PFS=5.0 mo • median OS=9.4 mo	1 Gr 4 neutropenia, Gr3 neurotox	(Alberts 2012)
Docetaxel	2L squamous r or mCC N=23	NA		• ORR=8.7% PR (1.1–28.0) • No CRs	AEs were neutropenia and	(Garcia 2007)

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Product Names	Relevant Indication/Trial Population (N)	Year of Approval And Type of Approval *	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Reference
				• RECIST v1.0 • median PFS=3.8 mo • median OS=7.0 mo	infections	
Fluorouracil	-	NA	200 mg/m ² IV leucovorin, 5-FU 370 mg/m ² IV bolus q5D every 4 W x 2	• No data for efficacy in 2L	Leukopenia, grade 3 + 4 GI toxicity	(Look 1996)
Gemcitabine	2L only persistent/recurrent CC N=22	NA	800 mg/m ² 3Q4W	• ORR=4.5% (NR) • No CRs • Non-RECIST evaluation of response • median PFS=2.1 mo • median OS=6.5 mo	none	(Schilder 2005)
Ifosfamide ^a	N=9 2L subjects Advanced or relapsed CC (FIGO stages III or IV)	1987	5x 1.2 g/m ² /day IV 1Q3W	• ORR=0% (NR) • 0 CRs • Best response after CRT for locally advanced disease	Low WBC and platelet counts, Nausea, vomiting, mild neurotoxicity	(Coleman 1986)
Irinotecan	2L squamous r or mCC N = 42	NA	125 mg/m ² given as a weekly 90-minute IV infusion for 4 weeks, 1Q6W	• ORR=21% (10-35) • 1 CR • WHO Response assessment • median OS=6.4 mo	DLTs of nausea and vomiting 62% anemia, 48% alopecia, 43% drug fever	(Verschraegen 1997)
Mitomycin + cisplatin	-	NA	6 mg/m ² IV 1Q4W	• ORR=42% (CI 26-61%) • 5 CRs • WHO Response assessment • median PFS=5 mo • median OS=11.2 mo • No data in 2L	10/15 gastrointestinal toxicity	(Wagenaar 2001)

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Product Names	Relevant Indication/Trial Population (N)	Year of Approval And Type of Approval *	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Reference
Pemetrexed	2L advanced or recurrent CC N = 27	NA	900 mg/m ² IV q21d	• ORR=15% PR (4.2-33.7) • No CRs • RECIST v1.0 • median PFS=3.1 mo • median OS=7.4 mo	anemia 41%, leukopenia 30%, neutropenia 26%, and infection 26%.	(Miller 2008)
Vinorelbine	2L squamous persistent or recurrent CC N = 44	NA	30 mg/m ² given on days 1 and 8 every 21 days.	• ORR=13.7% (5.2-27.4) • 1 CR • Non-RECIST evaluation of response	Severe myelosuppression may occur	(Muggia 2004)
Other Treatments – [Combine by Pharmacologic Class, if relevant]						
Surgery (a)						
Radiation (a)			localized			

1L = first-line, 2L = second-line, 1Q3W = one dose every three weeks, 1Q4W = 1 dose every 4 weeks, 3Q4W = 3 doses every 4 weeks, 1Q6W = one dose every 6 weeks, AEs = adverse events, CC = cervical cancer, CRs = complete responses, CRT = clinical review template, DLT = dose-limiting toxicity, GI = gastrointestinal, Gr 3 = grade 3, Gr 4 = grade 4, IV = intravenous, mCC = metastatic cervical cancer, MSI H/dMMR = microsatellite instability-high / mismatch repair deficiency, NA = not applicable, NR = not reported, ORR = overall or objective response rate, PR = partial response, 1Q3W = one dose every three weeks, q5D = one dose every 5 days, RECIST = response evaluation criteria in solid tumors, SD = stable disease, WBC = white blood cell, WHO = world health organization

*Accelerated approval or full approval

a. Friedlander and Grogan, 2002

b. <https://www.cancer.net/cancer-types/cervical-cancer/types-treatment>

The Applicant's Position:

Patients with recurrent or metastatic cervical cancer have poor survival and no standard of care treatment options in the second line and beyond. With the exception of KEYNOTE-158, results from trials of currently-used therapies in the second line and beyond were conducted prior to the adoption of chemotherapy doublet plus bevacizumab as the standard of care first-line therapy. The trial results do not reflect the current US population being treated after first-line progression and thus it is difficult to extrapolate the data to current second-line treatment outcomes for patients. In addition, these trials generally had small sample sizes, often included unconfirmed response rates in the ORR calculation, and were not independently assessed by an IRC. These trials also do not have consistent eligibility criteria for first-line therapy: some trials allowed single agent chemotherapy to be used as the standard of care in the first line therapy, some included adjuvant and neoadjuvant therapy as well as chemotherapy plus radiation as prior lines of therapy before the utilization of single-agent chemotherapy, and one excluded patients subjects who that have received taxanes in the first line. Too few patients derive clinical benefit from these therapies, including pembrolizumab. Significant medical need remains for patients whose disease does not respond to or progress after first-line therapy.

The FDA's Assessment:

FDA agrees with the Applicant that current standard-of-care first-line treatment for patients in the U.S. with recurrent or metastatic cervical cancer is a chemotherapy doublet with bevacizumab.

In the Applicant's table of available therapies, FDA did not consider the following therapies to be available therapies for patients enrolled to GCT1015-04:

- FDA does not consider single agent bevacizumab as an available 2L therapy for patients enrolled to GCT1015-04 as most patients enrolled to this trial had already received bevacizumab in combination with chemotherapy in the first line metastatic setting.
- FDA does not consider pembrolizumab as an available 2L therapy for patients with recurrent or metastatic cervical cancer, as this product is under an accelerated approval and clinical benefit has not yet been confirmed.
- FDA does not consider fluorouracil or mitomycin+cisplatin as available 2L therapies, as the studies evaluating those products only enrolled patients in the 1L metastatic/recurrent setting, not in the 2L setting or beyond.
- FDA did not consider nab-paclitaxel as an available therapy for patients enrolled to GCT1015-04, as the nab-paclitaxel trial excluded patients who had received prior paclitaxel. All patients enrolled to GCT1015-04 had received prior paclitaxel.

In the Applicant's table of available therapies, FDA has the following clarifications:

- Docetaxel is listed as having an ORR of 8.7% without information on DOR. The median DOR was 3.8 months.
- Ifosfamide is listed in the table as having an ORR of 0%. In a separate study (not reported in the table), ifosfamide had an ORR of 11% (95% CI: 4.5, 24.8) with DOR range

reported as 10-16 months (no median DOR reported) in the 2L setting (Sutton 1989).

- In one study described in the table, irinotecan is listed as having an ORR=21% (95% CI: 10-35). The median DOR was 3 months, with no data on range available. FDA notes that in another study of irinotecan as 2L treatment, the ORR was 0% (Irvin 1998). It is not clear why there is a discrepancy in ORRs between these trials, as both were conducted in similar treatment settings.
- Pemetrexed is listed as having an ORR of 15% and the median DOR was 4.4. months, with no range available. In a separate trial, pemetrexed had an ORR of 12.9% and a median DOR of 1.75 months (Lorusso 2010).

In summary, FDA disagrees with the Applicant that patients have no standard-of-care treatment options in the 2L setting and beyond, but FDA does think treatment options in this setting are limited. There are no 2L therapies for recurrent or metastatic cervical cancer that are approved under FDA regular approval but based on guideline recommendations standard of care available therapies include chemotherapies with response rates ranging from 5-21%. The median DOR ranges from 2-4 months. There are important caveats to this assessment. These data come from small studies and the efficacy of existing 2L therapies after a 1L regimen with a chemotherapy doublet with bevacizumab is unknown. Bevacizumab was not considered standard-of-care treatment at the time that many trials described above were conducted. The review team expects that the efficacy (namely ORR) of several of the available single agent chemotherapies would be worse in the current 2L or later setting, following bevacizumab-containing doublet chemotherapy. In conclusion, FDA agrees that there is an unmet need for new treatments for patients with advanced, metastatic cervical cancer following first-line combination chemotherapy (+/- bevacizumab).

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Tisotumab vedotin has not been approved for marketing in any country worldwide.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

3.2 Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Regulatory History

Tisotumab vedotin is being co-developed by Seagen Inc. and Genmab A/S for the treatment of cervical cancer (b) (4). A summary of key pre-submission regulatory interactions related to BLA 761208 are summarized in [Table 2](#).

Table 2: Key FDA Interactions

Date	Regulatory Activity	Description
IND (b) (4)		
18-Jul-2013	IND Submission	Submission of new IND (b) (4) for FIH Trial GEN701. The IND was open on 17-Aug-2013 and the study was allowed to proceed.
IND 135476		
15-Aug-2017	FDA Type B Pre-IND/EOP1 Meeting	Discussed the clinical development strategy, as well as, the CMC development plan.
17-Nov-2017	IND Submission	Submission of new IND (cervical cancer) for Trial GCT1015-04. IND was open on 15-Dec-2017 and the study was allowed to proceed.
29-Apr-2019	FDA Type B FDA Pre-Phase 3 Meeting	Agreed on the sufficiency of the nonclinical safety package to support a BLA, and overall design of the proposed Phase 3 trial.
20-Jun-2019	Initial Pediatric Study Plan (iPSP) Agreement	FDA agreed with the iPSP for a full waiver for tisotumab vedotin in pediatric patients with cervical cancer, from birth to 16 years.
15-Aug-2019	FDA Type C Meeting	FDA provided written responses to the sponsor's systematic literature review and proposed designs for real world evidence studies.
10-Sep-2019	FDA Type B Pre-BLA Meeting	Received feedback on the proposed content and format of the proposed BLA. The sponsor cancelled the meeting after receiving FDA's preliminary comments.
31-Aug-2020	FDA Type B Pre-BLA Meeting	The sponsor provided a summary of the topline clinical results from Trial GCT1015-04 and provided an update on the Phase 3 trial plan.

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment, with the following additions.

At the Type B Pre-Phase 3 Meeting on April 29, 2019, FDA stressed the importance of ensuring that the confirmatory study is fully accrued or at least well underway at time of an accelerated approval action. At the August 31, 2020 meeting, FDA expressed concern that the proposed confirmatory study had not yet started enrolling patients. As the confirmatory study is enrolling patients in the same treatment line as the study supporting the accelerated approval, accrual could be challenging following an accelerated approval.

FDA continued to express concerns regarding enrollment to the confirmatory trial, innovaTV 301, throughout review of this application. FDA and the Applicant had a Type C meeting on July 12, 2021 to discuss the status of the confirmatory trial. The Applicant had consented 18 patients and enrolled 8 patients. FDA recommended that the Applicant continue to make efforts to increase enrollment, including broadening eligibility criteria. FDA also stated that they would be requesting periodic updates regarding enrollment from the Applicant.

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

4.1 Office of Scientific Investigations (OSI)

Division of Oncology 1 consulted OSI to perform an audit of the Applicant and the overall trial conduct. FDA selected three sites (US11, US01, and BE01) for clinical inspection based on

enrolling a large number of patients and/or higher tumor response rate compared to the ORR reported for GCT1015-04. The study sponsor, Genmab U.S., Inc. was also selected for inspection given that tisotumab vedotin is an NME and there have been no prior inspections of this sponsor. Based on these inspections, there were no significant regulatory violations, the trial conduct for GCT1015-04 appears adequate, and the submitted data from the three investigator sites appear reliable.

Clinical inspection summaries are included here:

Site US11: Dr. Bradley Monk

Dr. Monk was inspected on May 3-7, 2021, as a surveillance and data audit for Study GCT1015-04. This was the first FDA inspection of Dr. Monk's conduct of clinical trials.

The investigator site screened six subjects and enrolled four of them into the study. As of the data cutoff date of 02/06/2020, all the four subjects were discontinued from study treatment due to disease progression or AE(s) [i.e., severe or moderate ocular toxicities in Subjects (b) (6) - (b) (6)] but remained on study for follow-up. As of the inspection, all the subjects were off study with death reported.

All subjects' source records were reviewed during the inspection and were compared with the Applicant's submitted data for this site. The source records reviewed at the site included the informed consent forms, subject inclusion and exclusion criteria, prior chemotherapy, enrollment log, scans performed and subsequent submissions the IRC, AEs and serious AEs (SAE), protocol deviations, and other documents in subject study charts as well as subject data in electronic case report forms (eCRF). Regulatory records and study procedures were also reviewed, including the Institutional Review Board (IRB) approvals of all the protocol/amendments and related informed consents, site training documentation and updates during the study, FDA 1572s, delegation of responsibility, financial disclosures, access to the eCRF system, reports to the sponsor, study monitoring, study product control and accountability, and records retention.

The inspection found no regulatory violations. All the enrolled subjects were eligible and were properly consented. The primary endpoint data and adverse events, including the reported ocular toxicities, were verifiable with source records at the site. All the scans were found to have been submitted to the IRC according to the Imaging Manual provided to the site. There was no evidence of underreporting AEs or protocol deviations.

At the conclusion of this inspection, no Form FDA 483, Inspectional Observations, was issued to Dr. Monk.

Site US01: Dr. Michael Gold

Dr. Gold was inspected on June 8-9, 2021, as a data audit for Study GCT1015-04. For the investigator, this was the first FDA inspection. His site enrolled and treated two of the three screened subjects for the study. As of the data cutoff date, the two subjects were discontinued from study treatment due to disease progression. At the time of this inspection, both subjects had died.

The inspection included data verification with source documentation and a review of the subject study charts, informed consents, eligibility, medical records, efficacy assessments, adverse events, case report forms, drug accountability, monitoring logs, study correspondences, regulatory documents (i.e., IRB approvals and communications, investigator's agreements, financial disclosures), training records, and protocol adherence.

The inspection revealed no regulatory deficiencies, with no Form FDA 483 issued to Dr. Gold at the closeout. The enrolled subjects met the eligibility criteria and their efficacy and safety data, as submitted by the Applicant to the BLA, were verifiable with source documentation. Protocol deviations and adverse events were found to have been properly reported according to the protocol.

Site BE01: Dr. Ignace Vergote

Dr. Vergote was inspected between 5/24/2021 and 5/28/2021 as a data audit for Study GCT1015-04. This was the first FDA inspection of the foreign investigator. The site screened 10 subjects and enrolled 7 of them into the study. As of the data cutoff, all the seven subjects stopped study treatment, with six subjects secondary to disease progression and one (Subject (b) (6)) due to severe ocular toxicities. At the time of this inspection, one subject (b) (6) who started treatment on (b) (6) was actively followed, with the last survival checked date (b) (6).

This inspection audited the reported efficacy and safety endpoint data and examined the Independent Ethics Committee (IEC) oversight of the study, protocol adherence, financial disclosures, enrollment log, informed consent and process, subject eligibility checklists and medical history records, scans performed and subsequent submission for central review, concomitant medications, adverse events, test article accountability and data entry to the electronic data capture system for the study.

The inspection identified no significant regulatory violations, with no Form FDA 483 issued to Dr. Vergote. All the subjects were found to have met the eligibility criteria, consented prior to study-related procedures, and had the protocol-required assessments performed properly, including ophthalmology examinations at study entry and during the study. The submitted efficacy and safety data were confirmable with site's source records. Of note, there was no clear documentation of the reason that five additional vials of study product were dispensed for

Subject (b) (6) while only four vials were needed for the intended dose. The inspection revealed that those five vials, including the initial shipped four vials and one replaced vial upon replacement, were noted to have particulates for which the five vials were discarded and destroyed accordingly.

Genmab U.S., Inc. (Trial Sponsor)

The study sponsor was inspected from 4/20/2021 through 4/28/2021 to evaluate the conduct and management of Study GCT1015-04. This was the first inspection of Genmab US Inc., a subsidiary of Genmab A/S.

The inspection reviewed the study sponsor's history and its co-development of tisotumab vedotin with the current Applicant Seagen Inc., sponsor's responsibilities and activities in the study conduct, standard operating procedures, key individuals and their responsibilities, contract research organizations involved in the study and related agreements, selection of clinical investigators and monitors for the study and related training, financial disclosure forms, documentation of IRBs/IECs, monitoring plans, monitoring visit reports, adverse event reporting, protocol deviations, quality assurance procedures and activities, data collection and management as well as related meeting minutes.

The inspection found no objectionable regulatory violations in the conduct of Study GCT1015-04, with no Form FDA-483 issued to Genmab US at the conclusion of this inspection. There were no study sites closed due to non-compliance. The sponsor's oversights of study monitoring, safety reporting, and data management were performed properly, with no deficiencies noted during the inspection. In addition, the study was confirmed to be ongoing as of the inspection but was closed to enrollment, with the last subject dosed with tisotumab vedotin (b) (6). At the closeout meeting, no discussion items were presented to the sponsor.

4.2 Product Quality

The OPQ review team completed their review dated 8/24/21, signed by Kelly Ballard and Patrick Lynch. The review summarizes the quality assessment finding of the manufacturing information provided in the BLA submission and the review team did not find any approvability issues and have recommended approval. There are four PMCs related to the CMC review and they are described in section 14 of this review.

4.3 Clinical Microbiology

As noted in Section 4.2, the OPQ team completed a combined review, inclusive of microbiology recommendations. The review team has recommended approval for this BLA.

4.4 Devices and Companion Diagnostic Issues

Tisotumab vedotin is an anti-TF-targeted antibody-drug conjugate. The Applicant seeks an indication in patients with recurrent or metastatic cervical cancer, regardless of tumor TF status. FDA agrees with this indication, and there is no need for a companion diagnostic to support this indication. For more details on TF analysis, refer to Sections 6.3.2 and 8.1.4.

5 Nonclinical Pharmacology/Toxicology

5.1 Executive Summary

The FDA's Assessment:

Tisotumab vedotin (Tivdak) belongs to the pharmacological class of tissue factor (TF)-directed antibody and microtubule inhibitor conjugate, composed of a TF specific human IgG1 κ antibody linked to the microtubule disrupting agent monomethyl auristatin E (MMAE) via a protease-cleavable maleimidocaproyl-valyl-citrullinyl-p-aminobenzyloxycarbonyl (mc-val-cit-PABC) linker. The average drug to antibody ratio is approximately 4. Tisotumab vedotin is administered by intravenous infusion once every 3 weeks and is proposed for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy at a recommended dose of 2 mg/kg. The nonclinical development program for tisotumab vedotin and the cytotoxic payload, MMAE, consisted of studies in mice, rats, and monkeys to evaluate the primary and safety pharmacology, general and developmental toxicology, and genotoxicity. During the nonclinical development, tisotumab vedotin was referred to as IgG1-1015-011-vcMMAE or HuMax-TF-ADC (IgG1-1015-011 or HuMax-TF for the unconjugated antibody, tisotumab) and MMAE as SGD-1010.

Human tissue factor is a 43-47 kDa plasma membrane glycoprotein, consisting of an extracellular domain (aa 1-218), a hydrophobic transmembrane domain (aa 220-242), and a cytoplasmic domain (aa 243-263). Tissue factor is the main physiological initiator of the blood coagulation cascade. The extracellular domain binds to serine protease factor VII (FVII) to activate coagulation. The TF:FVIIa complex initiates the extrinsic pathway of blood coagulation by producing activated FX (FXa) and FIX (FIXa) resulting in production of thrombin and clot formation composed of insoluble fibrin and activated platelets. In addition to its role as a pro-coagulant activator, TF plays a role in both vasculogenesis in the developing animal and angiogenesis in normal and malignant adult tissues.

In vitro, the unconjugated TF-directed antibody, tisotumab, bound TF with a KD of 3.15 nM;

tisotumab and tisotumab vedotin bound to the recombinant extracellular domain of TF in a dose dependent manner with similar EC₅₀ values of 2.5 nM (373 ng/mL) and 3.1 nM (469 ng/mL), respectively. Additionally, they bound similarly to TF expressing human cancer cells with EC₅₀ values ranging from 0.19 nM (30 ng/mL) to 2.30 nM (346 ng/mL) depending on the cell line. The data suggests that conjugation of tisotumab does not affect the binding affinity to TF. Upon binding to TF on the cell membrane, tisotumab vedotin is internalized into the cell and localized to the lysosomes. In vitro, the extent of cytotoxicity depends on the level of TF cell surface expression; tisotumab vedotin IC₅₀ values ranged from approximately 1.63 ng/mL to 575 ng/mL amongst the cell lines tested. Tisotumab and tisotumab vedotin induced antibody-dependent cellular cytotoxicity (ADCC) in a similar manner with EC₅₀ values ranging from 0.031 nM (4.7 ng/mL) to 0.103 nM (15.4 ng/mL) at the conditions tested. Additionally, data suggests that tisotumab and tisotumab vedotin may have antibody-dependent cellular phagocytosis (ADCP) activity.

In vivo, anti-tumor activity and/or tumor regression was seen in cervical cancer patient derived xenograft (PDX) models when mice were administered tisotumab vedotin at 4 mg/kg twice in the first week of study via intravenous dosing. Tisotumab vedotin or paclitaxel treated tumors that exhibited tumor re-growth (>300 mm³) between days 42 and 60 showed regression following re-treatment with two doses of tisotumab vedotin. Intra-tumor hemorrhages were noted in 2/36 xenograft models (human pancreatic and lung adenocarcinoma) treated with tisotumab or tisotumab vedotin. Based on the data, it appears that one of the xenograft models (lung) is prone to hemorrhages in the absence of treatment; however, treatment with tisotumab vedotin enhanced the degree of hemorrhage observed.

Secondary pharmacology studies to assess the effects of tisotumab on FXa generation and coagulation were evaluated using several in vitro assays. Generally, the assays showed that tisotumab can inhibit FXa and thrombin generation, delay clotting but not affect the strength of the formed clot in human plasma or whole blood. Similar results were seen with monkey plasma or whole blood when tested alongside human. In a non-GLP intra-animal dose escalation study in monkeys, a dose-dependent increase in bleeding time was noted 1-hour post dose; statistical significance was reached at the high dose (100 mg/kg, 55-fold the exposure at the recommended dose based on C_{max}) compared to the Day 1 vehicle dose. Hemorrhage in the heart and urinary bladder were noted in one female monkey at the end of the study. Bleeding/hemorrhage was an adverse event (AE) in patients with the most common being epistaxis, vaginal hemorrhage, and hematuria.

The Applicant evaluated the effects of tisotumab vedotin on the nervous, cardiovascular, or respiratory systems in vitro and in animals. In vitro inhibition of the hERG channel was not evaluated with tisotumab vedotin; however, up to 100 μM MMAE had limited (<50%) inhibition on hERG potassium channel. Additionally, tisotumab vedotin did not have effects on the nervous, cardiovascular, or respiratory systems in monkeys after repeated dosing up to 5 mg/kg

(4.2-fold the exposures at the recommended dose based on AUC). Clinically, all grade peripheral neuropathy and grade 2 pneumonitis (leading to death in one patient) occurred in patients. Peripheral neuropathy is a commonly seen toxicity with antibody-drug conjugates with cytotoxic payloads but is generally not observed in nonclinical studies with the MMAE payload (Saber and Leighton 2015; Stagg et al. 2016). In a non-GLP dose range finding study in monkeys, one animal given 6 mg/kg tisotumab vedotin (4.9-fold the exposure at the recommended dose based on AUC) experienced respiratory symptoms described as gasping, wheezing, and shallow, labored breathing with macroscopic observation of discolored spongy lungs and microscopic findings of mild edematous congestion/hemorrhage 10 days after the first dose. Additionally, in the monkey GLP repeat dose toxicology study, two animals (1M, 1F) had microscopic findings of focal alveolar foamy macrophage accumulation at the high dose of 5 mg/kg (4.2-fold the exposure at the recommended dose based on AUC).

In vitro, tisotumab vedotin was stable in human and monkey plasma with limited release of free MMAE over a two-week period, and the binding of MMAE to human plasma proteins ranged from 68 to 82%. In the 13-week GLP repeat-dose toxicology study after a single dose of tisotumab vedotin, the plasma exposure (C_{max} and AUC) increased in an approximately dose proportional manner with no apparent gender differences. The T_{max} was reached within 30 to 40 minutes post infusion, and the half-life was in the range of 1 to 2 days. The levels of free MMAE were minimal compared to those of tisotumab vedotin suggesting stability in plasma. Upon repeated infusions of tisotumab vedotin, no to minimal (≤ 1.3 -fold) accumulation was observed; T_{max} and the half-life maintained as compared to the single dose. After repeated dosing, animals developed anti-drug antibodies (ADA) especially at the high dose of 5 mg/kg, but ADA did not appear to affect the peak plasma concentration or total exposure. Animal to human exposure margins were calculated using the mean clinical AUC_{0-21} (57.5 day· μ g/mL) for tisotumab vedotin, C_{max} (40.8 ng/mL) for tisotumab, and C_{max} (5.91 ng/mL) and AUC_{0-21} (50 ng·day/mL) for MMAE after the first dose. Per the clinical pharmacology team, there was no accumulation with repeated dosing of tisotumab vedotin; therefore, the steady state exposures after repeated dosing were similar to exposures seen after the first dose.

In monkeys receiving single intravenous doses up to 3 mg/kg radiolabeled tisotumab, >10% tissue uptake of tisotumab was observed in the liver and bone marrow and <10% tissue uptake was noted in the lungs, kidneys, heart, small intestine, and gall bladder; limited ($\leq 1.2\%$) tissue uptake, but above background levels, was seen in the spleen, salivary gland, testes, and urinary bladder. In mice bearing TF-high or TF-low pancreatic tumors, the distribution of tisotumab vedotin and tisotumab were 23-fold and 5-fold higher, respectively, in TF-high compared to TF-low tumors while normal tissue distribution was generally comparable regardless of tumor type. MMAE was metabolized primarily by CYP3A4. MMAE is an inhibitor of CYP3A4 in vitro and a substrate for P-gp1. The major route of MMAE elimination was via feces in rats with similar observations in humans as 72% of MMAE was recovered in feces over a 1-week period.

Tisotumab bound human and cynomolgus monkey TF similarly with EC₅₀ values of 8.3 ng/mL and 6 ng/mL, respectively, with approximately 100% binding achieved at <100 ng/mL. Tisotumab did not bind to mouse, rat, rabbit, pig, or dog TF. In a GLP-compliant tissue cross-reactivity study using tisotumab, membrane TF staining was generally similar across a variety of normal human and cynomolgus monkey tissues. Additionally, the plasma stability of tisotumab vedotin in pooled human and cynomolgus monkey plasma was similar with 99.3% and 99.5% of MMAE remaining conjugated to the antibody, respectively, up to 14 days. The data suggests that the cynomolgus monkey was the only relevant toxicological species.

A GLP compliant repeat-dose toxicology study with tisotumab vedotin was conducted in monkeys (13-week), and the payload was assessed in rats (4-week) and monkeys (11-week) using the clinical intravenous route of administration. Toxicities that were TF specific and not observed in the rat and monkey studies assessing the payload included skin toxicities at ≥ 3 mg/kg (≥ 2.2 -fold the exposure at the recommended dose based on AUC) leading to death from severe skin toxicity at 5 mg/kg (4.2-fold the exposure at the recommended dose based on AUC). Additionally, ocular toxicity without microscopic correlates were noted at 5 mg/kg and 25 mg/kg tisotumab vedotin and tisotumab, respectively. Skin and ocular toxicities could be expected from the TF-directed antibody portion of tisotumab vedotin as tisotumab was shown to positively stain skin epithelial cells (squamous epidermis, hair follicle), and corneal and conjunctiva epithelial cells, in both human and monkey in a tissue cross reactivity study. Rash and ocular toxicity in the form of dry eye, and conjunctival or corneal toxicity with some cases of moderate to marked decreases in visual acuity were observed in patients.

Toxicities that were likely MMAE mediated based on their presence in both the toxicology study with tisotumab vedotin and those with the payload only included decreased erythropoiesis, neutropenia, toxicities to the liver, bone marrow, lymphoid (thymus and/or spleen) and male reproductive (testes, epididymides) organs at comparable exposures as the recommended dose. In the monkeys treated with tisotumab vedotin at ≥ 3 mg/kg, animals received antibiotics due to marked neutropenia. All grade anemia and neutropenia (no neutropenic fever) were observed in patients including one patient death from neutropenic sepsis. Toxicology findings in rats (MMAE) and monkeys (tisotumab vedotin, MMAE) were reversible once dosing ceased except for findings in the male reproductive organs.

Genetic toxicology studies were not conducted with tisotumab vedotin; rather, the applicant submitted studies that evaluated the payload. MMAE was negative in the in vitro bacterial reverse mutation assay and the mouse lymphoma forward mutation assay but was positive in the rat bone marrow micronucleus assay through an aneugenic mechanism. Carcinogenicity studies were not conducted with tisotumab vedotin in accordance with ICH S9 guidance.

Dedicated fertility, early embryonic development, embryofetal development (EFD), pre- and postnatal development studies were not conducted with tisotumab vedotin in accordance with

ICH S9 based on the expected adverse effects of MMAE on rapidly dividing cells and the intended indication for the treatment of patients with advanced cancer. The Applicant assessed the effects of tisotumab vedotin on reproductive organs as part of the repeat-dose toxicology study in monkeys and provided results from an EFD study in rats evaluating the MMAE payload. Toxicity to the male reproductive organs (testes, epididymis) in monkeys was decreased testicular size and seminiferous tubule atrophy, reduction or absence in sperm count, and decreased sperm motility at doses ≥ 1 mg/kg (≥ 0.6 -fold exposures at the recommended dose based on AUC). There were no effects on the female reproductive organs or the duration of menstrual cycles in monkeys. MMAE was teratogenic and embryo lethal when administered to pregnant rats via two intravenous doses of 0.2 mg/kg during the period of organogenesis on gestational days 6 and 13. MMAE-related toxicities included post-implantation loss and external and skeletal malformations of fetuses at a dose of 0.2 mg/kg (~ 0.5 -fold the MMAE exposure at the recommended dose based on AUC). Additionally, MMAE was present in the amniotic fluid and fetal serum suggesting placental transfer. The label advises females of reproductive potential to use effective contraception during treatment and for 2 months after the last dose of tisotumab vedotin based on the recommendations for duration of contraception for genotoxic pharmaceuticals that are embryo-fetal toxic from the FDA guidance, "Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations". The guidance recommends a contraception period of 1 month with an additional 5 half-lives (tisotumab vedotin half-life = 4 days) for aneugenic pharmaceuticals for females. The label advises male patients with female partners of reproductive potential to use effective contraception during treatment and for 4 months after the last dose based on the FDA guidance (3 months with an additional 5 half-lives of the drug). Additionally, the label advises lactating women not to breastfeed during treatment and for 3 weeks (5 half-lives of tisotumab vedotin) after the last dose due to the potential for severe adverse reactions in a breastfed child.

Recommendation:

The nonclinical data submitted to this BLA are adequate to support approval of Tivdak for the proposed indication.

During the review cycle, the review team determined that a new pediatric study plan was needed to investigate Tivdak in pediatric tumors as TF is a relevant target in certain pediatric malignancies. A post-marketing requirement to conduct preclinical studies in pediatric-specific preclinical models to support the conduct of clinical investigations of Tivdak in pediatric tumors was communicated to the Applicant and Applicant agreed.

5.2 Referenced NDAs, BLAs, DMFs

The Applicant's Position:

N/A

The FDA's Assessment:

Tisotumab vedotin shares the same linker-drug conjugation as the marketed product Adcetris

(brentuximab vedotin, BLA 125388). The Applicant provided original study reports for the assessment of the payload that have been previously submitted and reviewed under BLA 125388; the primary nonclinical review was referenced for these studies.

5.3 Pharmacology

Primary pharmacology

Original studies were submitted to support the mechanism of action of tisotumab vedotin and the unconjugated TF-directed antibody tisotumab. Key studies that support the label are summarized below.

Binding Affinity

Study# (b) (4) 1015-083: Binding of tisotumab and tisotumab vedotin to TF was evaluated using surface plasmon resonance, ELISA, and flow cytometry assays. Binding to TF via surface plasmon resonance demonstrated a KD of 3.15 nM for tisotumab. Avidity studies using DNA shuffling between human and murine TF resulted in loss of tisotumab binding to TF when the human sequence encoding amino acids 42 to 84 was replaced by the murine sequence; tisotumab did not bind mouse TF. Tisotumab and tisotumab vedotin bound to the recombinant extracellular domain of TF in a dose dependent manner with similar EC₅₀ values of 2.5 nM (373 ng/mL) and 3.1 nM (469 ng/mL), respectively. Additionally, membrane binding to TF expressing (>300,000 TF molecules/cell) A431 epidermoid carcinoma, BXP3 pancreatic adenocarcinoma, and MDA-MB-231 breast cancer cells resulted in EC₅₀ values for tisotumab in the range of 0.19 nM (30 ng/mL) to 1.01 nM (150 ng/mL). As seen with binding to recombinant extracellular domain of TF, membrane binding of tisotumab and tisotumab vedotin to pancreatic adenocarcinoma cell line HPAF-II (>350,000 TF molecules/cell) resulted in similar EC₅₀ values of 2.08 nM (313 ng/mL) and 2.30 nM (346 ng/mL), respectively, suggesting that conjugation of the TF specific antibody does not affect the binding affinity.

Study# (b) (4) 1015-088: Human TF shares 94.1%, 98.6%, 75.8%, 57.3%, and 56.4% amino acid sequence homology with TF from cynomolgus monkey, chimpanzee, dog, rat, and mouse, respectively. Cross-reactivity of tisotumab was evaluated using immunohistochemistry, flow cytometry, and ELISA assays. Tisotumab showed cross reactivity with cynomolgus TF by immunohistochemistry, but not with dog, pig or rabbit TF as evaluated using normal kidney tissues where TF is expressed in human renal corpuscles under normal physiological conditions; however, the conservation of TF expression in renal corpuscles across the different species was not confirmed. In a flow cytometry assay, tisotumab bound human embryonic kidney HEK293F cells expressing exogenous TF from human, chimpanzee, and cynomolgus monkey with similar EC₅₀ values of 8.3 ng/mL, 6.8 ng/mL, and 6 ng/mL, respectively, with approximately 100% binding achieved at <100 ng/mL. Tisotumab did not bind to HEK293F cells expressing exogenous mouse, rat, rabbit, pig, or dog TF. Additionally, tisotumab did not cross-react with recombinant mouse TF in an ELISA assay.

In Vitro Functional Activity

Study# (b) (4) 1015-087: In TF expressing SK-OV-3 (ovarian, 50,000-175,000 TF molecules/cell) and A431 (epidermoid carcinoma, >300,000 TF molecules/cell) cells an average of approximately 50% of tisotumab co-localized with the lysosomal marker LAMP-1 after 16 hours and was degraded over time. Tisotumab vedotin induced cytotoxicity in a panel of TF expressing cancer cell lines; sensitivity to tisotumab vedotin was dependent on the level of cell membrane TF expression. In three cervical cancer cell lines expressing different levels of TF, IC₅₀ values ranged from approximately 1.63 ng/mL to 575 ng/mL; tisotumab vedotin produced 87% cell kill at 10 ng/mL in the highest TF expressing and most sensitive cervical cancer (CaSki) cell line.

Study# (b) (4) 1015-084: Tisotumab induced antibody-dependent cellular cytotoxicity (ADCC) with EC₅₀ values ranging from 0.031 nM (4.7 ng/mL) to 0.103 nM (15.4 ng/mL) in three cancer cell lines co-cultured with PBMCs from three to six healthy donors; tisotumab vedotin was able to induce ADCC in a similar manner, suggesting that ADCC activity was preserved with conjugation.

Study# TRN-5631: A concentration of 2 µg/mL tisotumab and tisotumab vedotin mediated antibody-dependent cellular phagocytosis (ADCP) with 41% to 93% and 38% to 72% activity, respectively, using BxPC3 or A431 target cells and one or two macrophage donors as effector cells. Baseline activity up to 26% and 34% was detected in the no drug and isotype control groups, respectively.

In Vivo Functional Activity

Study# (b) (4) 1015-149: The cervical squamous cell carcinoma CEXF773 PDX showed 25-50% TF positive high intensity (3+) staining in the tumor when evaluated via IHC. The tumors showed regression (tumor volume <200 mm³) or complete response (no measurable tumor noted as 0 mm³) up to approximately day 42 when mice were given two intravenous doses (day 0, 7) of tisotumab vedotin at 4 mg/kg or three intravenous doses (day 0, 7, 14) of paclitaxel at 20 mg/kg. Then, 3/8 tisotumab vedotin treated and 4/8 paclitaxel treated tumors began to show re-growth and by day 60 had mean tumor volumes of 345 mm³ and 392 mm³, respectively. These animals were re-treated with 4 mg/kg HuMax-TF-ADC on Day 60 and 67. Re-treated tumors showed regression to ≤65 mm³ tumor volume between Day 63 and 84. One animal that received HuMax-TF-ADC during the main study and was re-treated was euthanized on day 70 during the re-treatment phase due to 22% body weight loss; weight loss was not otherwise observed in any of the groups.

Study# (b) (4) 1015-223: In the CEXF633 PDX model, a statistically significant (p=0.007) decrease in mean tumor volume between tumors treated with tisotumab vedotin compared to the isotype control ADC was observed when mice were given two intravenous doses (day 0, 7) of tisotumab vedotin at 4 mg/kg. Based on the dot plot provided (no raw data available in the study report), 4/8 tumors did not appear to progress from the size at which they were

randomized when treated with tisotumab vedotin. Tisotumab vedotin treatment effects were more pronounced in the CV1664 PDX model, where tisotumab vedotin treated tumors regressed over time with a statistically significant difference ($p=0.0022$) compared to the isotype control ADC when mice were given two intravenous doses (day 0, 7) of tisotumab vedotin at 4 mg/kg. According to the Applicant, although no data was presented, there were no to minor effects on body weight in both PDX models.

Study# (b) (4) 1015-102: Intra-tumoral hemorrhages were observed in 1/5 xenograft models (BxPC-3 pancreatic adenocarcinoma) when treated with tisotumab at 50 mg/kg followed by 25 mg/kg weekly and in 1/31 xenograft models (NCI-H441 lung adenocarcinoma) when treated with tisotumab vedotin at 3 mg/kg twice weekly for 2 weeks or a single administration in the range of 0.5 to 4.5 mg/kg. In the NCI-H441 model, hemorrhages were seen in the absence of treatment as well but were enhanced with tisotumab vedotin treatment. Additionally, tumors treated with a cMet inhibitor were also observed to hemorrhage; therefore, it's likely that the tumor model itself is prone to hemorrhaging. In general, hemorrhages were restricted to the tumor area and did not appear to be dependent on the level of TF expressed by tumor cells, resolved spontaneously, and were not associated with clinical signs of illness or weight loss.

Secondary Pharmacology data

In vitro inhibition of activated factor X (FXa) Generation by Tisotumab: Tisotumab (~6.6 nM, ~1 µg/mL) inhibited FXa generation by 19% ((b) (4) 1015-086). Tisotumab vedotin was not tested.

In vitro coagulation: The effects of tisotumab (unconjugated antibody) on outcomes related to clot formation were investigated in four in vitro studies: standard prothrombin time (PT), modified PT, thromboelastography (TEG), and thrombin generation assay (TGA) ((b) (4) 264005, (b) (4) 1015-086, HxTFADC N Study Report 0361, HxTFADC N Study Report 0364). Results show that tisotumab (10-20 µg/mL) can increase time to clot formation and surrogate substrate generation when standard assay concentrations for TF are drastically reduced (≥ 1000 -fold dilution). Tisotumab vedotin (up to 20 µg/mL) was only tested in the standard PT study (no TF dilution) and no effect was observed on clotting time. Tisotumab did not affect the strength of clot formation.

Skin Bleeding Time in Cynomolgus Monkey: A non-GLP intra-animal dose escalation study was conducted in cynomolgus monkeys to explore potential effects of tisotumab on coagulation and bleeding via a skin incision test ((b) (4) 514850). Tisotumab was administered as weekly doses of 0 (Phosphate Buffered Saline), 1, 10 and 100 mg/kg on days 1, 8, 15 and 22, respectively. There was no relationship between tisotumab dose level (1-100 mg/kg) and bleeding times. No effects on coagulation parameters were observed, and there were no toxicologically meaningful effects with supra-pharmacologic exposures.

The Applicant's Position:

The translation of the in vitro coagulation outcomes to in vivo or humans is likely limited. The in vitro assays (PT, TEG, and TGA) were not designed or validated to investigate effects of

functional inhibition of TF on coagulation initiation and clotting time in vitro. Positive controls for in vitro coagulation assays known to have a clinically relevant inhibition of TF do not exist. Furthermore, there were no toxicologically meaningful effects in cynomolgus monkey with supra-pharmacologic exposures of tisotumab (unconjugated antibody). Thus, any mechanistic potential for tisotumab vedotin to interfere with TF-dependent coagulation initiation is not anticipated to lead to adverse effects in vivo.

The FDA's Assessment:

The FDA generally agrees with the Applicant's position. However, in the in vivo skin bleeding time assessment in monkeys (Study# (b)(4) 514850; reviewed in more detail under Section 5.5.1) bleeding time increased in a dose dependent manner by 13%, 65% and 93% at 1, 10, and 100 mg/kg, respectively, 1 hour after the infusion compared to the saline dosed Day 1 measurement, corresponding to approximately 0.6, 5, and 55-fold the exposure at the recommended dose based on C_{max} . Additionally, minimal hemorrhage and myocardial degeneration in the heart and hemorrhage in the urinary bladder of one female was noted at necropsy.

Data (presented by the FDA):

Study# (b)(4) 1015-086: Tisotumab inhibited TF:FVIIa induced FXa generation by 19% at the highest concentration of 0.9 $\mu\text{g}/\text{mL}$. Tisotumab led to delayed clotting by 2.5-fold at the highest concentration of 10 $\mu\text{g}/\text{mL}$; however, it did not inhibit clot formation.

Study# (b)(4) 264005: In the standard PT assay, neither tisotumab or tisotumab vedotin up to 20 $\mu\text{g}/\text{mL}$ had an effect on prothrombin time in human or monkey pooled plasma (single experiment). In the diluted (x3000) PT assay, a 1.4-fold increase in PT was seen with both tisotumab and tisotumab vedotin at 20 $\mu\text{g}/\text{mL}$ compared to the control in human plasma; the variation between replicates was greater than those seen in the standard PT assay. In monkey plasma, there appears to be a trend towards increased PT; however, the variation between replicates in the control sample were too large to reliably compare to the treatment groups. In the 13-week repeat-dose monkey toxicology study, a 10-20% increase in PT at an exposure (C_{max}) >8-fold higher than in this assay (100 $\mu\text{g}/\text{mL}$) was observed; no change in PT was observed with tisotumab vedotin near the highest dose (100 $\mu\text{g}/\text{mL}$) tested in this assay. Per the Applicant, the diluted assay was run for the first time and was not optimized; therefore, the results may not accurately reflect those that may be obtained had the assay been optimized.

Study# HxTFADC-N-Study-Report-0361: Tisotumab increased time to clot and clot formation time in a dose dependent manner up to 2.6-fold and 1.6-fold, respectively, compared to control in human whole blood (single donor) at 20 $\mu\text{g}/\text{mL}$ in the rotational thermoelectrometry assay; the maximal clot formation was not affected by tisotumab. Tisotumab delayed thrombin generation in plasma; the lag time increased by 15-fold, and thrombin activity decreased by 20-fold at 20 $\mu\text{g}/\text{mL}$ compared to control in the calibrated automated thrombography (CAT) assay.

Study# HxTFADC-N-Study-Report-0364: In the TEG assay, tisotumab prolonged clotting time by

an average of 1.8-fold in human whole blood (n=3 donors) and by 2.5-fold in monkey whole blood (n=3 donors) at 20 µg/mL corresponding to an average of 21% and 80% inhibition of TF activity, respectively. The clot strength was not affected by tisotumab in either human or monkey. In the TGA assay, tisotumab led to an increase in lag time by an average of 2.3-fold in human and 3.7-fold in monkey plasma at 20 µg/mL.

Safety Pharmacology

Data (presented by the Applicant):

Limited inhibition (<50%) of potassium conductance via the human ether-a-go-go-related gene (hERG) channel was observed with the highest concentration of monomethyl auristatin E (MMAE) (100 µM, 71.8 µg/mL), which was ~12,000-fold higher than the clinically observed C_{max} of MMAE. At 10 µM MMAE (7.18 µg/mL) there was no significant inhibition of hERG channel activity. No effect was observed on the Fridericia corrected QT interval and RR-interval in cynomolgus monkeys treated with MMAE. Tisotumab vedotin was not evaluated in the hERG channel assay as the antibody component is too large to cross plasma membranes and therefore would be unable to access and block the promiscuous inner pore of the hERG channel.

No effect was observed on electrocardiogram (ECG), heart rate, blood pressure, respiratory, or central nervous system (CNS) safety pharmacology parameters evaluated as part of the general toxicology studies performed in cynomolgus monkeys with tisotumab vedotin and tisotumab.

The Applicant's Position:

Tisotumab vedotin has no effects on safety pharmacology endpoints. In addition, there was no evidence of clinical effects relating to safety pharmacology endpoints. 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 antibody-drug conjugate (ADC). No effect was observed on cynomolgus monkeys at physiological concentrations of MMAE. It is unlikely that MMAE derived from tisotumab vedotin would block hERG K⁺ channels in vivo.

The FDA's Assessment:

The FDA generally agrees with the Applicant's position. There were no tisotumab vedotin related effects on the safety pharmacology evaluations of the nervous, cardiovascular or respiratory systems at doses up to 5 mg/kg (4.2-fold the exposures at the recommended dose based on AUC) (Study# (b)(4) 522531) nor MMAE-related effects at a dose of 0.058 mg/kg (exposures similar to those at the recommended dose based on C_{max}) (Study# (b)(4) 163.16). However, in a non-GLP dose range finding study in monkeys (Study# (b)(4) 521988), one animal given 6 mg/kg tisotumab vedotin (4.9-fold the exposure at the recommended dose based on AUC) experienced respiratory symptoms described as gasping, wheezing, shallow, and labored breathing that led to early euthanasia.

5.4 ADME/PK

The Applicant's Position:

Following the first dose of tisotumab vedotin in cynomolgus monkeys, tisotumab vedotin exhibited a limited volume of distribution and an apparent terminal half-life ($t_{1/2}$) of 1 to 2 days. Tisotumab vedotin exposure over a dose-range of 1-6 mg/kg was approximately dose proportional after the first dose. Molar concentrations of MMAE were approximately 0.01% of peak tisotumab vedotin concentrations, confirming a high stability of tisotumab vedotin in the systemic circulation. In some animals that had high ADA titers, a decrease in tisotumab vedotin and an increase in unconjugated MMAE in circulation were observed upon subsequent dose administrations. However, in general, tisotumab vedotin exposures were sufficiently maintained during the treatment period even in the presence of ADA, particularly at the high dose (5 mg/kg). Since tisotumab vedotin shares the same linker-drug conjugation of the marketed product Adcetris[®] (brentuximab vedotin) and Padcev[™] (enfortumab vedotin), historical data on the distribution, metabolism, excretion, and drug interaction potential of MMAE are applicable and discussed. MMAE was identified as a substrate and a metabolism-based inhibitor of CYP3A4 in vitro. In humans, coadministration of brentuximab vedotin with a strong CYP3A4 inhibitor (ketoconazole) increased MMAE exposures by 34%, and a CYP3A4 inducer (rifampin) decreased MMAE exposures by 46% (Han 2013), but coadministration of brentuximab vedotin did not affect exposure to midazolam, a sensitive CYP3A substrate (Han 2013). Results from in vitro studies suggest that MMAE is a substrate of P-gp but not a substrate of BCRP, MRP2, OCT2, OAT1, OAT3, OATP1B1, or OATP1B3. Furthermore, MMAE is not an inhibitor of P-gp, BCRP, BSEP, MRP2, OCT1, OCT2, OAT1, OAT3, OATP1B1, or OATP1B3 at clinically relevant concentrations.

The FDA's Assessment:

The FDA agrees with the Applicant's position. See the clinical pharmacology Section 6 for information regarding human data and drug interaction studies.

BLA Multi-disciplinary Review and Evaluation {Biologics License Application (BLA) 761208}
{tisotumab vedotin}

Data (presented by the FDA):

Type of Study	Major Findings																																																																																																																																																																												
Absorption																																																																																																																																																																													
Thirteen-week repeat dose toxicity study in monkeys (Study# (b) (4) 522531)	Monkey After a single dose of tisotumab vedotin: • C_{max} and AUC increased in an approximately dose proportional manner. • There were no apparent gender differences in exposure. • T_{max} was reached within 30 to 40 minutes post infusion, and the half-life was approximately 1 to 2 days. • Free MMAE levels were ≤0.24 ng/mL compared to ≥150 µg/mL tisotumab vedotin at the 5 mg/kg dose level suggesting stability in plasma. Mean TK parameters of total antibody (IgG1 ELISA) <table border="1"> <thead> <tr> <th>Treatment</th> <th>Dose (mg/kg)</th> <th>Sex</th> <th>C_{max} (µg/mL)</th> <th>T_{max} (hr)</th> <th>AUC_{0-t} (µg.h/mL)</th> <th>T_{1/2} (hr)</th> <th>CL (mL/hr/kg)</th> <th>Vd (mL/kg)</th> </tr> </thead> <tbody> <tr> <td rowspan="6">HuMax-TF-ADC</td> <td rowspan="2">1</td> <td>M</td> <td>28.4</td> <td>0.5</td> <td>895</td> <td>29.7</td> <td>1.04</td> <td>44.5</td> </tr> <tr> <td>F</td> <td>30.9</td> <td>0.5</td> <td>1010</td> <td>29.5</td> <td>0.971</td> <td>40.7</td> </tr> <tr> <td rowspan="2">3</td> <td>M</td> <td>82.9</td> <td>0.5</td> <td>3540</td> <td>44.8</td> <td>0.733</td> <td>47.3</td> </tr> <tr> <td>F</td> <td>79.3</td> <td>0.5</td> <td>3340</td> <td>45.6</td> <td>0.791</td> <td>51.4</td> </tr> <tr> <td rowspan="2">5</td> <td>M</td> <td>114</td> <td>0.667</td> <td>4670</td> <td>46.6</td> <td>0.866</td> <td>57.9</td> </tr> <tr> <td>F</td> <td>152</td> <td>0.667</td> <td>7400</td> <td>49.7</td> <td>0.589</td> <td>41.6</td> </tr> <tr> <td rowspan="2">HuMax-TF</td> <td rowspan="2">25</td> <td>M</td> <td>729</td> <td>0.667</td> <td>50700</td> <td>NR</td> <td>NR</td> <td>NR</td> </tr> <tr> <td>F</td> <td>829</td> <td>0.667</td> <td>68500</td> <td>NR</td> <td>NR</td> <td>NR</td> </tr> </tbody> </table> CL: clearance; Vd: volume of distribution; NR: not reported Mean TK parameters of tisotumab vedotin and free MMAE (MMAE ELISA) <table border="1"> <thead> <tr> <th>Analyte</th> <th>Dose (mg/kg)</th> <th>Sex</th> <th>C_{max} (µg/mL)</th> <th>T_{max} (hr)</th> <th>AUC_{0-t} (µg.h/mL)</th> <th>T_{1/2} (hr)</th> <th>CL (mL/hr/kg)</th> <th>Vd (mL/kg)</th> </tr> </thead> <tbody> <tr> <td rowspan="6">HuMax-TF-ADC</td> <td rowspan="2">1</td> <td>M</td> <td>32.7</td> <td>0.5</td> <td>813</td> <td>25</td> <td>1.2</td> <td>43.1</td> </tr> <tr> <td>F</td> <td>28.5</td> <td>0.667</td> <td>781</td> <td>23.9</td> <td>1.27</td> <td>43.5</td> </tr> <tr> <td rowspan="2">3</td> <td>M</td> <td>93.2</td> <td>0.5</td> <td>1080</td> <td>31.4</td> <td>0.879</td> <td>39.7</td> </tr> <tr> <td>F</td> <td>93.8</td> <td>0.5</td> <td>3190</td> <td>33.9</td> <td>0.894</td> <td>43</td> </tr> <tr> <td rowspan="2">5</td> <td>M</td> <td>150</td> <td>0.667</td> <td>5030</td> <td>33</td> <td>0.882</td> <td>41.9</td> </tr> <tr> <td>F</td> <td>174</td> <td>0.667</td> <td>6970</td> <td>39.4</td> <td>0.658</td> <td>37</td> </tr> <tr> <td rowspan="6">Free MMAE</td> <td rowspan="2">1</td> <td>M</td> <td>5.3x10⁻⁵</td> <td>24.5</td> <td>0.005</td> <td>-</td> <td>-</td> <td>-</td> </tr> <tr> <td>F</td> <td>4.3x10⁻⁵</td> <td>24.5</td> <td>0.003</td> <td>-</td> <td>-</td> <td>-</td> </tr> <tr> <td rowspan="2">3</td> <td>M</td> <td>1.2x10⁻⁴</td> <td>24.5</td> <td>0.012</td> <td>-</td> <td>-</td> <td>-</td> </tr> <tr> <td>F</td> <td>1.3x10⁻⁴</td> <td>72.5</td> <td>0.012</td> <td>-</td> <td>-</td> <td>-</td> </tr> <tr> <td rowspan="2">5</td> <td>M</td> <td>2.4x10⁻⁴</td> <td>72.5</td> <td>0.023</td> <td>-</td> <td>-</td> <td>-</td> </tr> <tr> <td>F</td> <td>2x10⁻⁴</td> <td>72.5</td> <td>0.020</td> <td>-</td> <td>-</td> <td>-</td> </tr> </tbody> </table> CL: clearance; Vd: volume of distribution; -: no data available Note: Per the assay validation report # (b) (4) 315274 both the IgG1 ELISA and MMAE ELISA assays are suitable for the determination of tisotumab vedotin in monkey plasma; mouse IgG2a anti-MMAE was used in the MMAE ELISA and mouse anti-human IgG1-HRP was used in the IgG1 ELISA for detection.	Treatment	Dose (mg/kg)	Sex	C _{max} (µg/mL)	T _{max} (hr)	AUC _{0-t} (µg.h/mL)	T _{1/2} (hr)	CL (mL/hr/kg)	Vd (mL/kg)	HuMax-TF-ADC	1	M	28.4	0.5	895	29.7	1.04	44.5	F	30.9	0.5	1010	29.5	0.971	40.7	3	M	82.9	0.5	3540	44.8	0.733	47.3	F	79.3	0.5	3340	45.6	0.791	51.4	5	M	114	0.667	4670	46.6	0.866	57.9	F	152	0.667	7400	49.7	0.589	41.6	HuMax-TF	25	M	729	0.667	50700	NR	NR	NR	F	829	0.667	68500	NR	NR	NR	Analyte	Dose (mg/kg)	Sex	C _{max} (µg/mL)	T _{max} (hr)	AUC _{0-t} (µg.h/mL)	T _{1/2} (hr)	CL (mL/hr/kg)	Vd (mL/kg)	HuMax-TF-ADC	1	M	32.7	0.5	813	25	1.2	43.1	F	28.5	0.667	781	23.9	1.27	43.5	3	M	93.2	0.5	1080	31.4	0.879	39.7	F	93.8	0.5	3190	33.9	0.894	43	5	M	150	0.667	5030	33	0.882	41.9	F	174	0.667	6970	39.4	0.658	37	Free MMAE	1	M	5.3x10 ⁻⁵	24.5	0.005	-	-	-	F	4.3x10 ⁻⁵	24.5	0.003	-	-	-	3	M	1.2x10 ⁻⁴	24.5	0.012	-	-	-	F	1.3x10 ⁻⁴	72.5	0.012	-	-	-	5	M	2.4x10 ⁻⁴	72.5	0.023	-	-	-	F	2x10 ⁻⁴	72.5	0.020	-	-	-
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BLA Multi-disciplinary Review and Evaluation {Biologics License Application (BLA) 761208}
{tisotumab vedotin}

Type of Study	Major Findings
Distribution	
Determination of Whole Body Distribution of IV Bolus [Zr-89]-Df- IAb456_FL by Positron Emission Tomography (PET) (Study# KVU0001)	Monkey Following a single intravenous infusion of positron emitting radionuclide Zirconium-89 (⁸⁹Zr) labelled and iron chelating agent deferoxamine conjugated tisotumab at 0.4, 1, and 3 mg/kg (n=1/sex/dose): - Highest tissue uptakes were observed in the liver (21%), bone marrow (19%), lungs (9.5%), kidneys (4.2%), heart (11%), small intestine (5.9%), and gall bladder (1.7%). Tissue uptake that was above background activity but ≤1.2% was seen in spleen, salivary gland, testes and urinary bladder. - There was no apparent difference in the tissue uptake between males and females or the different doses tested.
Biodistribution of ⁸⁹ Zr-Df IAb37_FL and ⁸⁹ Zr-Df- IAb37_FL in a high TF-expressing pancreas cancer xenograft model (Study# IMA001)	Mouse Following a single intravenous injection of positron emitting radionuclide Zirconium-89 (⁸⁹Zr) labelled and iron chelating agent deferoxamine conjugated tisotumab or tisotumab vedotin at 1 mg/kg to TF-high pancreatic (HPAF-II; n=6/group) or TF-no/low pancreatic (PANC-I; n=3/group) tumor bearing SCID mice: - Higher distribution of both tisotumab vedotin (23-fold) and tisotumab (5-fold) in TF-high tumors compared to TF-low tumors (6 days post dose). - Generally similar distribution of tisotumab vedotin and tisotumab in normal tissues of both TF-high and TF-low tumor bearing mice, except: - A higher distribution of tisotumab vedotin in liver (>3-fold) and kidney (~2-fold) compared to tisotumab in both TF-high and TF-low tumor bearing mice. - In the blood and spleen, distribution was higher in mice with TF-low bearing tumors.
The study evaluating the payload, MMAE, was previously reviewed by the FDA under the Applicant’s BLA 125388 (brentuximab vedotin). The major findings from the primary review were included below.	
Plasma Protein Binding Assay of MMAE by Ultracentrifugation (Study# XS-0025)	[³H]-MMAE at 1, 10, and 100 nM was added to plasma of ICR mouse, Wistar rat, cynomolgus monkey, and human. Radioactivity in plasma and supernatant was measured by a liquid scintillation counter (LSC). - The [³H]-MMAE plasma protein binding ratio was 19 to 29% in mouse, 72 to 74% in rat, 17 to 19% in monkey, and 68 to 82% in human. - The plasma protein binding of [³H]-MMAE was species-dependent. - There was no change in binding from 1 to 100 nM with rat and monkey plasma, but small differences were observed with mouse and human plasma.
Metabolism	
The metabolism studies with MMAE provided by the Applicant were previously reviewed by the FDA under the Applicant’s BLA 125388 (brentuximab vedotin). The major findings from the primary review were included below.	
Reaction Phenotyping: Identification of Human CYP Enzymes Involved in the In Vitro Metabolism of [³ H]-MMAE (Study# XT084006)	[³H]-MMAE was converted to 8 radioactive compounds by NADPH-fortified human liver microsomes. - The major metabolites identified by high-performance liquid chromatography (HPLC) retention time (min) were 7.0 (by O-demethylation), 8.6 (by N-demethylation), and 11.1 (by dehydrogenation). - The formation of these major metabolites was primarily mediated by CYP3A4. Additional CYP450 enzymes (i.e. CYP2D6) might be minor contributors to the formation of these metabolites.

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{tisotumab vedotin}

Type of Study	Major Findings
Metabolite Characterization of [³ H]-MMAE in Rat, Monkey, and Human Hepatocytes (Study# XT084007)	- The extent of 10 μM [³H]-MMAE metabolism by rat, monkey, and human hepatocytes was analyzed by liquid chromatography mass spectrometry (LC/MS/MS) over 240 minutes. - Up to 32% (in rat), 18% (in monkey), and 31% (in human) loss of [³H]-MMAE in hepatocytes was reported. The rank order (greatest to least) of observed substrate loss over the 240-minute incubations was rat ≈ human > monkey. 12 metabolites formed by hydroxylation, demethylation, dehydrogenation or hydrolysis were detected following incubation of 10 μM [³H]-MMAE with hepatocytes. - All 12 metabolites were detected from monkey hepatocytes, two of which were specific to the monkey (C2, C11) and one of which was specific to rat and monkey (C1). According to the Applicant, two metabolites, C4 and C6, formed by O-demethylation and hydroxylation, respectively, could be major metabolites in all three species.
Excretion	
The excretion study provided by the Applicant was previously reviewed by the FDA under the Applicant's BLA 125388 (brentuximab vedotin). The major findings from the primary review for ³ H-MMAE were included below.	
Excretion, Mass Balance and Pharmacokinetics of Radioactivity in Sprague-Dawley Rats Following a Single Intravenous Bolus Dose of cAC10-vc-3H-MMAE or [³ H]-MMAE (Study# (b) (4) 420501)	- The major route of MMAE elimination in rats was via feces, suggesting biliary excretion with some recovery in urine. - Approximately 97% (males) or 102% (females) of the radiolabeled material was detected in feces. Approximately 15% (males) or 9% (females) of the radiolabeled materials was detected in urine. - No radioactivity was recovered in the carcass (with ³H-MMAE) at 28 days post dose, suggesting that elimination was complete at this time after a single dose administration. - In the 1st 48 hours post-dose, approximately 90-95% [³H]-MMAE was excreted during this period. The half-life of [³H]-MMAE was 1-2.3 days. It is expected that excretion of tisotumab vedotin will be slower compared to unconjugated MMAE due to higher plasma stability and longer half-life of tisotumab vedotin compared to free MMAE. - The majority of radiolabeled components seen in urine and feces was identified as [³H]-MMAE rather than the parent ADC.
Other	
In vitro stability assessment of HuMax-TF-ADC (Study# SR1015-109-01)	Plasma (pooled mouse, cynomolgus monkey, human) and PBS with 1% bovine serum albumin were incubated with 50 μg/mL HuMax-TF-ADC up to 14 days at 37°C. Release of free MMAE in PBS/1%BSA, mouse, monkey, and human over the two-week period was 0.2%, 20%, 0.5%, and 0.7%, respectively.

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Type of Study	Major Findings																																																																																																																		
TK data from general toxicology studies Thirteen-week repeat dose toxicity study in monkeys (Study# (b)(4) 522531)	Monkey Dosing schedule: once every 3 weeks Accumulation: No to minimal accumulation, 1.1 to 1.3x in males at 5 mg/kg HuMax-TF-ADC and 25 mg/kg HuMax-TF (Day 85 vs. Day 1) T_{1/2} and T_{max}: 1 to 2 days (T_{1/2}) increased with dose, and 0.5 to 0.67 hours (T_{max}) independent of dose. Mean plasma levels of tisotumab vedotin and tisotumab <table border="1" data-bbox="513 510 1328 1079"> <thead> <tr> <th>Study Day</th> <th>Dose (mg/kg)</th> <th>Sex</th> <th>C_{max} (µg/mL)</th> <th>C_{max} Ratio</th> <th>AUC_{0-t} (µg.h/mL)</th> <th>AUC_{0-t} Ratio</th> <th>Accum. Ratio (AUC_{0-t})</th> </tr> </thead> <tbody> <tr> <td rowspan="10">Day 1</td> <td rowspan="2">1</td> <td>M</td> <td>28.4</td> <td>1</td> <td>895</td> <td>1</td> <td>-</td> </tr> <tr> <td>F</td> <td>30.9</td> <td>1</td> <td>1010</td> <td>1</td> <td>-</td> </tr> <tr> <td rowspan="2">3</td> <td>M</td> <td>82.9</td> <td>2.9</td> <td>3540</td> <td>3.9</td> <td>-</td> </tr> <tr> <td>F</td> <td>79.3</td> <td>2.6</td> <td>3340</td> <td>3.3</td> <td>-</td> </tr> <tr> <td rowspan="2">5</td> <td>M</td> <td>114</td> <td>4</td> <td>4670</td> <td>5.2</td> <td>-</td> </tr> <tr> <td>F</td> <td>152</td> <td>4.9</td> <td>7400</td> <td>7.3</td> <td>-</td> </tr> <tr> <td rowspan="2">HuMax-TF 25</td> <td>M</td> <td>729</td> <td>-</td> <td>50700</td> <td>-</td> <td>-</td> </tr> <tr> <td>F</td> <td>829</td> <td>-</td> <td>68500</td> <td>-</td> <td>-</td> </tr> <tr> <td rowspan="10">Day 85</td> <td rowspan="2">1</td> <td>M</td> <td>14.5</td> <td>1</td> <td>822</td> <td>1</td> <td>0.9</td> </tr> <tr> <td>F</td> <td>10.8</td> <td>1</td> <td>835</td> <td>1</td> <td>0.8</td> </tr> <tr> <td rowspan="2">3</td> <td>M</td> <td>55.2</td> <td>3.8</td> <td>2470</td> <td>3</td> <td>0.7</td> </tr> <tr> <td>F</td> <td>62</td> <td>5.7</td> <td>3540</td> <td>4.2</td> <td>1</td> </tr> <tr> <td rowspan="2">5</td> <td>M</td> <td>124</td> <td>8.6</td> <td>5130</td> <td>6.2</td> <td>1.1</td> </tr> <tr> <td>F</td> <td>149</td> <td>13.8</td> <td>6580</td> <td>7.9</td> <td>0.9</td> </tr> <tr> <td rowspan="2">HuMax-TF 25</td> <td>M</td> <td>829</td> <td>-</td> <td>68500</td> <td>-</td> <td>1.3</td> </tr> <tr> <td>F</td> <td>826</td> <td>-</td> <td>63200</td> <td>-</td> <td>0.9</td> </tr> </tbody> </table> NR: not reported; “-”: not applicable No apparent differences in peak plasma concentration or total exposure after repeat dosing between ADA negative and ADA positive animals.	Study Day	Dose (mg/kg)	Sex	C _{max} (µg/mL)	C _{max} Ratio	AUC _{0-t} (µg.h/mL)	AUC _{0-t} Ratio	Accum. Ratio (AUC _{0-t})	Day 1	1	M	28.4	1	895	1	-	F	30.9	1	1010	1	-	3	M	82.9	2.9	3540	3.9	-	F	79.3	2.6	3340	3.3	-	5	M	114	4	4670	5.2	-	F	152	4.9	7400	7.3	-	HuMax-TF 25	M	729	-	50700	-	-	F	829	-	68500	-	-	Day 85	1	M	14.5	1	822	1	0.9	F	10.8	1	835	1	0.8	3	M	55.2	3.8	2470	3	0.7	F	62	5.7	3540	4.2	1	5	M	124	8.6	5130	6.2	1.1	F	149	13.8	6580	7.9	0.9	HuMax-TF 25	M	829	-	68500	-	1.3	F	826	-	63200	-	0.9
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Type of Study	Major Findings																																																																																								
A 4-week intravenous injection toxicity and toxicokinetic study of SGN-35, SGD-1010, and SGN-30 in rats with a 4-week recovery (Study# 7646-118)	Rat Dosing schedule: once weekly Accumulation: ≤2 (Day 22 vs. Day 1) T_{max}: 0.25 to 0.5 hours, independent of dose and sex Mean serum MMAE (SGD-1010) concentration <table border="1"> <thead> <tr> <th>Study Day</th> <th>Dose (mg/kg)</th> <th>Sex</th> <th>C_{max} (ng/mL)</th> <th>C_{max} Ratio</th> <th>AUC₀₋₂₄ (ng.h/mL)</th> <th>AUC₀₋₂₄ Ratio</th> <th>Accum. Ratio (AUC₀₋₂₄)</th> </tr> </thead> <tbody> <tr> <td rowspan="6">Day 1</td> <td rowspan="2">0.0097</td> <td>M</td> <td>0.59</td> <td>1</td> <td>2.61</td> <td>1</td> <td>-</td> </tr> <tr> <td>F</td> <td>0.49</td> <td>1</td> <td>2.6</td> <td>1</td> <td>-</td> </tr> <tr> <td rowspan="2">0.097</td> <td>M</td> <td>3.53</td> <td>5.9</td> <td>25.7</td> <td>9.8</td> <td>-</td> </tr> <tr> <td>F</td> <td>3.75</td> <td>7.6</td> <td>28.6</td> <td>11</td> <td>-</td> </tr> <tr> <td rowspan="2">0.194</td> <td>M</td> <td>5.8</td> <td>9.8</td> <td>49.4</td> <td>18.9</td> <td>-</td> </tr> <tr> <td>F</td> <td>12.5</td> <td>25.5</td> <td>91</td> <td>35</td> <td>-</td> </tr> <tr> <td rowspan="6">Day 22</td> <td rowspan="2">0.0097</td> <td>M</td> <td>0.70</td> <td>1</td> <td>4</td> <td>1</td> <td>1.5</td> </tr> <tr> <td>F</td> <td>0.84</td> <td>1</td> <td>3</td> <td>1</td> <td>1.1</td> </tr> <tr> <td rowspan="2">0.097</td> <td>M</td> <td>5.49</td> <td>7.8</td> <td>52.4</td> <td>13.1</td> <td>2</td> </tr> <tr> <td>F</td> <td>4.84</td> <td>5.8</td> <td>28.6</td> <td>9.5</td> <td>1</td> </tr> <tr> <td rowspan="2">0.194</td> <td>M</td> <td>11</td> <td>15.7</td> <td>71</td> <td>17.8</td> <td>1.4</td> </tr> <tr> <td>F</td> <td>7</td> <td>8.3</td> <td>49.2</td> <td>16.4</td> <td>0.5</td> </tr> </tbody> </table> T_{1/2} was only available for the low dose (4.68 to 5.76 hours) for both males and females Data for SGN-30 and SGN-35 are not shown.	Study Day	Dose (mg/kg)	Sex	C _{max} (ng/mL)	C _{max} Ratio	AUC ₀₋₂₄ (ng.h/mL)	AUC ₀₋₂₄ Ratio	Accum. Ratio (AUC ₀₋₂₄)	Day 1	0.0097	M	0.59	1	2.61	1	-	F	0.49	1	2.6	1	-	0.097	M	3.53	5.9	25.7	9.8	-	F	3.75	7.6	28.6	11	-	0.194	M	5.8	9.8	49.4	18.9	-	F	12.5	25.5	91	35	-	Day 22	0.0097	M	0.70	1	4	1	1.5	F	0.84	1	3	1	1.1	0.097	M	5.49	7.8	52.4	13.1	2	F	4.84	5.8	28.6	9.5	1	0.194	M	11	15.7	71	17.8	1.4	F	7	8.3	49.2	16.4	0.5
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An 11-week repeat-dose intravenous infusion toxicity study of SGN-35 and SGD-1010 in cynomolgus monkeys with a five-week recovery period (Study# (b) (4) 163.16)	Monkey Dosing schedule: once every 3 weeks Accumulation: None after repeated dosing Mean serum MMAE (SGD-1010) concentration <table border="1"> <thead> <tr> <th>0.058 mg/kg MMAE</th> <th>Male (ng/mL)</th> <th>Female (ng/mL)</th> </tr> </thead> <tbody> <tr> <td>Day 1 PD</td> <td>2.02</td> <td>1.72</td> </tr> <tr> <td>Day 22 PD</td> <td>4.95</td> <td>4.3</td> </tr> <tr> <td>Day 43 PD</td> <td>5.3</td> <td>3</td> </tr> <tr> <td>Day 64 PD</td> <td>3.24</td> <td>5.6</td> </tr> <tr> <td>Day 71</td> <td>0.016</td> <td>0.013</td> </tr> </tbody> </table> PD = post dose immediately after infusion; Serum levels of MMAE were <10 pg/mL at the pre-dose timepoints; data for SGN-35 are not shown.	0.058 mg/kg MMAE	Male (ng/mL)	Female (ng/mL)	Day 1 PD	2.02	1.72	Day 22 PD	4.95	4.3	Day 43 PD	5.3	3	Day 64 PD	3.24	5.6	Day 71	0.016	0.013																																																																						
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5.5 Toxicology

5.5.1 General Toxicology

Data (presented by the FDA):

The 3-month GLP repeat dose toxicology study in the monkey was initially reviewed by the FDA under IND (b) (4) and findings are presented as in the original IND or reformatted for the BLA review.

Study title/number: HuMax-TF-ADC: 13 Week Repeat Dose Toxicity Study in Cynomolgus Monkeys with a 6 Week Recovery Period/522531

- The major clinical signs were skin toxicity (dry, red, flaky skin and skin sloughing) at ≥ 3 mg/kg and ocular toxicity at 5 mg/kg HuMax-TF-ADC and 25 mg/kg HuMax-TF without microscopic correlates.
- A decrease in erythropoiesis (hemoglobin, red blood cells, and hematocrit), total leukocytes, neutrophils, lymphocytes, eosinophils, and basophils at ≥ 4 mg/kg; animals received antibiotics throughout the study due to neutropenia.
- Major target organs included the spleen and testis/epididymis at ≥ 1 mg/kg, bone marrow and skin at ≥ 3 mg/kg, and the eye at 5 mg/kg. All findings were reversible except in the testes/epididymides and spleen.

GLP compliance: Yes

Methods

Dose:	<u>HuMax-TF-ADC</u> Main study: 0, 1, 3, and 5 mg/kg Interim study: 4 mg/kg
	<u>HuMax-TF</u> Main study: 25 mg/kg
Frequency of dosing:	Once every 3 weeks
Route of administration:	Intravenous infusion
Formulation/Vehicle:	Sodium chloride 0.9% w/v, USP
Species/Strain:	Cynomolgus monkey/ <i>Macaca fascicularis</i>
Number/Sex/Group:	Main: 3/sex/group Recovery: 2/sex/group
Age:	4-6 years
Satellite groups/Unique design:	2/sex/group (interim study; 4 mg/kg) In the interim study (Group 6), animals were treated with a single dose of 4 mg/kg HuMax-TF-ADC on Day 1 and sacrificed on Day 12 to better evaluate drug-related skin reactions.
Deviation from study protocol affecting interpretation of results:	No

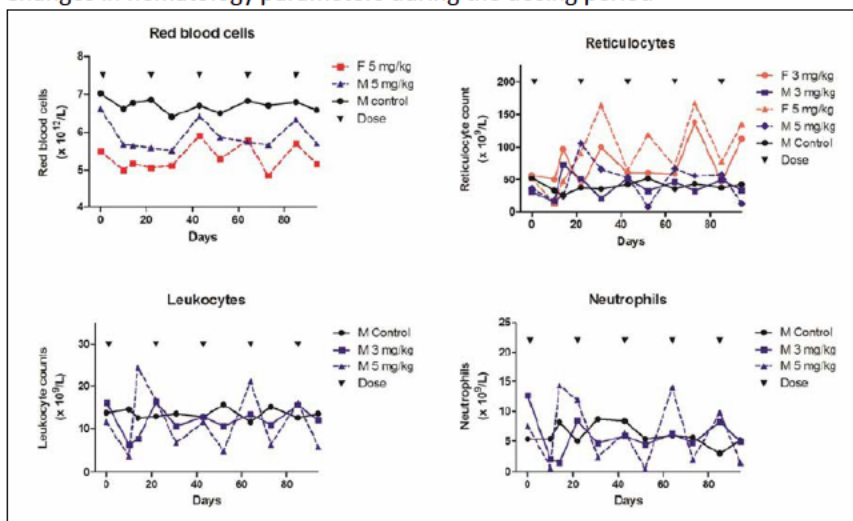
Observations and Results: Changes from control

Parameters	Major findings																																																																																																																																																																																																																																																																																																									
Mortality	One female given 4 mg/kg (interim study) was euthanized on Day 11; one male and two females given 5 mg/kg were euthanized on Day 10, 26, and 41, respectively. The cause of death was due to adverse skin reactions (noted below for clinical signs).																																																																																																																																																																																																																																																																																																									
Clinical Signs	Observations for both 3 and 5 mg/kg groups were generally noted by day 6. Animals dosed at 3 mg/kg generally recovered prior to the second dose, and the observations did not recur with subsequent dosing. Observations in the animals dosed at 5 mg/kg generally persisted or recurred with subsequent dosing. The clinical signs fully recovered by the end of the recovery period. Clinical Observations During the Dosing Period <table border="1"> <thead> <tr> <th>Treatment</th> <th colspan="6">HuMax-TF-ADC</th> <th colspan="2">HuMax-TF</th> </tr> <tr> <th>mg/kg</th> <th colspan="2">1</th> <th colspan="2">3</th> <th colspan="2">5</th> <th colspan="2">25</th> </tr> <tr> <th>Sex (n=5/sex)</th> <th>M</th> <th>F</th> <th>M</th> <th>F</th> <th>M</th> <th>F</th> <th>M</th> <th>F</th> </tr> </thead> <tbody> <tr> <td>Skin reddening</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>- chest</td> <td></td> <td></td> <td>5</td> <td></td> <td>4</td> <td>1</td> <td></td> <td></td> </tr> <tr> <td>- shoulder</td> <td></td> <td></td> <td>3</td> <td></td> <td>3</td> <td></td> <td></td> <td></td> </tr> <tr> <td>- arms</td> <td></td> <td></td> <td>2</td> <td>1</td> <td>3</td> <td>2</td> <td></td> <td></td> </tr> <tr> <td>- neck</td> <td></td> <td></td> <td>1</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>- eye lids</td> <td></td> <td></td> <td>1</td> <td></td> <td>1</td> <td></td> <td></td> <td></td> </tr> <tr> <td>- legs</td> <td></td> <td></td> <td>1</td> <td></td> <td>2</td> <td>2</td> <td></td> <td></td> </tr> <tr> <td>- femoral areas</td> <td></td> <td></td> <td>3</td> <td>3</td> <td>4</td> <td>5</td> <td></td> <td></td> </tr> <tr> <td>Dry, flaky skin</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>- chest</td> <td></td> <td></td> <td></td> <td></td> <td>5</td> <td>5</td> <td></td> <td></td> </tr> <tr> <td>- arms</td> <td></td> <td></td> <td></td> <td></td> <td>3</td> <td>2</td> <td></td> <td></td> </tr> <tr> <td>- lips</td> <td></td> <td></td> <td></td> <td></td> <td>2</td> <td></td> <td></td> <td></td> </tr> <tr> <td>- legs</td> <td></td> <td></td> <td></td> <td></td> <td>1</td> <td>3</td> <td></td> <td></td> </tr> <tr> <td>- femoral areas</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>2</td> <td></td> <td></td> </tr> <tr> <td>Scratch marks</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>- shoulder</td> <td></td> <td></td> <td></td> <td></td> <td>1</td> <td></td> <td></td> <td></td> </tr> <tr> <td>- arms</td> <td></td> <td></td> <td></td> <td></td> <td>1</td> <td></td> <td></td> <td></td> </tr> <tr> <td>- chest</td> <td></td> <td></td> <td></td> <td></td> <td>3</td> <td></td> <td></td> <td></td> </tr> <tr> <td>- femoral areas</td> <td></td> <td></td> <td></td> <td></td> <td>4</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Swelling</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>- lower back</td> <td></td> <td></td> <td></td> <td></td> <td>1</td> <td>1</td> <td></td> <td></td> </tr> <tr> <td>- abdomen</td> <td></td> <td></td> <td></td> <td></td> <td>1</td> <td>1</td> <td></td> <td></td> </tr> <tr> <td>Skin sloughing</td> <td></td> <td></td> <td></td> <td></td> <td>1</td> <td>3</td> <td></td> <td></td> </tr> <tr> <td>Eyes</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>- reddened</td> <td></td> <td></td> <td>1</td> <td></td> <td>4</td> <td>2</td> <td></td> <td></td> </tr> <tr> <td>- closing</td> <td></td> <td></td> <td>1</td> <td></td> <td>4</td> <td>3</td> <td></td> <td></td> </tr> <tr> <td>- watery</td> <td></td> <td></td> <td></td> <td></td> <td>2</td> <td></td> <td></td> <td></td> </tr> <tr> <td>- swollen</td> <td></td> <td></td> <td></td> <td></td> <td>1</td> <td>1</td> <td></td> <td></td> </tr> <tr> <td>Ear</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>- oily discharge</td> <td></td> <td></td> <td></td> <td></td> <td>1</td> <td></td> <td></td> <td></td> </tr> </tbody> </table>	Treatment	HuMax-TF-ADC						HuMax-TF		mg/kg	1		3		5		25		Sex (n=5/sex)	M	F	M	F	M	F	M	F	Skin reddening									- chest			5		4	1			- shoulder			3		3				- arms			2	1	3	2			- neck			1						- eye lids			1		1				- legs			1		2	2			- femoral areas			3	3	4	5			Dry, flaky skin									- chest					5	5			- arms					3	2			- lips					2				- legs					1	3			- femoral areas						2			Scratch marks									- shoulder					1				- arms					1				- chest					3				- femoral areas					4				Swelling									- lower back					1	1			- abdomen					1	1			Skin sloughing					1	3			Eyes									- reddened			1		4	2			- closing			1		4	3			- watery					2				- swollen					1	1			Ear									- oily discharge					1			
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BLA Multi-disciplinary Review and Evaluation {Biologics License Application (BLA) 761208}
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Ophthalmoscopy	<u>Examinations were performed at pre-test, end of main study (week 12) and end of recovery (week 5).</u> <u>5 mg/kg:</u> glassy appearance of the fundus in both eyes (3M), conjunctiva appeared reddened and swollen (2M); findings were reversible Fucithalamic eye drops for reddened eyes and/or reddened conjunctiva/swelling were given to animals (4M, 3F) for several days (multiple times for most animals) during the treatment period. <u>HuMax-TF, 25 mg/kg:</u> glassy appearance of the fundus in both eyes (5M); findings were reversible
ECG	Unremarkable
Behavioral Assessments	Unremarkable
Respiratory Rates	Unremarkable
Hematology	Hematology parameters were evaluated at pre-test, during dosing (pre-dose, 3-, 5-, 9-, 13- and 17-days post dose), and weekly during the recovery period. Coagulation parameters were evaluated at pre-test, during dosing (pre-dose, 1- and 13-days post dose), and week 1, 3, and 6 of the recovery period. - Statistically significant decrease in erythropoiesis was observed at 5 mg/kg beginning day 10 to 14 and lasted for the duration of the study; parameters were generally lower compared to control and baseline levels. Mean changes included up to -23% in red blood cell, up to -20% in hemoglobin, and up to -23% in hematocrit values compared to control. - Variable changes in reticulocytes were noted with generally decreased values in the range of approximately -50% to -90% up to 5 days post dose compared to control, followed by increased values prior to the subsequent dose at 5 mg/kg. A generally similar trend to a lesser magnitude was observed at 3 mg/kg. - A decrease in leukocytes (generally in the range of -35 to -50%) were observed up to about 9 to 10 days post dosing often reaching statistical significance at all doses in males and mostly at 5 mg/kg in females. - Generally, 3 days post dosing, an approximately 1.5-fold and 1.5 to 2-fold decrease in lymphocytes compared to baseline was observed at 3 and 5 mg/kg, respectively, with recovery prior to the next dose. The decrease was seen after the first two doses at the mid dose and after all doses at the high dose. - Approximately 9 days post dosing up to 6-fold and up to 18-fold decrease in neutrophils compared to baseline was observed at 3 and 5 mg/kg, respectively, with recovery trends prior to the next dose. - No drug-related changes in coagulation parameters were noted for all dose levels of tisotumab vedotin, but a 10 to 20% increase in prothrombin time was noted in the 25 mg/kg unconjugated tisotumab group. Animals were treated with antibiotics (Baytril) due to marked neutropenia: <u>3 mg/kg:</u> 20% of the animals after the first dose (week 2). <u>5 mg/kg:</u> 100% of animals received antibiotics as a precaution following the first dose (Day 5 to 14) in anticipation of neutropenia; 70% of the animals received antibiotics due to marked neutropenia after the second and/or third dose.

Changes in hematology parameters during the dosing period



[Excerpted from the original IND (b) (4) review]

The graphs where only male animals are shown are representative of results from both sexes.

Clinical Chemistry

Clinical chemistry parameters were evaluated at pre-test, during dosing (pre-dose, 1- and 13-days post dose), and week 1, 3, and 6 of the recovery period.

Changes in albumin, globulin, haptoglobin, and iron were observed at 5 mg/kg. Changes in other parameters were noted throughout the dosing period but were transient, within pretrial values, and/or independent of dose.

- Decrease in albumin up to -20% and an increase in globulin up to 28% led to overall decrease in the albumin/globulin ratio up to -38% from Day 14 until the end of dosing period in both genders. Changes were most pronounced after the first dose.
- Transient increase in haptoglobin up to 160% in both sexes throughout the dosing period with the most pronounced change after the first dose.
- Decrease in iron (males only) up to -48%, however, not reaching statistical significance at every timepoint examined.

Urinalysis

Unremarkable

Gross Pathology

Summary of Macroscopic Findings

Treatment	HuMax-TF-ADC											
	mg/kg		1		3		4*		5		25	
Sex (n=5/sex)	M	F	M	F	M	F	M	F	M	F	M	F
Lung												
- dark discoloration	1											
- adhesion	1R	1					1		1R			
- failure to collapse				1								1
Lymph node												
- enlargement				1R								
Skin												
- abnormal appearance	1R					1	2		2			
- area raw						1	1					
- discoloration						1						
- scab						1						
Testis												
- abnormal consistency			-	1	-				2	-		-

*interim study; -: not applicable; R: recovery

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Organ Weights	None of the changes in organ weights attained statistical significance, but macroscopic findings in the lung (dark discoloration, adhesion, failure to collapse), microscopic findings in lymphoid tissues (decreased granulopoiesis and cellularity in bone marrow, decreased germinal centers in spleen) and macroscopic and microscopic findings in male reproductive organs (abnormal consistency, tubular atrophy in testes, and decreased or absence of sperm in epididymis) suggest toxicological relevance.

Summary of Organ Weigh Changes, Percent Deviation from Control

Organ		1 mg/kg	3 mg/kg	4 mg/kg ^a	5 mg/kg	25 mg/kg unconjugated antibody
Male						
Adrenal glands	R/BW		-11.0	26.0		
Brain	R/BW		18.6		28.2	31.2
Epididymides	R/BW		24.4			21.3
Lung	R/BW	16.5	19.9	15.7	16.5	12.3
Pituitary	R/BW	55.6	66.7		33.3	44.4
Prostate	R/BW		72.2	177.8	66.7	44.4
Spleen	R/BW	32.7	25.5	73.2	52.7	20.9
Testes	R/BW		-26.4	-15.6	-56.7	
Thymus	R/BW	40.6			25	75
Thyroid glands	R/BW	-21	14.7	-52.6		16.8
Female						
Adrenal glands	R/BW	15.0	14.5	34.0	26.6	
Kidneys	R/BW		12.0	29.0	17.8	16.5
Liver	R/BW		15.3	13.5	18.3	
Lung	R/BW			33.0		30.6
Pituitary	R/BW	-23.5	17.6	17.6	-11.8	
Spleen	R/BW		44.1		48.8	-21.3
Thymus	R/BW		-42.3	-28.1	-19.2	-15.4
Thyroid glands	R/BW			-16.2	16.7	27.5
Uterus	R/BW	15.7	40.5			

^aIn the interim study, organ weights were measured on Day 12; R – relative weight; BW – body weight
 [Excerpted from the original IND (b) (4) review]

Histopathology Adequate battery: Yes Peer Review: Yes	Microscopic findings are summarized in the table below. Similar findings were also observed at the end of study necropsy (Day 12) in 4 mg/kg interim study animals. An additional finding was noted in the thymus (moderate atrophy/involution) of all 4 mg/kg animals. The interim study animals were also evaluated for test article-related skin abnormalities 12 days after the first dose. Findings included ulcerative dermatitis, mixed subepidermal inflammatory cell infiltration, epithelial hydropic degeneration/hyperplasia, and subcutis hemorrhaging. At the end of recovery, microscopic findings were still present in the testis, epididymis and spleen, although findings in spleen were also in control animals.

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Summary of Microscopic Findings										
Dose mg/kg	HuMax-TF-ADC								HuMax-TF	
	0		1		3		5		25	
Sex	M	F	M	F	M	F	M	F	M	F
Bone marrow Decreased granulopoiesis										
<i>Minimal</i>					1	2		1		
<i>Mild</i>					2			1		
<i>Marked</i>							2			
Spleen Decreased germinal center size										
<i>Present</i>		1/2R	1	2/1R	1	1/1R	2/1R	1/1R		3/1R
Sternum Decreased cellularity, bone marrow										
<i>Minimal</i>						1		2	1	
<i>Mild</i>					1			2	1	
Skin and subcutis Hyperkeratosis										
<i>Mild</i>								1		
Mononuclear cell infiltration, dermal, focal										
<i>Minimal</i>								1		
Epididymis Absence of sperm										
Sperm content, decrease		-		-	2/1R	-	2/2R	-		-
<i>Marked</i>		-	1	-		-		-		-
Sperm content decreased, unilateral		-		-		-		-	1	-
Epithelial vacuolation, tubular										
<i>Mild</i>		-		-	1	-	1	-		-
Spermatogenic cells, luminal										
<i>Minimal</i>		-		-		-	1R	-		-
<i>Mild</i>		-		-		-	1R	-		-
<i>Moderate</i>		-		-	1R	-		-		-
Eosinophilic material, luminal										
<i>Minimal</i>		-		-		-	1R	-		-
<i>Mild</i>		-		-	1R	-	1R	-		-
Testis Tubular atrophy, seminiferous, diffuse										
<i>Moderate</i>		-	1	-	1	-		-		-
<i>Marked</i>		-		-	1	-		-		-
<i>Severe</i>		-		-		-	2	-		-

T: treatment; R: recovery; Blank: unremarkable; "-" not applicable

Anti-drug Antibodies	- After the first dose of HuMax-TF-ADC, anti-drug antibodies were detected in 7/10, 10/10, 1/3, and 6/10 animals administered 1, 3, 4, and 5 mg/kg, respectively. Following subsequent doses, nearly all animals produced anti-drug antibodies. - An increase in antibody titers was reported over time. - No gender differences were noted in anti-drug antibody formation.
Reproductive Investigations	- No remarkable changes in the duration of menstrual cycles were noted. - A decrease in testicular size was reported for all dose levels and the 25 mg/kg HuMax-TF group. - A reduction in sperm count and motility was noted at the 3 and 5 mg/kg dose levels. These findings were still present in recovery animals consistent with macroscopic and microscopic toxicities in the male reproductive organs.

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Mean testicular size, percent deviation from control

Dose Levels	Week of treatment	Left			Right		
		TW (mm)	TL (mm)	TV (cm ³)	TW (mm)	TL (mm)	TV (cm ³)
1 mg/kg	Week 11	-15.44	-11.04	-9.22	-2.44	-5.06	-9.41
3 mg/kg		-12.30	-15.83	-31.43	-17.68	-8.38	-35.30
5 mg/kg		-16.70	-20.89	-43.24	-23.21	-21.31	-52.27
25 mg/kg HuMax-TF	Week 5 Recovery	-3.28	-9.33	-12.29	-9.01	-4.52	-19.08
1 mg/kg		-8.83	-8.09	-23.96	-2.89	-10.53	-15.75
3 mg/kg		-26.99	-23.95	-59.34	-19.36	-33.98	-56.80
5 mg/kg		-29.98	-36.71	-68.96	-22.24	-51.32	-69.99
25 mg/kg HuMax-TF		-14.05	-7.58	-31.10	-10.96	-22.05	-35.62

*TW – testicular width, TL – testicular length, TV – testicular volume

[Excerpted from the original IND (b) (4) nonclinical review]

Summary of sperm counts and motility during dosing and recovery

Group	Animal No.	No. of sperm/mL (x10 ⁶)			Motility (%)		
		Pretrial†	Week 11/12	Week 5 Recovery	Pretrial†	Week 11/12	Week 5 Recovery
1	4	3505	2660	1770	88	86	84
	5	2370	1860	3800	NS	86	85
2	8	1410	405	-	83	72	-
	9	3840	2240	-	80	92	-
	10	4085	266	-	66	38	-
	11	2260	1225	1375	75	88	68
3	15	1920	*	-	85	NS	-
	16	4290	*	-	92	0	-
	17	1940	1790	-	71	86	-
	18	3190	68	*	87	4	2
	19	214	174	1060	96	91	88
4	22	2293	*	-	70	7	-
	24	2965	*	-	86	0	-
	25	3075	1915	*	89	79	0
	26	2080	690	*	90	47	0
5	30	924	720	473	36	82	64
	31	3190	3990	187	73	79	81

† Pretrial data from last collected sperm sample, where available

* Sperm sample obtained but no visible sperm for analysis or insufficient volume for count

- Not a recovery animal

NS no sample for motility assessment

[Excerpted from the Applicant's submission]

General toxicology; additional studies

The main findings in the 13-week GLP toxicology study were reflective of toxicities seen with early non-GLP toxicology assessments with tisotumab vedotin. A noteworthy observation in the 10-week dose range finding study (Study# (b) (4) 521988) involved one animal given the high dose of 6 mg/kg tisotumab vedotin that experienced respiratory symptoms ten days after the first dose described as gasping, wheezing, shallow, and labored breathing that led to early euthanasia the same day. Necropsy revealed discolored spongy lungs with microscopic findings of mild edematous congestion/hemorrhage. In Study# (b) (4) 514850 bleeding time was assessed, the main findings are summarized below.

Study/ID: HuMab-TF (IgG1-1015-011): Pilot Repeat Dose Toxicology Study in Cynomolgus Monkeys ^{(b) (4)} 514850 (non-GLP)

Dosing: In a non-GLP, intra-animal dose escalation study, cynomolgus monkeys (n=2/sex) were given an intravenous infusion over a 30-minute time period (10 mL/kg) of phosphate buffered saline on Day 1 and unconjugated HuMax-TF at 1, 10, and 100 mg/kg on Days 8, 15, and 22, respectively. The animals were observed for an additional 5 days after the last dosing and sacrificed on Day 27. Bleeding time was assessed in the study at 1, 24, and 120 hours post dose. A Simplate Bleeding Time Device was used to make an incision on the muscular area of the forearm, and the flow of blood was evaluated using a filter paper every 30 seconds until blood did not stain the filter paper twice. A TEG analyzer was used to assess the mechanical properties of the developing clot (clot formation, kinetics, strength, stability and resolution).

Results: Bleeding time increased in a dose dependent manner by 13%, 65% and 93% at 1, 10, and 100 mg/kg, respectively, 1 hour after the infusion compared to the saline dosed Day 1 measurement. Statistical significance (p=0.012) was reached at 100 mg/kg. The mean serum concentration at 1, 10, and 100 mg/kg 1-hour post infusion was 23.5, 213, and 2255 µg/mL, respectively. Microscopic findings of up to moderate focal myocardial degeneration (females) with some inflammation and minimal hemorrhage in the heart (one female), perivascular cuffing of the brain (males), dark appearance of the urinary bladder with microscopic findings of hemorrhage (one female) and up to moderate pylorus gastritis in the stomach (one male, females) was noted at the end of the study. The Applicant did not attribute the findings as drug-related but rather as spontaneous background findings in the cynomolgus monkey; however, the study did not include a vehicle dosed control group for comparison.

Additional GLP compliant general toxicology studies with MMAE in rat and monkey were previously reviewed by the FDA under the Applicant's BLA 125388 (brentuximab vedotin). The major findings based on the primary nonclinical review are summarized below for the MMAE dosed animals.

Study/ID: A 4-week intravenous injection toxicity and toxicokinetic study of SGN-35, SGD-1010, and SGN-30 in rats with a 4-week recovery/7646-118

Dosing: Rats were administered 0, 0.0097, 0.097, 0.194 mg/kg SGD-1010 (MMAE, lot# SGD-1010-0-09, 97.35% purity) once weekly via intravenous injection for 4 weeks.

Results: No toxicities were observed at ≤0.097 mg/kg SGD-1010. The following were noted:

- One animal at the mid dose died on Day 26 after blood collection and was evaluated as accidental.
- A -60% decrease in body weight was observed in animals given the high dose during Week 1. Body weight gradually increased and was within the range of control animals by Week 3.
- A decrease in erythropoiesis was reported at the high dose:
 - Decrease in red blood cells (-43%), hemoglobin (-36%), and hematocrit (-38%) was noted. Reticulocytes were decreased at the mid and high dose by -49% and -91%, respectively.

- An overall decrease of $\geq 40\%$ was noted for leukocytes, neutrophil, lymphocytes, monocytes, and eosinophils in animals given the high dose.
- Elevated levels of total bilirubin, AST, ALT, ALP, and GGT were reported in animals given the high dose with microscopic correlates of necrosis in 3/10 males, suggesting liver damage.
- The major target organs were the bone marrow, testes/epididymides, and thymus generally in animals given the high dose.
 - Bone marrow: mild to severe hypocellularity
 - Testes: tubule degeneration and spermatocytes
 - Thymus: mild to severe lymphocyte depletion and mild necrosis, correlating with an overall decrease in thymus weight
 - All findings were reversible except in the testes and epididymides.

Study/ID: Study/ID: An 11-week repeat-dose intravenous infusion toxicity study of SGN-35 and SGD-1010 in cynomolgus monkeys with a five-week recovery period/ (b) (4) 163.16

Dosing: Monkeys were dosed with MMAE at 0.058 mg/kg (MMAE, lot# SGD-1010-0-09, 97.35% purity) once every three weeks via intravenous infusion for four total doses.

Results: No changes in the body weight, blood pressure, heart rate, respiration, body temperature, ophthalmology, electrocardiogram, coagulation and urinalysis. The following changes were observed:

- Decreased red blood cells (-10%), reticulocytes (-85%), white blood cells (-50%), monocytes (-50%), neutrophils (-65%), lymphocytes (-45%) and eosinophils (-85%) was observed at the end of treatment.
- Histopathology findings included:
 - Hypocellularity, hemorrhage, congestion, and necrosis in hematopoietic tissues and lymphoid organs (thymus, spleen)
- All findings were reversible.

The Applicant's Position:

The toxicity profile of tisotumab vedotin was established in a comprehensive series of nonclinical safety studies in cynomolgus monkeys, the only cross-reactive toxicology species.

Target-mediated uptake of tisotumab vedotin led to dose limiting skin toxicity at approximately 4-fold the human systemic exposure (AUC) at the clinically recommended dose. Skin toxicity, in addition to conjunctival changes, correlated with TF expression. Bone marrow hypocellularity and testicular toxicity were the primary target-independent toxicities and were observed with both tisotumab vedotin and MMAE. Additional target organs identified following MMAE treatment included lymphoid organs, gastrointestinal tract, and liver. The target organs of skin, bone marrow and conjunctiva correlated with clinically observed toxicities and were reversible following cessation of treatment. No toxicities were observed with the unconjugated antibody (tisotumab), suggesting no impact from antigen binding alone.

The FDA's Assessment:

The FDA generally agrees with the Applicant's position. Increased prothrombin time (10 to 20%) and ocular observations of glassy appearance of the fundus were observed with unconjugated tisotumab at a dose of 25 mg/kg (approximately 30-fold the exposure at the recommended dose based on AUC). Toxicities observed in the bone marrow, lymphoid organs (thymus, spleen), liver, gastrointestinal and male reproductive organs (tested/epididymides) are similarly seen in other approved ADCs with MMAE as the toxic payload. Skin and ocular toxicities are likely due to TF expression in the epithelial cells.

5.5.2 Genetic Toxicology

Data (presented by the FDA):

The genetic toxicology studies were initially reviewed by the FDA under the Applicant's BLA 125388 (brentuximab vedotin) and summarized below.

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/number: Bacterial Reverse Mutation Assay: SGD-1010/AA66EH.503 (b) (4)

Key Study Findings:

- MMAE, the small molecule cytotoxic agent of tisotumab vedotin, was negative in the bacterial reverse mutation assay under the conditions tested.

GLP compliance: Yes; except the stability of the drug and homogeneity, concentration, and stability of the drug preparations were not determined.

Test system: MMAE was evaluated at 75, 200, 600, 1800 and 5000 µg per plate with *Salmonella typhimurium* TA98, TA100, TA1535, TA1537, and *Escherichia coli* WP2uvrA tester strains in the absence and presence of S9.

Study is valid: Yes

In Vitro Assays in Mammalian Cells

Study title/ number: L5178Y TK+/- Mouse Lymphoma Forward Mutation Assay with a Confirmatory Assay/8204155

Key Study Findings:

- MMAE, the small molecule cytotoxic agent of tisotumab vedotin, was negative in the mouse lymphoma forward mutation assay under the conditions tested.

GLP compliance: Yes; except, the stability and concentration of the dosing preparations were not analyzed.

Test system: Mouse lymphoma L5178Y TK^{+/-} cell line was treated with MMAE, ≤50 ng/mL in the absence of S9 and ≤100 ng/mL in the presence of S9, for 4-hours.

Study is valid: Yes.

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title/number: In Vivo Rat Bone Marrow Micronucleus Assay/8204151

Key Study Findings:

- MMAE, the small molecule cytotoxic agent of tisotumab vedotin, was positive for genotoxicity under the conditions of the assay with an aneugenic mechanism at ≥ 0.1 mg/kg.
- MMAE was cytotoxic to the bone marrow at 0.2 mg/kg.

GLP compliance: Yes

Test system: Sprague Dawley rats were administered a single intravenous injection of MMAE at 0.01, 0.1, and 0.2 mg/kg; bone marrow micronuclei were assessed.

Study is valid: Yes.

The Applicant's Position:

MMAE was positive for genotoxicity in the in vivo rat bone marrow micronucleus study through an aneugenic mechanism. MMAE was not mutagenic in the bacterial reverse mutation (Ames) assay or the L5178 TK[±] mouse lymphoma forward mutation assay.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

5.5.3 Carcinogenicity

The Applicant's Position:

Carcinogenicity studies were not conducted for tisotumab vedotin per ICH S6(R1), ICH S1A, and ICH S9 guidance.

The FDA's Assessment:

The FDA agrees with the Applicant's position; carcinogenicity studies are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer in accordance with ICH S9.

5.5.4 Reproductive and Developmental Toxicology

Data (presented by the FDA):

The Applicant assessed effects on reproductive organs as part of the GLP 13-week repeat-dose toxicology study in the monkey. Dedicated embryo-fetal developmental toxicity studies were not conducted with tisotumab vedotin. However, MMAE (SGD-1010) was evaluated in rats as part of a GLP embryo-fetal developmental and TK study that was initially reviewed by the FDA under BLA 125388 for brentuximab vedotin. Fertility and early embryonic development and pre- and post-natal studies were not needed to support the proposed advanced cancer population in accordance with ICH S9.

Embryo-Fetal Development

Study title/ number: Intravenous Injection Study for Effects on Embryofetal Developmental and Toxicokinetics with SGN-35 and SGD-1010 in Rats/8204397

Key findings in rats given 0.2 mg/kg MMAE:

- No viable fetuses due to post-implantation loss in 1/24 dams.

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- Presence of fetal external and skeletal variations and malformations.
- MMAE transferred across the placenta.

GLP compliance: Yes; the characterization of SGD-1010 was performed by the Applicant under non-GLP conditions.

Methods

Dose and frequency of dosing: 0, 0.2 mg/kg;
On gestational day (GD) 6 and 13

Route of administration: Intravenous (5 mL/kg)

Formulation/Vehicle: SGD-1010 (MMAE) was diluted in 3.9% of 0.01N HCl and 96.1% of 0.9% sodium chloride for injection

Species/Strain: Rat/Sprague-Dawley

Number/Sex/Group: 25 females

Satellite groups: 9 females (toxicokinetics)

Study design: Cesarean section performed on GD 21: gross observations, uterine contents and weights, live/dead fetuses, early/late resorptions, abnormalities, number of corpora lutea. Fetal examinations included: sex, body weights, external abnormalities, visceral and skeletal examinations.

Deviation from study protocol affecting interpretation of results: No

Observations and Results

Parameters	Major findings						
Mortality	All animals survived to their scheduled necropsy except one dam (B57447) who delivered on GD 21 and was sacrificed.						
Clinical Signs	paleness (both ears [5/25] and entire body [1/25]), red/black vaginal discharge (2/25), and red fluid in cage pan (1/25)						
Body Weights	Decrease in body weight compared to control was observed starting GD 8 (-3%) and up to -10% on GD 18; mean maternal body weight gain based on the corrected weight (terminal body weight – gravid uterine weight) decreased by -14% compared to control during GD 4 to 21. Food consumption decreased after the first and second dose by -25% and -17%, respectively; the mean maternal food consumption decreased by -12% compared to control during GD 6 to 21. Mean male fetal weight was -5% lower than those of control; mean female fetal weight was unremarkable.						
Necropsy findings Cesarean Section Data	Summary of Cesarean Section Data <table border="1"> <thead> <tr> <th>Treatments</th> <th>Control</th> <th>SGD-1010</th> </tr> </thead> <tbody> <tr> <td>Dose mg/kg</td> <td>0</td> <td>0.2</td> </tr> </tbody> </table>	Treatments	Control	SGD-1010	Dose mg/kg	0	0.2
Treatments	Control	SGD-1010					
Dose mg/kg	0	0.2					

Version date: March 2021 (ALL NDA/ BLA reviews)

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.

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	Gravid uterine weights (g) (mean)	97.73	74.2
	Females mated (n)	25	25
	Pregnancy rate (%)	100	96
	Delivered early (n)	0	1
	Dams with viable fetuses (n)	25	23
	Corpora lutea (mean)	13.8	14.2
	Implantation sites (mean)	12.8	12.8
	Preimplantation loss (mean%)	6.8	9.3
	Post implantation loss (mean%)	1	27.4
	Resorptions:		
	Early (mean%)	1	22.2
	Late (mean%)	0	5.2
	Live fetuses (mean%)	99	72.6
	Value: outside of the historical control range		
Necropsy findings Offspring	Summary of Fetal Necropsy Findings		
	Treatments	Control	SGD-1010
	Dose mg/kg	0	0.2
	Litters evaluated	25	23
	Fetal External Findings		
	Fetuses evaluated (live)	317	220
	Variations [n (%)]		
	Curly tail*	0 (0)	1 (0.5)
	Malformations [n (%)]		
	Protruding tongue	0 (0)	1 (0.5)
	Malrotated hindlimbs	0 (0)	2 (0.9)
	Gastroschisis	0 (0)	2 (0.9)
	Agnathia	0 (0)	1 (0.5)
	Fetal Skeletal Findings		
	Fetuses evaluated (live*)	161	112
	Variations [n (%)]		
	Less than four metatarsals ossified*	0 (0)	1 (0.9)
	Malformations [n (%)]		
	Malformed mandible	0 (0)	1 (0.9)
	Misaligned, fused and/or absent caudal vertebrae*	0 (0)	1 (0.9)
	Split sternbrae*	0 (0)	1 (0.9)
	Shortened long bone	0 (0)	1 (0.9)
	Value: outside the percent incidence rate seen in the historical control data for the reporting laboratory		
	*no available historical data for this finding		

The C_{max} and AUC_{last} for MMAE in pregnant females was 50.2 ng/mL and 25.6 ng*day/mL, respectively, on gestational day 13, which was approximately 60% higher than the values seen on gestational day 6. The mean clinical C_{max} and AUC_{0-21} for MMAE at the recommended dose

was 5.9 ng/mL and 50 ng*day/mL, respectively; therefore, embryo-fetal toxicity (EFT) was seen at approximately 0.5-fold the exposure at the recommended dose based on AUC. MMAE concentration in amniotic fluid and fetal serum on gestational day 18 was higher than those seen in maternal serum suggesting placental transfer. The maternal serum was below the level of quantitation for all animals; therefore, a quantitative assessment was not available.

Note: Tissue factor is expressed both on the plasma membrane and intracellularly during embryonic development. TF was reported to be expressed in the cardiovascular and central nervous systems, esophagus, respiratory system, stomach, duodenum, pancreas, and liver (Luther et al. 1996). Therefore, tisotumab vedotin is likely to cause EFT from both the TF-directed antibody and the MMAE payload.

The Applicant's Position:

Fertility and Early Embryonic development

Stand-alone fertility and early embryonic studies were not performed with tisotumab vedotin. However, testicular toxicity was observed in the 13-week repeat dose study in monkeys which manifested as reduced or absent sperm motility at exposures approximately 0.6- to 4-fold times the human systemic ADC exposure (AUC) at the clinically recommended dose. There was partial recovery of the testes and epididymis findings at 3 and 5 mg/kg; and full recovery at 1 mg/kg after a 6-week postdose treatment-free period. The testicular toxicity is consistent with the pharmacologic disruption of microtubules caused by MMAE. No adverse effects were evident in the female reproductive system and menstrual cyclicity was not affected by treatment.

Embryofetal Development

Intravenous administration of MMAE to pregnant rats during organogenesis (gestational Days 6 and 13) resulted in malformations and embryo fetal toxicity at a dose of 0.2 mg/kg (approximately 0.5 times the human AUC at the clinically recommended dose). MMAE was transferred across the placenta and present in fetal serum. The embryo-fetal developmental toxicity is consistent with the pharmacologic disruption of microtubules caused by MMAE.

Pre- and Postnatal Development

In accordance with ICH S9, pre- and postnatal development studies were not conducted for tisotumab vedotin as it is intended for treatment of metastatic cervical cancer.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

5.5.5 Other Toxicology Studies

The Applicant's Position:

Phototoxicity:

MMAE, valine-citrulline MMAE (vcMMAE), and N-acetylcysteine (NAC)-vcMMAE had no absorption in the range of 290 to 700 nm and do not present a direct phototoxicity concern.

Species Cross-Reactivity:

Cynomolgus monkeys were considered the relevant nonclinical test species for tisotumab vedotin based on comparable antigen binding affinities to human TF. Tisotumab vedotin did not bind to pig, dog, rabbit or rodent TF.

Tissue Cross-Reactivity:

Positive immunohistochemical staining was observed both on the membrane and in the cytosol of normal human and cynomolgus monkey tissues and was generally consistent with reported sites of TF expression. Staining patterns were generally similar between the tissue panels examined, although overall, staining of fewer tissue elements was present in cynomolgus monkey tissue compared to human.

The FDA’s Assessment:

The FDA agrees with the Applicant’s position.

Data (presented by the FDA):

Study# ^{(b) (4)} 20023264: A Tissue Cross-Reactivity Study of IgG1-1015-011-FITC and IgG1-1015-011-vcMMAE-FITC in Normal Human and Cynomolgus Monkey Tissues (GLP compliant)

Human and cynomolgus monkey TF staining pattern (membrane) using tisotumab was generally similar across a variety of normal tissues.

Membrane Tissue Factor Staining

Staining Frequency	Human and Monkey Tissue	Human Tissue	Monkey Tissue
Frequent (50 to 100% of cells) Epithelium	Eye (cornea, conjunctiva), kidney, lung (alveolar), pituitary (adenohypophysis), thymus (lymphoepithelium and Hassall’s corpuscles), tonsil	uterus (cervix)	Thyroid (duct)
Stroma	*Eye (choroid and in stroma of ciliary muscle), *fallopian tube (submucosal and perivascular areas), lung (perivascular areas), lymph node (capsule and perivascular areas), *pancreas, placenta (chorionic villi and decidual plate), testis (seminiferous tubule)		
Other	eye (retina), heart (cardiomyocyte), kidney (glomerular tuft cells), spinal cord (glial cell)	Cerebellum (arachnoid cap cells), pancreas (islet cells), testis (spermatogenic cells)	Mesothelium in fallopian tube, esophagus, small intestine, lung, pancreas, spleen
Occasional (5 to 50% of cells) Epithelium	Breast, esophagus, *parathyroid, prostate, salivary gland (acini and ducts), skin (squamous epidermis, hair follicle), prostate, ureter, uterus (endometrium)		Ovary (follicular)
Stroma	Adrenal (capsule and trabeculae), cerebellum (meninges and perivascular areas), *cerebrum (meninges in perivascular areas), stomach (epithelial basal lamina), small intestine (epithelial basal lamina), colon (epithelial basal lamina), liver (portal triads), ovary, pituitary (perivascular areas and capsule), prostate, salivary gland (perivascular areas and stroma supporting acini), spinal cord (meninges,		

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	perivascular areas, spinal nerve roots), thyroid, ureter (perivascular areas), uterus (endometrial)		
Other	Stomach (smooth myocytes), lung (alveolar macrophages)	Eye (striated skeletal myocytes), stomach (intrinsic smooth myocytes)	
Rare (1 to 5% of cells)			
Epithelium	Skin (sweat gland)		Thyroid (follicular)
Stroma	Bone marrow, breast (perivascular areas), esophagus, heart (pericardial stroma and perivascular areas), kidney (capsule and perivascular areas), parathyroid (perivascular area), peripheral nerve, skin (perivascular area), spleen (trabeculae and perivascular areas), striated skeletal muscle (perivascular areas), thymus (perivascular areas), tonsil, urinary bladder (submucosal)		
Other	Testis (Leydig cells)	Esophagus (intrinsic smooth myocytes)	

Note: Staining frequency was listed based on the human tissues; *staining frequency in the monkey is lower than in human tissue; *staining frequency in monkey is higher than in human tissue; IgG1-1015-011-FITC (batch# 2438-034-F), IgG1-1015-011-vcMMAE-FITC (batch# 2438-032-F) or non-targeting control ADC B12-FITC and B12-vcMMAE-FITC were applied to cryosections of normal human and cynomolgus monkey tissues (3 donors per tissue) at two concentrations (2 and 0.5 µg/mL). A431 cancer cells were used as a positive control for TF expression and human kidney (vascular smooth myocytes) was used as a negative control.

X

X

Nikolett Biel
Primary Reviewer

Tiffany Ricks
Supervisor

6 Clinical Pharmacology

6.1 Executive Summary

The FDA's Assessment:

Tisotumab vedotin is an antibody drug conjugate (ADC) consisting of a human tissue factor (TF)-specific monoclonal antibody linked to monomethyl auristatin E (MMAE), an anti-microtubule small molecule that induces cell cycle arrest and apoptosis, via a protease-cleavable valine-citrulline (vc) linker. The applicant is seeking accelerated approval of tisotumab vedotin (b) (4)

The proposed dosing regimen of tisotumab vedotin is 2 mg/kg (up to a maximum of 200 mg in patients ≥ 100 kg) as an IV infusion over 30 minutes every 3 weeks (Q3W) until disease progression or unacceptable toxicity.

The clinical pharmacology review focused on the appropriateness of the proposed dosing regimen for the general patient population and dosing recommendations for patients with hepatic impairment (HI).

Dosages ranging from 0.3-2.2 mg/kg Q3W were investigated in the dose escalation study GEN701; 2.0 mg/kg Q3W IV was selected as the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D). The 2 mg/kg Q3W with a dose cap of 200 mg in patients $\geq$ 100 kg dosing regimen was evaluated in the phase 2, single-arm, open label study GCT1015-04 (Study 04). The observed ORR was 23.8% (95% CI: 15.9- 33.3%) with a DoR of 8.3 months (95% CI: 4.2 months, NR). Exposure-safety analyses identified a relationship between tisotumab vedotin exposure at the 2 mg/kg dose level and safety findings including the probability of treatment-related (TR) TEAEs leading to dose modifications, TR Grade $\geq$ 3 AEs, TR SAEs and grade $\geq$ 2 ocular TEAEs. Exposure-efficacy analysis at the 2 mg/kg dose level indicated that over the range of exposures achieved at this dose level, lower exposure was correlated with lower ORR. Despite limited evaluation of the benefit-risk profile of dosages lower than 2 mg/kg, further evaluation of alternative dosing regimens to mitigate the high incidence of ocular toxicities at the proposed dose was not recommended, as lower exposures may lead to lower efficacy, based on exposure-response relationships at the 2 mg/kg dose level. As further lowering of efficacy is undesirable given the currently observed ORR and DoR, and considering the late-line setting, the proposed dose was assessed as acceptable for the proposed recurrent or metastatic cervical cancer indication.

Population PK analysis indicated that patients with mild HI had higher MMAE exposure (37% higher average concentration over a dose interval i.e. Cave) compared to patients with normal function. However, no dose modification is necessary because this increase in MMAE exposure was not associated with a substantial decrease in tolerability of tisotumab vedotin in patients with mild HI. As unconjugated MMAE exposures are expected to increase in moderate and severe hepatic impairment and the proposed dosage of tisotumab vedotin was identified as the MTD, patients with moderate or severe HI should avoid treatment with tisotumab vedotin.

Recommendations

The Office of Clinical Pharmacology recommends the approval of BLA 761208 from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Primary evidence of the effectiveness of tisotumab vedotin in the proposed indication is derived from Study 04. The observed ORR by IRC (primary endpoint) was 23.8% (95% CI: 15.9- 33.3%). BORs included 7 patients (6.9%) with CR and 17 patients (16.8%) with

	PR. The median DOR was 8.3 months (95% CI: 4.2 months, NR) by IRC.
General dosing instructions	The proposed recommended dosing regimen of tisotumab vedotin is 2 mg/kg Q3W (up to 200 mg in patients $\geq$ 100 kg), as a 30 min IV infusion.
Dosing in patient subgroups (intrinsic and extrinsic factors)	• No dose modification is recommended for patients with mild HI (NCI-ODWG criteria). Tisotumab vedotin should be avoided in moderate and severe HI. • No dose modification is recommended for patients with mild to moderate renal impairment ($CL_{cr} \geq 30$ mL/min). There are no data in patients with severe renal impairment ($CL_{cr} < 30$ mL/min). • No tisotumab vedotin dose modification is recommended when used concomitantly with CYP3A inhibitors.
Labeling	The clinical pharmacology review team has specific content and formatting change recommendations for the product labeling. Key modifications to the label made by the FDA include the recommendation to avoid dosing in moderate and severe HI in Section 8.6, and the format and content in Section 12.3.
Bridge between the to-be-marketed and clinical trial formulations	During development, there were no changes to the formulation.

6.2 Summary of Clinical Pharmacology Assessment

6.2.1 Pharmacology and Clinical Pharmacokinetics

Data:

Following tisotumab vedotin IV infusion, peak tisotumab vedotin concentrations were attained at the end of infusion. Plasma concentrations of free MMAE increased until ~2-3 days after tisotumab vedotin dosing. No accumulation of tisotumab vedotin or free MMAE was observed on repeat dosing.

Based on population PK, the typical value of nonspecific linear clearance (CL) of tisotumab vedotin was 1.42 L/day. Following a tisotumab vedotin dose of 2.0 mg/kg, ~ 60% of tisotumab vedotin was eliminated by linear CL. Terminal median half-lives were 4.04 days for tisotumab vedotin and 2.56 days for MMAE, respectively. Following 2.0 mg/kg tisotumab vedotin IV, the typical values for tisotumab vedotin central volume of distribution and peripheral volume of distribution were 3.10 L and 4.47 L, respectively.

A small fraction of MMAE released from tisotumab vedotin is metabolized. In vitro data indicates that 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. 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 (Han 2013), ~72% of which was recovered unchanged in the feces. A similar excretion profile for MMAE is expected after tisotumab vedotin administration.

The Applicant's Position:

Population PK indicated that distribution of tisotumab vedotin was limited to the central vascular compartment, with a median elimination half-life of ~4.04 days and no accumulation upon repeat dosing. MMAE has a mean elimination half-life of ~2.56 days with no accumulation on repeat dosing. MMAE exhibited moderate binding to plasma proteins. MMAE is metabolized predominantly by CYP3A4 and excreted mainly by hepatobiliary routes.

The FDA's Assessment:

FDA agrees with the Applicant's position.

6.2.2 General Dosing and Therapeutic Individualization

6.2.2.1 General Dosing

Data:

The dose escalation part in GEN701 evaluated tisotumab vedotin at doses ranging from 0.3 to 2.6 mg/kg. At the 2.2 mg/kg dose level, 3 subjects experienced 1 dose-limiting toxicity (DLT) each. Because the protocol specified that intermediate dose levels could be evaluated, the DMC recommended to include 3 subjects on 2.0 mg/kg, which was not a preplanned dose level in the protocol. None of the 3 subjects on the 2.0 mg/kg dose level experienced DLTs and, therefore, 2.0 mg/kg was identified as the recommended phase 2 dose (RP2D) for the expansion part.

In the pivotal trial GCT1015-04, in subjects treated with 2.0 mg/kg 1Q3W, the probability of response significantly increased with increase of tisotumab vedotin Cycle 1 C_{max} . The exposure-efficacy relationships explored in the analyses indicate an increase of efficacy with increase in tisotumab vedotin Cycle 1 exposure, however, responses were observed across the entire exposure range. Lower risk of death is associated with increase of tisotumab vedotin exposure. DOR and PFS were not correlated with ADC exposure (full covariate model).

Weight-based dosing at 2.0 mg/kg 1Q3W up to 200 mg for body weight ≥ 100 kg ensured exposure was similar across tertiles of weight for both ADC and MMAE and is therefore an appropriate dosing paradigm for tisotumab vedotin.

Tisotumab vedotin and MMAE exposure and safety endpoint relationships suggest increased exposure was associated with increased incidence of AEs, but that 2.0 mg/kg 1Q3W (up to 200 mg for body weight ≥ 100 kg) was tolerated with a high relative dose intensity of 96% and overall manageable safety profile.

Overall, tisotumab vedotin administered at 2.0 mg/kg 1Q3W (up to 200 mg for body weight ≥ 100 kg), demonstrates robust activity in patients with cervical cancer. This dosing regimen was selected based on the benefit/risk ratio observed in the Phase 1 clinical trial GEN701 where a range of doses was tested. While activity was observed at lower dose levels, 2.0 mg/kg was associated with greater antitumor activity compared to lower doses, with a manageable safety profile.

The Applicant's Position:

The recommended clinical dose of tisotumab vedotin is 2.0 mg/kg administered by IV infusion 1Q3W. Tisotumab vedotin at 2.0 mg/kg 1Q3W had a manageable safety profile and provided clinical benefit to subjects with recurrent or metastatic cervical cancer.

The FDA's Assessment:

FDA agrees that the proposed 2 mg/kg Q3W IV with a cap of 200 mg for patients ≥ 100 kg is acceptable for the general population. However, FDA notes that benefit-risk balance at doses lower than the proposed 2 mg/kg Q3W was not adequately characterized due to limited sample sizes in the lower dose cohorts. In Study GEN701, n=3 patients were evaluated at all dose levels (0.3, 0.6, 0.9, 1.2, 1.5, 1.8 and 2 mg/kg) other than 2.2 mg/kg where n=6 patients were evaluated. Of note, in the dose escalation phase of Study GEN 701, only one patient responded at the 1.2 mg/kg dose level and there were no responders at the proposed 2 mg/kg dose. Despite limited evaluation of the benefit-risk profile of dosages lower than 2 mg/kg, further evaluation of alternative dosing regimens to mitigate the high incidence of ocular toxicities at the proposed dose was not recommended, as lower exposures may lead to lower efficacy based on limited exposure-response relationship assessment at only the 2 mg/kg Q3W dosage. Further lowering of efficacy is undesirable given the currently observed ORR and DoR, and the late-line setting.

6.2.2.2 Therapeutic Individualization

Data:

Tisotumab vedotin has been administered based on subject body weight, with the exception of subjects ≥ 100 kg for which a dose cap (200 mg) is in place.

Impact of intrinsic factors on tisotumab vedotin and MMAE PK was assessed in the population PK model. The final model included body weight, baseline serum albumin, and sex as covariates for tisotumab vedotin PK and age, sex, body weight, cancer type, albumin, estimated glomerular filtration rate (eGFR), Eastern Cooperative Oncology Group (ECOG) status, hepatic impairment and baseline tumor burden as covariates for MMAE PK. The model-predicted cycle 1 average serum concentration (C_{ave}) values were evaluated for these covariates following 2.0 mg/kg tisotumab vedotin (up to 200 mg for body weight ≥ 100 kg). Comparison of exposures indicated no meaningful difference in tisotumab vedotin or MMAE exposures between male and female subjects, or across the age range. Subjects with higher weight had slightly higher tisotumab vedotin and MMAE exposures, with C_{ave} values for ADC ($C_{ave,ADC}$) being 5% higher in

the highest tertile of weight and C_{ave} values for MMAE ($C_{ave,MMAE}$) being 18% higher. The range of effects relative to a reference population was within the observed variability in the modeling dataset for both tisotumab vedotin and free MMAE.

A population PK analysis of the effects of hepatic function on tisotumab vedotin and free MMAE was conducted in subjects with mild hepatic impairment at baseline, as determined by the criteria of the NCI Organ Dysfunction Working Group. Predicted tisotumab vedotin exposure for patients with mild hepatic impairment was similar to patients with normal hepatic function, while MMAE exposures were 37% higher. The range of both tisotumab vedotin and MMAE exposures was similar between the 2 groups. Subjects who had mild hepatic impairment did not appear to have a notably increased incidence of treatment emergent serious adverse events (SAEs), or grade ≥ 3 treatment-emergent adverse events (TEAEs), indicating the increase of MMAE exposure in mild hepatic impairment patients is not clinically meaningful.

A population PK analysis of the effects of renal function on tisotumab vedotin and free MMAE was conducted in subjects with mild and moderate renal impairment based on estimated creatinine clearance (CrCl) at baseline as determined using the Cockcroft-Gault Formula (Cockcroft 1976). Predicted tisotumab vedotin and MMAE exposures for patients with mild and moderate renal impairment were similar to patients with normal renal function. Subjects who had mild or moderate renal impairment did not appear to have a notably increased incidence of treatment emergent SAEs, or grade ≥ 3 TEAEs.

Formal drug-drug interaction (DDI) studies with tisotumab vedotin have not been conducted. In vitro data and clinical drug-drug interaction study data from brentuximab vedotin (Han 2013), an ADC structurally similar to tisotumab vedotin, were used to support the clinical pharmacology evaluations of tisotumab 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 brentuximab vedotin were unchanged by either drug (Han 2013). Concomitant use of strong inhibitors or inducers of CYP3A4 with tisotumab vedotin may result in changes in free MMAE exposure, however the magnitude observed for brentuximab vedotin was not considered clinically meaningful.

The Applicant's Position:

Dose individualization is recommended on the basis of body weight, up to a maximum dose of 200 mg for subjects treated at 2.0 mg/kg with body weight of 100 kg or greater. Population PK modeling demonstrated body weight-based dosing is appropriate as resulting exposures were generally similar across tertiles of weight for both tisotumab vedotin and MMAE.

Dose adjustment is not required based on age or sex. No dose adjustment is required in patients with mild hepatic impairment. Tisotumab vedotin has not been evaluated in patients with moderate or severe hepatic impairment. No dose adjustment is required in patients with mild or moderate renal impairment. Tisotumab vedotin has not been studied in patients with severe renal impairment. No dose adjustment is required with concomitant administration of

tisotumab vedotin with strong inhibitors/inducers of CYP3A4. Closely monitor for adverse reactions when tisotumab vedotin is given concomitantly with strong CYP3A4 inhibitors. The safety and effectiveness of tisotumab vedotin in pediatric patients has not been established.

The FDA's Assessment:

FDA agrees with the Applicant's position. FDA recommends that tisotumab vedotin be avoided in patients with moderate and severe HI. This is because unconjugated MMAE exposures are expected to increase in moderate and severe hepatic impairment and the proposed dosage of tisotumab vedotin was identified as the MTD. Evaluation of lower doses in patients with moderate and severe HI was not recommended, as lowering the dose of tisotumab vedotin to match the exposure of MMAE may lead to lower ADC concentrations which could lead to lower efficacy (based on known exposure-response relationships of the ADC with efficacy).

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 tisotumab vedotin has been studied in subjects with solid tumors who received tisotumab vedotin by IV infusion 1Q3W. Levels of ADC, TAb, and free MMAE were measured using validated methods to evaluate PK parameters. The general pharmacology and PK characteristics are summarized in [Table 3](#).

Table 3: General pharmacology and PK characteristics of tisotumab vedotin

2a. General Information	
Proposed indication	Recurrent or metastatic cervical cancer that progressed on or after chemotherapy
Route and formulation type and formulation strengths	IV infusion Formulation Strengths: 40 mg/vial
Planned dose	2.0 mg/kg (up to 200 mg for body weight $\geq$ 100 kg) 1Q3W
Mechanism of action	MMAE-mediated disruption of microtubules and bystander cytotoxicity in neighboring tumor cells
2b. Dose and Adverse Events	

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Therapeutic dose and exposure	The proposed clinical dosing regimen of tisotumab vedotin is 2.0 mg/kg (up to 200 mg for body weight $\geq$ 100 kg) administered on day 1 of each 3-week (21 day) treatment cycle. Based on population PK analysis the predicted mean (STD) first cycle exposures are: ADC: C_{max} : 40.8 (8.12) $\mu\text{g/mL}$; AUC_{d0-21} : 57.5 (13.4) $\text{day} \cdot \mu\text{g/mL}$ MMAE: C_{max} : 5.91 (4.2) ng/mL ; AUC_{d0-21} : 50 (35.8) $\text{day} \cdot \text{ng/mL}$	
Maximum tolerated dose	2.0 mg/kg 1Q3W	
Principal adverse events	The most common TEAEs in subjects with cervical cancer were epistaxis, nausea, fatigue, and alopecia.	
2c. PK Features		
Maximum dose tested	Single Dose	2.2 mg/kg 1Q3W
	Multiple Dose	2.2 mg/kg 1Q3W until disease progression or unacceptable toxicity
Exposures Achieved at Maximum Tested Dose	First Cycle	ADC: Geometric Mean (%CV) at 2.2 mg/kg 1Q3W (n=6) C_{max} : 55.5 (10.31%) $\mu\text{g/mL}$; AUC_{0-t} : 84.9 (33.7%) $\text{day} \cdot \mu\text{g/mL}$ MMAE: Geometric Mean (%CV) at 2.2 mg/kg 1Q3W (n=6) C_{max} : 4.88 (31.4%) ng/mL ; AUC_{0-t} : 26.5 (59.4%)
Range of linear PK	Following the first dose of tisotumab vedotin, tisotumab vedotin C_{max} increased in an approximately dose proportional manner, while AUC_{0-t} and $\text{AUC}_{0-\infty}$ increased in a more than dose-proportional manner, across a 0.3–2.2 mg/kg dose range.	
Accumulation at steady-state	Based on Population PK analysis there was no accumulation of ADC or MMAE following 2.0 mg/kg 1Q3W dosing.	
Metabolites	Tisotumab vedotin is an ADC composed of a human tissue factor specific human monoclonal IgG1 antibody, conjugated to the microtubule-disrupting agent MMAE via a protease-cleavable vc maleimidocaproyl linker. • Clearance of the IgG1 antibody is believed to be similar to endogenous IgG1, ie, catabolism to small peptides and individual amino acids. • The metabolism of MMAE has been studied in vitro following incubation with human liver microsomes. Five key metabolic pathways were identified: N-demethylation (CYP3A4), O-demethylation (CYP3A4), dehydrogenation (CYP3A4), amide hydrolysis, and oxidation. Qualitative analysis confirmed the presence of several MMAE metabolites in clinical samples from patients who received brentuximab vedotin.	
Absorption	Absolute/Relative Bioavailability	Not applicable.
	T_{max}	Median (range) at 2.0 mg/kg based on population PK analysis: MMAE: 2.62 days (0.146- 3.71)
Distribution	V_d/F or V_d	Based on population PK analysis, the typical value of central volume of distribution of tisotumab vedotin was estimated to be 3.10 L, and the typical value of peripheral volume of distribution was estimated to be 4.47 L.
	% bound	In vitro, the binding of MMAE to human plasma proteins ranged from 68% to 82%.

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Elimination	Route	Tisotumab vedotin and its unconjugated antibody are eliminated from the systemic circulation by cellular uptake processes, while the elimination of unconjugated MMAE occurs primarily by hepatic and to a lesser extent by renal mechanisms of clearance. Nonclinical studies in rat showed unchanged MMAE was excreted primarily in feces after MMAE administration.
	t_½	Median (range) at 2.0 mg/kg based on population PK analysis: ADC: 4.04 (2.26 - 7.25) days
	CL/F or CL	Based on population PK analysis, the typical value of nonspecific linear clearance of tisotumab vedotin in subjects was estimated to be 1.42 L/day. Following a 2.0 mg/kg dose, about 60% of the ADC was estimated to be eliminated by linear CL.
Intrinsic Factors	Age	Not clinically significant
	Sex	Not clinically significant
	Race	Could not be assessed
	Hepatic and Renal Impairment	- Based on population PK analysis, no differences in ADC or MMAE exposures have been observed between patients with mild or moderate renal impairment and patients with normal renal function. - The effect of severe renal impairment on the PK of tisotumab vedotin is unknown. - Based on population PK analysis, no differences in ADC exposures were observed between patients with mild hepatic impairment and patients with normal hepatic function. Free MMAE exposures were 37% higher in subjects with mild hepatic impairment compared to subjects with normal hepatic function. - The effect of moderate and severe hepatic impairment on the PK of tisotumab vedotin is unknown.
Extrinsic Factors	Drug interactions	Drug interaction assessments have not been conducted with tisotumab vedotin. In clinical drug-drug interaction studies with brentuximab vedotin, concomitant administration of ketoconazole with brentuximab vedotin led to a 34% increase in free MMAE AUC exposure, while concomitant administration of rifampicin was associated with a 46% decrease in free MMAE AUC exposure. The pharmacokinetics of midazolam were not affected by concomitant administration with brentuximab vedotin.
	Meal Effects	Not applicable
Population PK Analyses	The final population PK model included body weight, baseline serum albumin, and sex as covariates for tisotumab vedotin PK and age, sex, body weight, cancer type, albumin, eGFR, ECOG, hepatic impairment and baseline tumor burden as covariates for MMAE PK.	

2d. Pharmacodynamic Features

Tisotumab vedotin at 2.0 mg/kg (1Q3W) did not appear to have adverse effects on ventricular repolarization and did not result in a clinically meaningful prolongation of the QTc interval.

As with all therapeutic proteins, there is potential for an immune response to tisotumab vedotin. In GCT1015-04, a total of 93 patients were tested for immunogenicity to tisotumab vedotin; 5 patients (5%) developed treatment-emergent anti-tisotumab vedotin antibodies. Neutralizing anti-tisotumab vedotin antibodies were detected in 2 patients. Across clinical trials, 4.3% (13/305) of patients developed treatment-emergent anti-tisotumab vedotin antibodies. The presence of anti-tisotumab vedotin antibodies had no clinically meaningful effect on the pharmacokinetics of tisotumab vedotin.

The Applicant's Position:

Based on population PK analysis, the terminal half-lives of tisotumab vedotin and free MMAE were 4.04 days and 2.56 days, respectively. The incidence of antidrug antibodies (ADA) in GCT1015-04 was low with no apparent effect on tisotumab vedotin PK.

No dedicated clinical drug-drug interaction studies with tisotumab vedotin in humans were conducted. However, a clinical drug-drug interaction study was conducted with another ADC that contains MMAE, and similar effects would be expected for tisotumab vedotin. Based on clinical data of brentuximab vedotin, concomitant use of strong inhibitors of CYP3A4 with tisotumab vedotin may result in an increase in free MMAE exposure. Monitoring for adverse reactions is recommended when tisotumab vedotin is given concomitantly with strong CYP3A4 inhibitors.

The FDA's Assessment:

FDA agrees with the Applicant's assessment provided in the data section above. Additional relevant information that is not included in the Applicant's assessment or where the FDA's assessment differs from the Applicant's, is summarized below in Table 4 .

Table 4 General Pharmacology and Pharmacokinetic Characteristics

Chemical structure and molecular weight	Tisotumab vedotin is an ADC consisting of a TF-specific human IgG1-κ monoclonal antibody bound to the microtubule-disrupting agent cytotoxic drug MMAE, via a protease-cleavable valine-citrulline (vc) linker. The average drug-to-antibody ratio is approximately 4. The molecular weight of tisotumab vedotin is approximately 153 kDa.
QT/QTc prolongation	Based on the FDA QT IRT's analysis, tisotumab vedotin treatment at 2 mg/kg Q3W IV does not cause large mean increases (>20 msec) in the QTc interval (Source: FDA QT IRT review).
Bioanalytical assay	ADC (tisotumab vedotin), total antibody and unconjugated MMAE concentrations were measured in Studies GEN701, GEN702, 04 and SGNTV-001. ELISA assays were used to measure tisotumab vedotin concentrations, which utilized TFECdHis as a capture reagent and an anti-MMAE antibody for detection. ELISA assays were used to measure total antibody concentrations, which utilized TFECdHis as a capture reagent and an anti-hIgG1 antibody for detection. Plasma unconjugated MMAE concentrations were measured using liquid chromatography with tandem mass spectrometry (LC-MS/MS). Please refer to section 19.4.1 for further information.
Dose proportionality	Tisotumab vedotin undergoes both linear and non-linear elimination. Following the first dose of tisotumab vedotin, ADC C _{max} increased in a dose-proportional manner while AUC _{0-t} increased in a more than dose-proportional manner over the 0.3–2.2 mg/kg dose range.

	Power analysis for ADC dose proportionality: Study GEN701 <table border="1"> <thead> <tr> <th>Parameter</th> <th>N</th> <th>Slope</th> <th>90% CI</th> </tr> </thead> <tbody> <tr> <td>C_{max} (µg/mL)</td> <td>27</td> <td>1.1</td> <td>(0.96,1.25)</td> </tr> <tr> <td>AUC_{0-t}(day*µg/mL)</td> <td>27</td> <td>1.6</td> <td>(1.37,1.79)</td> </tr> </tbody> </table> Source: 2.7.2 Summary of Clinical Pharmacology Studies, Table 4 Following the first dose of tisotumab vedotin, C_{max} and AUC_{0-t} of the total antibody increased in a more than dose-proportional manner over the 0.3–2.2 mg/kg dose range. Power analysis for total antibody dose proportionality: Study GEN701 <table border="1"> <thead> <tr> <th>Parameter</th> <th>N</th> <th>Slope</th> <th>90% CI</th> </tr> </thead> <tbody> <tr> <td>C_{max} (µg/mL)</td> <td>27</td> <td>1.1</td> <td>(1.01, 1.26)</td> </tr> <tr> <td>AUC_{0-t} (day*µg/mL)</td> <td>27</td> <td>1.7</td> <td>(1.51, 1.98)</td> </tr> </tbody> </table> Source: 2.7.2 Summary of Clinical Pharmacology Studies, Table 6 Following the first dose of tisotumab vedotin, MMAE C_{max} and AUC_{0-t} increased in a dose-proportional manner over the 0.3–2.2 mg/kg dose range, though the 90%CI for AUC_{0-t} was wide. Power analysis for MMAE dose proportionality: Study GEN701 <table border="1"> <thead> <tr> <th>Parameter</th> <th>N</th> <th>Slope</th> <th>90% CI</th> </tr> </thead> <tbody> <tr> <td>C_{max}(ng/mL)</td> <td>27</td> <td>0.9</td> <td>(0.66,1.18)</td> </tr> <tr> <td>AUC_{0-t}(day*ng/mL)</td> <td>27</td> <td>0.9</td> <td>(0.40,1.31)</td> </tr> </tbody> </table> Source: 2.7.2 Summary of Clinical Pharmacology Studies, Table 8	Parameter	N	Slope	90% CI	C _{max} (µg/mL)	27	1.1	(0.96,1.25)	AUC _{0-t} (day*µg/mL)	27	1.6	(1.37,1.79)	Parameter	N	Slope	90% CI	C _{max} (µg/mL)	27	1.1	(1.01, 1.26)	AUC _{0-t} (day*µg/mL)	27	1.7	(1.51, 1.98)	Parameter	N	Slope	90% CI	C _{max} (ng/mL)	27	0.9	(0.66,1.18)	AUC _{0-t} (day*ng/mL)	27	0.9	(0.40,1.31)
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AUC _{0-t} (day*ng/mL)	27	0.9	(0.40,1.31)																																		
Immunogenicity	Please see OBP review regarding the bioanalytical performance of the ADA and neutralizing antibody assays. In Study 04, 93 patients with cervical cancer treated at the proposed dosage had immunogenicity assessment at baseline and at least one time point post-dose. Five of 93 (5.4%) patients developed treatment-emergent ADA against tisotumab vedotin. Of these 5 patients, 2 patients first tested positive for treatment-emergent ADA at C4, 1 patient first tested positive at C7 and 2 patients first tested positive at the treatment discontinuation visit. Two of these 5 patients in Study 04, tested positive for neutralizing antibodies against tisotumab vedotin.																																				

	Across studies, 145 patients with cervical cancer treated at the proposed dosage in Studies GEN701, GEN702, 04 had immunogenicity assessment at baseline and at least one time point post-dose. Eight of 145 patients (5.5%) developed treatment-emergent ADA against tisotumab vedotin. Due the limited number of patients who were positive for ADA during treatment with tisotumab vedotin, the impact of ADA on the PK, safety and efficacy of tisotumab vedotin is not fully characterized.
Drug interaction liability	In vitro: • MMAE is a substrate of CYP3A4 and P-gp • MMAE does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6, but is an inhibitor of CYP3A • MMAE does not induce CYP450 enzymes • MMAE does not inhibit P-gp at clinically relevant concentrations No clinical drug-drug interaction studies have been conducted with tisotumab vedotin. Findings in clinical DDI studies with another MMAE-containing ADC, brentuximab vedotin, are expected to be relevant to tisotumab vedotin. In clinical drug-drug interaction studies, concomitant administration of a strong CYP3A inhibitor ketoconazole with brentuximab vedotin increased unconjugated MMAE Cmax by 25% and AUC by 34%, with no change in ADC exposure. Concomitant administration of a strong CYP3A4 inducer rifampicin with brentuximab vedotin decreased unconjugated MMAE Cmax by 44% and AUC by 46%, with no change in ADC exposure. The pharmacokinetics of a sensitive CYP3A substrate midazolam were not affected by concomitant administration with brentuximab vedotin.

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 tisotumab vedotin effectiveness in patients with recurrent or metastatic cervical cancer.

Data:

To support the clinical efficacy observed with tisotumab vedotin dosed at 2.0 mg/kg 1Q3W, exposure-efficacy response was evaluated in Study GCT1015-04 for the primary endpoint of ORR and secondary endpoints of PFS, OS, and DOR (m2.7.2, Section 3.6.4.2).

Logistic regression analysis determined a positive relationship between tisotumab vedotin Cycle 1 C_{max} and ORR. Tisotumab vedotin Cycle 1 AUC was also a predictor of ORR in the base model but not significant in the full covariate model. There was a relationship of increased probability of response with an increase in tisotumab vedotin C_{max} , but responses were observed across the exposure tertiles. In the lowest exposure tertile, an ORR of 14.7% was observed, indicating that even patients within the lowest tertile of exposure have the potential to derive benefit from tisotumab vedotin (Report No. SR1015-249). DOR and PFS were not correlated with ADC exposure in the full covariate model. The relationships between tisotumab vedotin exposure and efficacy endpoints suggest that treatment with 2.0 mg/kg tisotumab vedotin was associated with clinically meaningful efficacy across the entire range of tisotumab vedotin concentrations in recurrent or metastatic cervical cancer (m2.7.2, Section 3.6.4.4).

The Applicant's Position:

The relationships between tisotumab vedotin exposure and efficacy endpoints show that treatment with 2.0 mg/kg tisotumab vedotin 1Q3W was associated with clinically meaningful efficacy across the entire range of concentrations in subjects with recurrent or metastatic cervical cancer who have progressed on or after chemotherapy.

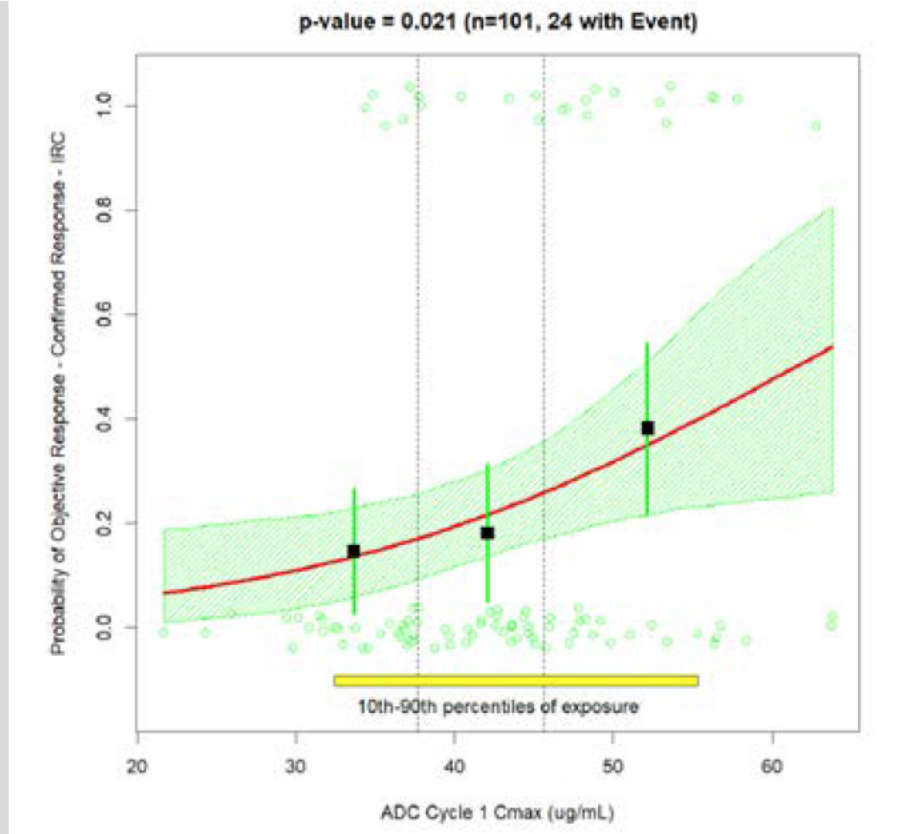
The FDA's Assessment:

The FDA agrees that the clinical pharmacology program provides evidence of efficacy at the 2 mg/kg Q3W IV dosage in the proposed indication.

The Applicant's exposure-response analyses support the proposed dose. Exposure-safety analysis included the data from 272 subjects administered tisotumab vedotin 2.0 mg/kg Q3W IV in studies GEN701 (expansion cohort), GEN702 (expansion cohort), and GCT1015-04. Exposure-efficacy analysis included the data from 101 subjects from Study GCT1015-04. As the population PK analysis showed that there was no appreciable accumulation of ADC and MMAE with repeated dosing, Cycle 1 exposure measures were used for all exposure-response analyses. The exposure-response analyses indicate relationships with both safety and efficacy at the range of exposures achieved after the first cycle of treatment at the 2 mg/kg Q3W IV dosage (please refer to the pharmacometrics review in section 19.4.2 for a detailed analysis).

Exposure-efficacy analyses indicated that the probability of achieving an objective response increased with increasing ADC exposure Figure 1.

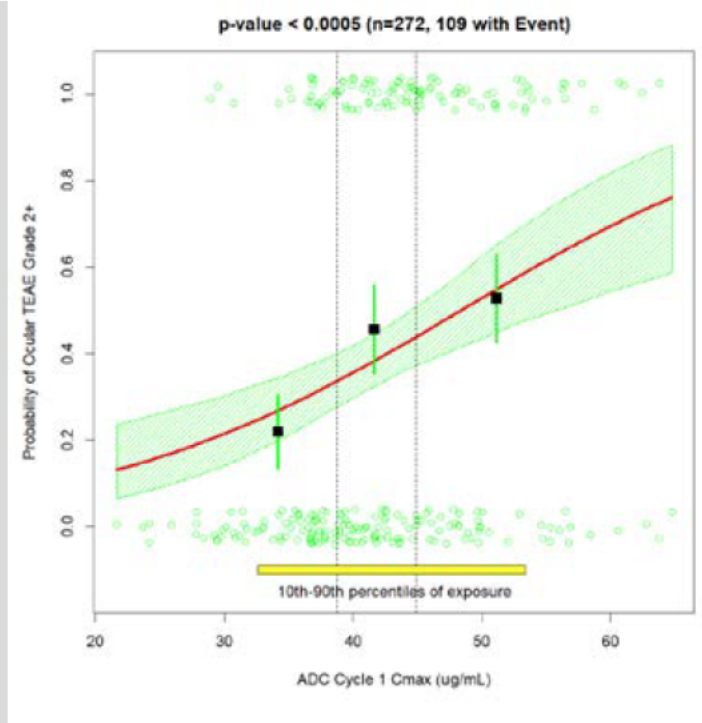
Figure 1: ADC exposure-response analysis for ORR at 2mg/kg



Source: Applicant's exposure-response analysis

Exposure-safety analyses indicated that increasing tisotumab vedotin exposure at the proposed dosage led to increased probability of treatment-related (TR) TEAEs leading to dose modifications, TR Grade ≥ 3 AEs, TR SAEs and grade ≥ 2 ocular TEAEs Figure 2.

Figure 2: ADC exposure-response analysis for Grade ≥ 2 ocular toxicity at 2mg/kg



Source: Applicant's exposure-response analysis

Overall, while interpretation of the exposure-response relationships is limited by the fact that these analyses are limited to exposures at a single dose level, these findings suggest that lower doses might be less toxic but also less efficacious.

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

Yes, tisotumab vedotin administered by IV infusion at 2.0 mg/kg, up to a maximum dose of 200 mg 1Q3W is appropriate for patients with recurrent or metastatic cervical cancer. The proposed dosing regimen is supported by the observed efficacy, safety, and PK data.

Data:

During dose escalation in the Phase 1 trial GEN701, the highest dose evaluated was 2.2 mg/kg 1Q3W, but due to 3 DLTs (diabetes mellitus type II, mucositis and neutropenic fever, all grade 3) reported in 3 subjects, the dose was reduced to 2.0 mg/kg 1Q3W, which was defined as the maximum tolerated dose and RP2D. Tisotumab vedotin doses were administered based on subject body weight, except for subjects >100 kg.

Logistic regression analysis, performed as part of the efficacy-response analysis, determined a positive relationship between tisotumab vedotin Cycle 1 Cmax and ORR (Report No. SR1015-249). Although there was a relationship of increased probability of response with an increase in tisotumab vedotin C_{max}, responses were observed across the exposure tertiles. In the lowest

exposure tertile, an ORR of 14.7% was observed, indicating that even patients within the lowest tertile of exposure have the potential to derive benefit from tisotumab vedotin. The risk of death significantly decreased with increase of tisotumab vedotin Cycle 1 AUC and Cycle 1 C_{max} exposure. However, DOR and PFS were not correlated with tisotumab vedotin exposure in the full covariate model.

Tisotumab vedotin exposure and safety relationships were evaluated in a safety population comprising subjects treated at the 2.0 mg/kg dose. Logistic regression analyses suggested that tisotumab vedotin exposure (cycle 1 AUC and C_{max}) was a predictor of the probability of treatment-related TEAEs leading to dose interruptions; tisotumab vedotin Cycle 1 AUC was a predictor of treatment-related TEAEs leading to dose reductions; tisotumab vedotin Cycle 1 AUC, Cycle 1 C_{max} and $C_{aveLast}$ were predictors of treatment-related TEAEs leading to dose discontinuations. Tisotumab vedotin Cycle 1 C_{max} was a predictor of the probability of treatment-related grade 3 or higher AEs. Tisotumab vedotin Cycle 1 AUC, Cycle 1 C_{max} and $C_{aveLast}$ were predictors of the probability of grade 2 and higher ocular AEs. In a sub-analysis of the GCT1015-04 trial, where a comprehensive OMP was used, tisotumab vedotin exposure (Cycle 1 AUC, Cycle 1 C_{max} , and $C_{aveLast}$) were predictors of the probability of grade 2 and higher ocular AEs. Logistic regression analyses suggested that MMAE Cycle 1 AUC was a predictor of the probability of treatment-related SAEs and all SAEs. Logistic regression analyses suggested that neither tisotumab vedotin or MMAE exposures were predictors of the probability of grade 2 or higher bleeding AEs or grade 2 or higher peripheral neuropathy. Although logistic regression analyses revealed relationships between tisotumab vedotin and MMAE exposures and reported safety outcomes, treatment with 2.0 mg/kg tisotumab vedotin was associated with a manageable safety profile across the entire range of concentrations in subjects with solid tumors.

The Applicant's Position:

Tisotumab vedotin administered by IV infusion at 2.0 mg/kg, up to a maximum dose of 200 mg 1Q3W demonstrates a favorable benefit-risk profile for patients with recurrent or metastatic cervical cancer.

The FDA's Assessment:

In general, the FDA agrees that the proposed dosing regimen of 2.0 mg/kg Q3W IV, up to a maximum dose of 200 mg in patients ≥ 100 kg, is acceptable for the general patient population in the recurrent or metastatic cervical cancer indication. The proposed dosing regimen is supported by efficacy data in the pivotal Study 04, and the exposure-response relationships of tisotumab vedotin with safety and efficacy at this dosage.

Selection of the proposed tisotumab vedotin dosage was based on findings in the phase 1/2 clinical trial, Study GEN701. Dosing regimens ranging from 0.3 to 2.2 mg/kg Q3W IV (0.3, 0.6, 0.9, 1.2, 1.5, 1.8, 2.0 and 2.2 mg/kg; n=3 in all cohorts except 2.2 mg/kg where n=6) were evaluated in patients with advanced or metastatic solid tumors, using a 3+3 design in the phase 1 dose escalation portion of Study GEN701. As 50% of the patients at the 2.2 mg/kg dose level

experienced DLTs, 3 patients were treated at the 2.0 mg/kg dose level. As no patients experienced DLTs at this dose level, the 2.0 mg/kg Q3W IV dosage was identified as the MTD and the RP2D for further evaluation in the dose expansion phase 2. Of note, only 1 confirmed PR was observed in the dose escalation phase, at the 1.2 mg/kg dose level. In the dose expansion phase of Study GEN701, 168 patients with solid tumors were treated at the 2 mg/kg Q3W IV dosage, including 55 patients with cervical cancer. An ORR of 22% (95% CI: 11.5-36%) was observed in a subset of 50 cervical cancer patients in the dose expansion phase who had received 1 or more prior lines of systemic therapy for recurrent or metastatic cervical cancer. The FDA notes that dose-response analyses with both safety and efficacy are limited by the small number of patients treated at dosages <2 mg/kg Q3W IV. Therefore, there are limited clinical safety and efficacy data at other dose levels to conclude that the benefit-risk balance at the proposed 2 mg/kg Q3W IV dosing regimen is optimal.

Primary evidence of clinical benefit in the proposed indication at the dosage of 2.0 mg/kg Q3W IV, up to a maximum dose of 200 mg in patients ≥ 100 kg, is derived from in Study 04 in 101 patients with cervical cancer. In Study 04, the observed ORR by IRC (primary endpoint) was 23.8% (95% CI: 15.9- 33.3 with a median DOR was 8.3 months (95% CI: 4.2 months, NR) by IRC. While a relatively high incidence of Grade ≥ 3 TEAEs (60.4%) and all Grade ocular toxicities (54.5%) was observed at the proposed dosage in Study 04, the mean ($\pm$ SD) relative dose intensity remained high at 91 ($\pm$ 13) %. In addition, the median time to first dose modification due to a TEAE was 3.1 months. This is of relevance as the median time to response in Study 04 was 1.4 months (range, 1.1 to 5.1 months) and the majority of responders (19/24 patients with CR or PR), had responses early i.e. at the first post-baseline scan, within the first two months of treatment. In addition, the majority of dose discontinuations were due to progressive disease, with 13/101 (12.9%) of patients requiring dose discontinuation due to TEAEs.

Additionally, as stated in section 6.3.2.1, the Applicant's exposure-response analyses support the proposed dose. Exposure-efficacy analyses indicated that the probability of achieving an objective response increased with increasing ADC exposure Exposure-safety analyses indicated that increasing tisotumab vedotin exposure at the proposed dosage led to increased probability of treatment-related (TR) TEAEs leading to dose modifications, TR Grade ≥ 3 AEs, TR SAEs and grade ≥ 2 ocular TEAEs.

Overall, the current exposure-response analyses suggest that lower doses might be less toxic but also less efficacious. As part of the review, FDA also considered whether alternative dosing approaches such as fractionated dosing or a pre-specified dose reduction after the initial cycles might help mitigate the high incidence of ocular toxicities observed at the proposed dosage. FDA concluded that evaluating lower doses or alternative regimens may have utility to lower toxicities but may also potentially further lower the efficacy of tisotumab vedotin which, given the current ORR and DoR, was assessed as unacceptable. Overall, given the considerations above, the proposed patient population i.e. patients with metastatic or

recurrent cervical cancer after 1 or 2 prior systemic treatment regimens for their recurrent or metastatic disease, and the limitations of available alternative therapeutic options in this setting, the benefit-risk balance at the proposed dose level in this indication was assessed as acceptable.

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

No, tisotumab vedotin administered by IV infusion at 2.0 mg/kg, up to a maximum dose of 200 mg 1Q3W is appropriate for subpopulations based on intrinsic patient factors.

Data:

The effects of intrinsic factors on tisotumab vedotin and MMAE PK were assessed in the population PK model. The model identified body weight, baseline serum albumin, and sex as covariates for tisotumab vedotin PK and age, sex, body weight, cancer type, albumin, eGFR, ECOG, hepatic impairment and baseline tumor burden as covariates for MMAE PK. The model-predicted cycle 1 C_{ave} values were evaluated for these covariates following 2.0 mg/kg tisotumab vedotin (up to 200 mg for body weight ≥ 100 kg). Comparison of exposures indicated no meaningful difference in ADC or MMAE exposures between male and female subjects, or across the age range. Subjects with higher weight had slightly higher tisotumab vedotin and MMAE exposures, with $C_{ave,ADC}$ being 5% higher in the highest tertile of weight and $C_{ave,MMAE}$ being 18% higher. The range of effects relative to a reference population was within the observed variability in the modeling dataset for both tisotumab vedotin and free MMAE.

A population PK analysis of the effects of hepatic function on tisotumab vedotin and free MMAE was conducted in subjects with mild hepatic impairment at baseline, as determined by the criteria of the NCI Organ Dysfunction Working Group. Predicted tisotumab vedotin exposure for patients with mild hepatic impairment was similar to patients with normal hepatic function, while MMAE exposures were 37% higher. The range of both tisotumab vedotin and MMAE exposures was similar between the 2 groups. Subjects who had mild hepatic impairment did not appear to have a notably increased incidence of treatment emergent SAEs, or grade ≥ 3 TEAEs, relative to those with normal hepatic function, indicating the increase of MMAE exposure in mild hepatic impairment patients is not clinically meaningful.

A population PK analysis of the effects of renal function on tisotumab vedotin and free MMAE was conducted in subjects with mild and moderate renal impairment based on estimated CrCl at baseline as determined using the Cockcroft-Gault Formula (Cockcroft 1976). Predicted tisotumab vedotin and MMAE exposures for patients with mild and moderate renal impairment were similar to patients with normal renal function. Subjects who had mild or moderate renal impairment did not appear to have a notably increased incidence of treatment emergent SAEs, or grade ≥ 3 TEAEs, relative to subjects with normal renal function.

The Applicant's Position:

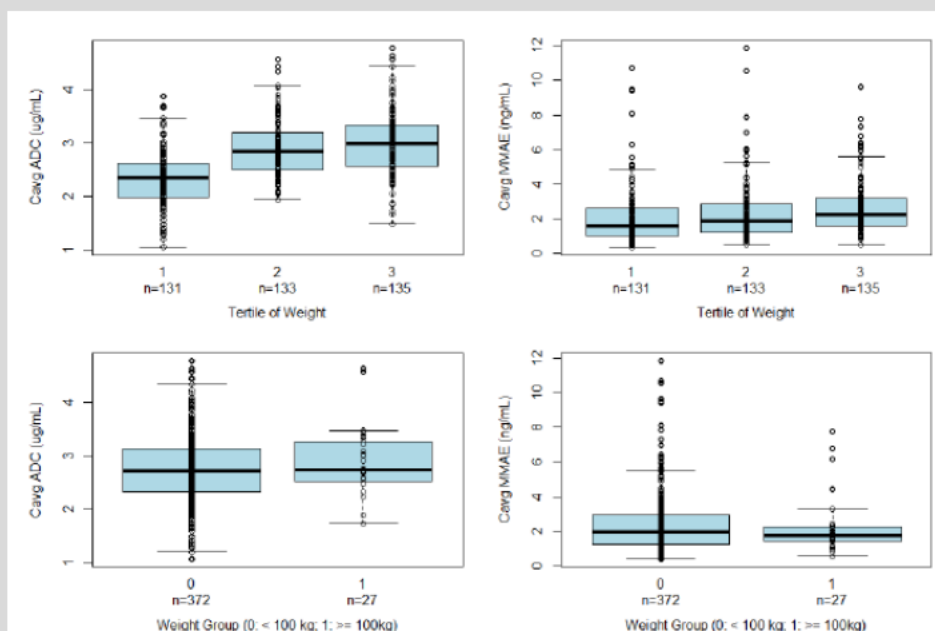
Tisotumab vedotin dose adjustment is not required for subjects with mild or moderate renal impairment. Tisotumab vedotin has not been evaluated in subjects with severe renal

impairment. Dose adjustment is also not required for subjects with mild hepatic impairment. Tisotumab 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 or sex.

The FDA's Assessment:

FDA agrees there is no clinically meaningful effect of age (21 to 81 years), sex, race (White vs Non-White) or ethnicity (Hispanic vs Non-Hispanic) on tisotumab vedotin or unconjugated MMAE exposure. Population PK analysis identified body weight to be a statistically significant covariate on clearance and volume of the distribution of tisotumab vedotin, which supports the bodyweight-based dosing regimen. ADC and MMAE C_{ave} were similar in patients with body weight < 100 kg and ≥ 100 kg (Figure 3), supporting the dose cap of 200 mg for patients ≥ 100 kg.

Figure 3: Model-predicted ADC and MMAE exposures Cycle 1 versus tertiles of weight and in patients < 100 kg vs ≥ 100 kg (2 mg/kg Q3W with 200 mg Cap)



Source: Applicant's PopPK report, Figure 110

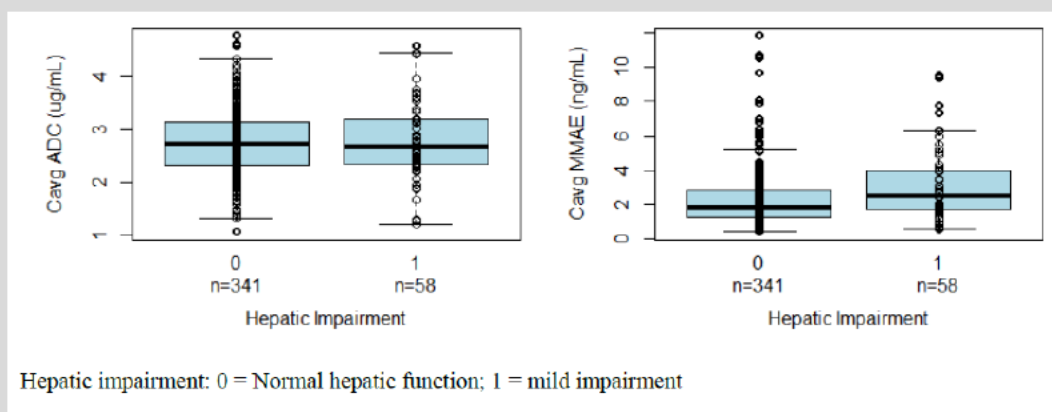
Based on exploratory analyses with observed PK data in Study 04, baseline tumor H-score (n=80) did not appear to impact tisotumab vedotin concentration at the end of infusion or MMAE C_{trough} after the first dose. Circulating tissue factor (cTF) was not included in the population PK model, but exploratory analyses based on the available matched PK and cTF data from subjects (N= 283) in studies GEN701, GEN702 and GCT1015-04, indicated that cTF did not impact tisotumab vedotin clearance or central volume of distribution. In addition, based on the

observed concentrations of cTF, the highest cTF molar concentration was much lower (~ 222-fold) than the predicted lower range of the ADC molar Cave concentration. Given the markedly higher concentrations of ADC to relative cTF, minimal impact to clearance might be expected.

Hepatic impairment:

No dose modification is recommended in patients with mild hepatic impairment. No formal clinical trial has been conducted to assess the effect of hepatic function on the PK of tisotumab vedotin. The effect of mild hepatic impairment on tisotumab vedotin and free MMAE exposure was assessed using the population PK model. The population PK analysis included patients with mild (n=58) hepatic impairment, in addition to patients with normal (n=341) hepatic function. Hepatic impairment status was identified as a covariate for MMAE clearance in the Applicant's population PK model. Model-predicted Cycle 1 ADC exposure in patients with mild hepatic impairment was similar to patients with normal hepatic function, while MMAE exposures were 37% higher in patients with mild hepatic impairment (Figure 4).

Figure 4: Model-predicted ADC and MMAE Cycle 1 exposures (2.0 mg/kg Q3W with 200 mg cap) in mild hepatic impairment vs normal hepatic function



Source: Applicant's PopPK Report SR1015-248, Figure 113

Comparison of safety by baseline hepatic function (per the NCI-ODWG criteria) across all subjects who received tisotumab vedotin at 2.0 mg/kg Q3W IV in studies GCT1015-04, GEN701, SGNTV-001, GCT1015-03, and GEN702 (Table 5) indicated no marked decrease in overall tolerability in mild hepatic impairment. However, patients with mild hepatic impairment had a higher incidence of liver enzyme (total bilirubin, AST and ALT) increases.

Table 5: Summary of Safety by Baseline hepatic Function

	All Tumor Types 2.0 mg/kg Q3W	
	Normal (N=299)	Mild (N=45)
Median total number of treatment cycles ^a	4.0	2.0
Median total duration of treatment (months) ^b	2.76	1.54
Any TEAE	295 (98.7%)	43 (95.6%)
Any treatment-related TEAE	272 (91.0%)	40 (88.9%)
Any Grade 3 and higher TEAE	164 (54.8%)	26 (57.8%)
Any TE SAE	122 (40.8%)	19 (42.2%)
Any TEAE resulting in dose modification	153 (51.2%)	16 (35.6%)
TEAE resulting in dose interruption	79 (26.4%)	8 (17.8%)
Median time to first dose interruption (months) ^c	1.35	0.87
TEAE resulting in dose reduction	47 (15.7%)	5 (11.1%)
Median time to first dose reduction (months) ^d	1.74	2.07
TEAE resulting in treatment discontinuation	60 (20.1%)	8 (17.8%)
Any ocular TEAE ^e	174 (58.2%)	23 (51.1%)
Any peripheral neuropathy TEAE ^f	121 (40.5%)	11 (24.4%)
Any bleeding TEAE ^f	190 (63.5%)	24 (53.3%)
Liver Laboratory Abnormalities (maximum grade)		
Total bilirubin increased		
Grade 1	3 (1.0%)	3 (6.7%)
Grade 2	1 (0.3%)	3 (6.7%)
AST increased		
Grade 1	117 (39.1%)	16 (35.6%)
Grade 2	8 (2.7%)	8 (17.8%)
Grade 3	1 (0.3%)	3 (6.7%)
ALT increased		
Grade 1	97 (32.4%)	19 (42.2%)
Grade 2	7 (2.3%)	5 (11.1%)
Grade 3	4 (1.3%)	3 (6.7%)

Source: Applicant's response in response to FDA IR

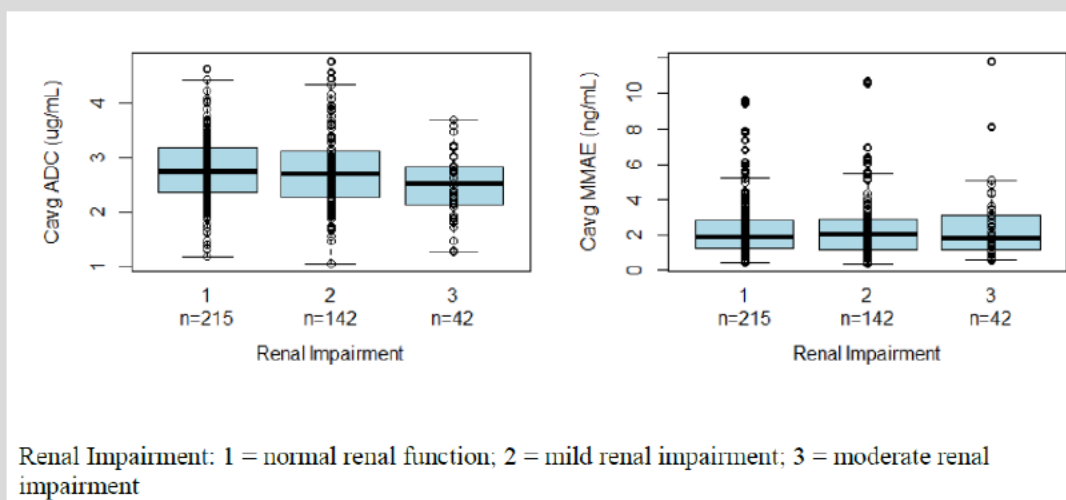
Given that there is no substantial decrease in the tolerability of tisotumab vedotin in patients with mild hepatic impairment, and as lowering the dose of tisotumab vedotin to match the exposure of MMAE may lead to lower ADC concentrations which could lead to lower efficacy (based on the exposure-response analysis with efficacy), no tisotumab vedotin dose adjustment is recommended for this population.

The effect of moderate or severe hepatic impairment on the PK and safety of tisotumab vedotin has not been assessed. However, unconjugated MMAE exposures are expected to further increase in the setting of moderate and severe hepatic impairment. As the proposed dosage of tisotumab vedotin was identified as the MTD and unconjugated MMAE exposure is correlated with increased SAEs based on exposure-safety analyses, tisotumab vedotin should be avoided in patients with moderate or severe hepatic impairment. This guidance is conveyed in Section 8.6 of product labeling.

Renal impairment:

No dose modification is recommended in patients with mild or moderate renal impairment. No formal clinical trial has been conducted to assess the effect of renal function on the PK of tisotumab vedotin. The effect of mild and moderate renal impairment on tisotumab vedotin and unconjugated MMAE exposure was assessed using the population PK model. The population PK analysis included patients with mild (n=142) and moderate (n=42) renal impairment, in addition to patients with normal (n=215) renal function. There was no marked difference in model-predicted Cycle 1 tisotumab vedotin and unconjugated MMAE exposures between patients with normal renal function and those with mild and moderate renal impairment (Figure 5).

Figure 5: Model-predicted ADC and MMAE Cycle 1 exposures (2.0 mg/kg Q3W with 200 mg cap) in mild and moderate renal impairment compared to normal renal function



Source: Applicant's PopPK Report SR1015-248, Figure 113

In addition, comparison of safety by baseline renal function (CL_{cr} per the Cockcroft-Gault formula) across all subjects who received tisotumab vedotin at 2.0 mg/kg Q3W IV in studies GCT1015-04, GEN701, SGNTV-001, GCT1015-03, and GEN702 (Table 6) indicated no marked differences in tolerability observed between patients with mild or moderate renal insufficiency at baseline and those with normal renal function.

Table 6: Summary of Safety by Baseline Renal Function

	All Tumor Types 2.0 mg/kg Q3W		
	Normal (N=187)	Mild (N=123)	Moderate (N=34)
Median total number of treatment cycles ^a	4.0	4.0	4.0
Median total duration of treatment (months) ^b	2.50	2.76	2.76
Any TEAE	183 (97.9%)	122 (99.2%)	33 (97.1%)
Any treatment-related TEAE	166 (88.8%)	115 (93.5%)	31 (91.2%)
Any Grade 3 and higher TEAE	99 (52.9%)	70 (56.9%)	21 (61.8%)
Any TE SAE	81 (43.3%)	46 (37.4%)	14 (41.2%)
Any TEAE resulting in dose modification	84 (44.9%)	68 (55.3%)	17 (50.0%)
Any TEAE resulting in dose interruption	42 (22.5%)	37 (30.1%)	8 (23.5%)
Median Time to first dose interruption (months) ^c	1.13	2.04	1.41
Any TEAE resulting in dose reduction	28 (15.0%)	20 (16.3%)	4 (11.8%)
Median Time to first dose reduction (months) ^d	1.61	2.09	0.82
Any TEAE resulting in treatment discontinuation	34 (18.2%)	27 (22.0%)	7 (20.6%)
Any ocular TEAE ^e	102 (54.5%)	76 (61.8%)	19 (55.9%)
Any peripheral neuropathy TEAE ^f	72 (38.5%)	50 (40.7%)	10 (29.4%)
Any bleeding TEAE ^g	116 (62.0%)	79 (64.2%)	19 (55.9%)

Source: Applicant's response in response to FDA IR

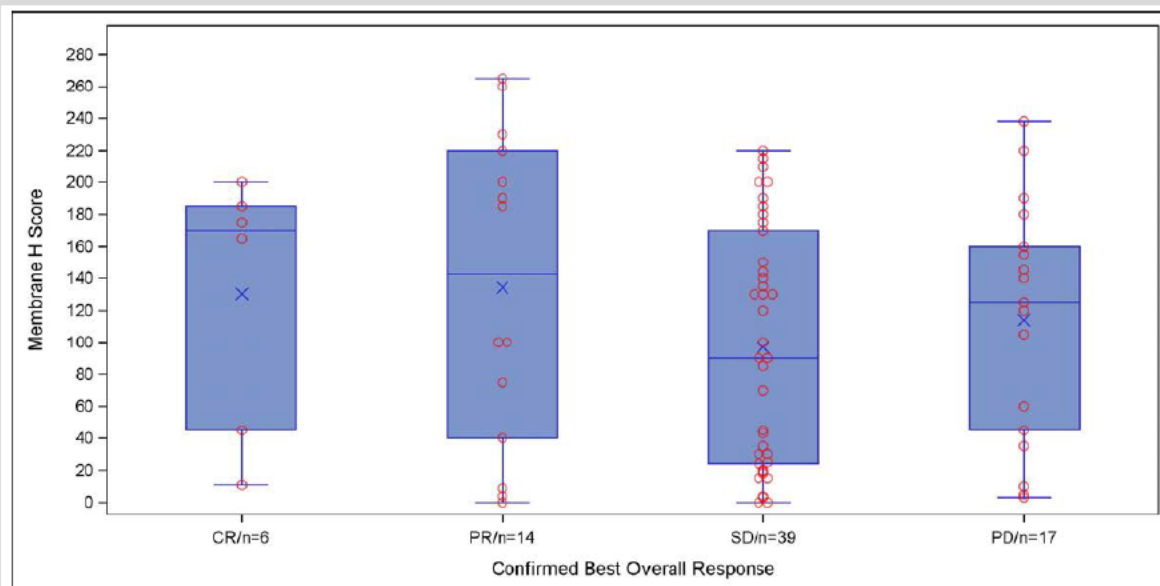
The effect of severe renal impairment on the PK of tisotumab vedotin and unconjugated MMAE has not been assessed, and this lack of information is conveyed in section 12 of product labeling.

Tissue factor (TF) expression and treatment response

Membrane and cytoplasm-associated TF expression was retrospectively tested by IHC on pre-treatment fresh or archival tumor biopsies from 87% (88/101) of patients enrolled in the GCT1015-04 study. IHC results were scored as percent of positive tumor cells (0-100%), and as a TF histology-score (H-score), which was calculated as described in Hong et al., 2020 (PMID: 31796521). Results from 80 samples were considered evaluable by the Applicant and were used for an exploratory analyses of TF expression and treatment response with tisotumab vedotin.

Of the 80 evaluable biopsies, 66 (82.5%) were obtained prior to last systemic therapy and 14 (17.5%) after their last systemic therapy. Approximately 96% (77/80) had detectable membrane TF expression. Median membrane H-score was 120 (range: 0-265) and median percentage of tumor cells positive for membrane TF expression was 60% (range: 0-100%). In the subgroup of patients who were evaluable for tumor response (N=76), confirmed objective responses (CR=6 and PR=14 by IRC) were observed over a wide range of membrane H-scores (Figure 6), including a partial response in a patient whose biopsy had a membrane H-score of 0. Similar results were observed when TF expression was analyzed as percent of tumor cells positive on the membrane or was based on cytoplasm staining. Refer to Section 8.1.4 for additional details and discussion.

Figure 6: Tumor Membrane H-score at Baseline by Confirmed Best Overall Response as Assessed by IRC, GCT1015-04 study (N=76).



Source: Applicant's Graph 14.04.01.01.01 – CSR. Whiskers extend to the most extreme observation within 1.5 times the interquartile range from the nearest quartile. Date of cut-off: Feb 06, 2020. Only patients with evaluable TF expression and response are represented.

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

No, based on available data from another ADC that contains MMAE, brentuximab vedotin, there is a low potential for clinically relevant interactions between tisotumab vedotin and concomitant medications. Tisotumab vedotin is intended for administration via IV infusion; therefore, food-drug interactions are not expected.

Data:

Coadministration of CYP3A4 Substrates with Tisotumab Vedotin

In a clinical DDI study with another MMAE-containing ADC, brentuximab vedotin (1.8 mg/kg), circulating levels of free MMAE (at levels similar to those observed following tisotumab vedotin administration) did not affect the PK of midazolam, a CYP3A4 substrate (Han 2013). Data suggest that circulating concentrations of free MMAE that result from tisotumab vedotin are not likely to cause clinically significant changes in the PK of drugs metabolized by CYP3A4.

Coadministration of CYP3A4 Inhibitors with Tisotumab Vedotin

Concomitant administration of ketoconazole with brentuximab vedotin led to a 34% increase in free MMAE AUC exposure (Han 2013). 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 tisotumab vedotin may result in a similar increase in free MMAE exposure.

Coadministration of CYP3A4 Inducers with Tisotumab Vedotin

Concomitant administration of rifampin with brentuximab vedotin led to a 46% decrease in free MMAE AUC exposure (Han 2013). Brentuximab vedotin PK were unchanged by concomitant use of rifampin. Concomitant use of strong inducers of CYP3A4 such as rifampin with tisotumab vedotin would likely result in similar effects of free MMAE and tisotumab vedotin.

The Applicant's Position:

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

The FDA's Assessment:

The FDA agrees that no tisotumab vedotin dose modifications are recommended in patients who are receiving concomitant strong CYP3A inhibitors or inducers. Tisotumab vedotin contains the same linker-payload combination, at the same average drug-to-antibody ratio of 4, as brentuximab vedotin. The geometric mean (CV%) of single dose systemic exposures of unconjugated MMAE at the proposed dosage of tisotumab vedotin [$C_{max} = 4.73$ (51%) ng/mL and $AUC_{0-inf} = 39.5$ (53%) day.ng/mL, model-predicted in Study 04] are similar to those observed at the approved 1.8 mg/kg Q3W dosage of brentuximab vedotin [$C_{max} = 4.97$ (43%) ng/mL and $AUC_{0-inf} = 37$ (47%) day.ng/mL, per the Adcetris clinical pharmacology review]. Therefore, similar effects of strong CYP3A inhibitors (34% increase in free MMAE AUC) and inducers on unconjugated MMAE PK might be expected with tisotumab vedotin as those observed with brentuximab vedotin. Due to the expected increase in unconjugated MMAE exposure with concomitant use of strong CYP3A inhibitors (which is expected to be similar in magnitude to that in patients with mild HI), patients receiving concomitant strong CYP3A inhibitors should be closely monitored for signs of toxicity.

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7 Sources of Clinical Data

7.1 Table of Clinical Studies

Data:

An overview of clinical studies supporting the efficacy and safety of tisotumab vedotin is presented in Table 7.

Table 7: Clinical Studies Supporting the Efficacy and Safety of Tisotumab Vedotin

Trial Identity	NCT no.	Trial Design	Regimen/schedule/route	Study Endpoints	Treatment Duration/Follow Up	No. of subjects enrolled ^a	Study Population	No. of Centers and Countries
Studies to Support Efficacy and Safety								
GCT1015-04	NCT03438396	Phase 2, single-arm, open-label	2.0 mg/kg 1Q3W	Confirmed ORR, DOR, TTR, PFS, and OS. AEs and safety laboratory parameters. PK. ADA.	<u>Treatment duration:</u> Until radiographic disease progression, unacceptable AEs, investigator decision, consent withdrawal, or death. <u>Follow up:</u> consent withdrawal, investigator decision, start of new anti-cancer treatment, or death.	101	Previously treated recurrent or metastatic cervical cancer	36 sites; 8 countries
GEN701	NCT02001623	Phase 1/2, first-in-human, single arm, open-label, dose-finding	Dose Escalation: 0.3, 0.6, 0.9, 1.2, 1.5, 1.8, 2.0 and 2.2 mg/kg 1Q3W Cohort Expansion (at RP2D): 2.0 mg/kg 1Q3W	AEs and safety laboratory parameters. Objective response (CR, PR), DC (CR, PR, SD), PFS, and DOR. PK. Tumor activity measured by tumor shrinkage.	<u>Treatment Duration:</u> 4 cycles. If subjects received benefit, up to 8 additional cycles. Continued treatment was allowed in GCT1015-03 for subjects still receiving clinical benefit. Or until unacceptable AEs, disease progression, pregnancy, consent withdrawal, or investigator decision. <u>Follow up:</u> 30 days after the last dose of tisotumab vedotin.	195	Locally advanced or metastatic solid tumor types known to express TF: Relapsed, advanced and/or metastatic cancer of the ovary, cervix, endometrium, bladder, prostate, squamous cell carcinoma of the head and neck (SCCHN), esophagus or NSCLC	21 sites; 5 countries
GCT1015-03	NCT03245736	Phase 2 extension trial after GEN701 or GEN702	Same 1Q3W dose regimen as administered in GEN701 or GEN702	Evaluation of AEs. ORR (confirmation not required).	<u>Treatment Duration:</u> Until unacceptable toxicity, pregnancy, disease progression, consent withdrawal, investigator decision.	5	Locally advanced or metastatic solid tumor types known to express TF (extension trial for GEN701 and GEN702)	4 sites; 2 countries

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Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of subjects enrolled ^a	Study Population	No. of Centers and Countries
					Follow up: 30 days after the last dose of tisotumab vedotin			
Studies to Support Safety								
GEN702	NCT02552121	Dose-escalating and cohort expansion safety	Dose Escalation: 0.9 mg/kg 3Q4W 1.2 mg/kg 3Q4W Cohort Expansion: 1.2 mg/kg 3Q4W 2.0 mg/kg 1Q3W	AEs and safety laboratory parameters. PK. ADA. Anti-tumor activity measured by tumor shrinkage. Objective Response (CR or PR), DC (CR, PR or SD), PFS and DoR.	Treatment Duration: Dose Escalation: Up to 12 cycles. Cohort Expansion: Up to 9 cycles. Or until unacceptable AEs, pregnancy, consent withdrawal, investigator decision, or sponsor decision. Follow up: Up to 24 weeks or until the start of new anti-cancer treatment.	33	Locally advanced and/or metastatic solid tumors known to express TF: Relapsed, advanced and/or metastatic cancer of the ovary, cervix, endometrium, bladder, prostate, esophagus, or NSCLC	10 sites; 4 countries
SGNTV-001	NCT03485209	Open-label phase 2	2.0 mg/kg 1Q3W, 0.9 mg/kg 3Q4W, or 1.2 mg/kg 3Q4W	Investigator-determined confirmed ORR. AEs. Unconfirmed ORR. DCR, DOR, TTR, PFS and OS. AEs. PK. ADA.	Treatment Duration: Until disease progression, unacceptable AEs, pregnancy, investigator decision, consent withdrawal, study termination, or subsequent anti-cancer treatment. Follow up: Until death, study closure, or consent withdrawal.	72	Locally advanced or metastatic solid tumor types known to express TF: Inoperable, locally advanced or metastatic colorectal cancer, exocrine pancreatic adenocarcinoma, SCCHN, or squamous NSCLC	22 sites; 7 countries

a. GCT1015-04 safety analysis N=101, efficacy analysis N=101; GEN701 safety analysis N=167, efficacy analysis N=50; GCT1015-03 safety analysis N=4, efficacy analysis N=2; GEN702 safety analysis N=4; SGNTV-001 safety analysis N=56

The Applicant's Position:

The primary evidence of efficacy and safety for tisotumab vedotin monotherapy in subjects with previously treated, recurrent or metastatic cervical cancer is based on the ongoing, open-label, phase 2 GCT1015-04 trial. This study enrolled 101 subjects.

Supportive evidence for efficacy and safety is provided by the expansion cohort of trial GEN701 including extension trial data from 2 subjects with cervical cancer who were subsequently enrolled in GCT1015-03. Additional supportive evidence for safety is provided by GEN702 and an ongoing trial, SGNTV-001, contributing data for analyses of ADA, ECG, and corrected QT interval by Fredericia (QTcF).

The FDA's Assessment:

FDA's evaluation of efficacy and safety is primarily based on results from GCT1015-04. GEN701/GCT1015-03 provided some secondary data to support efficacy and safety, and GEN702 provided secondary data to support safety.

8 Statistical and Clinical Evaluation

8.1 Review of Relevant Individual Trials Used to Support Efficacy

8.1.1 Pivotal Trial GCT1015-04 (innovaTV 204)

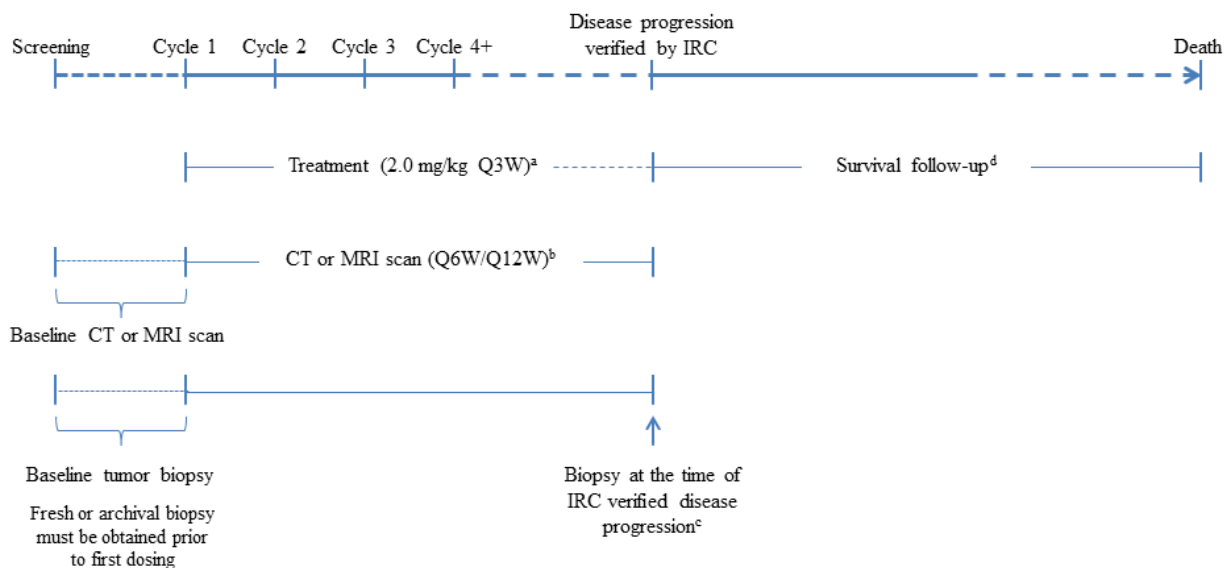
Trial Design

The Applicant's Description:

Basic Study Design

This is a single arm, international, multicenter trial of tisotumab vedotin in subjects with recurrent or metastatic cervical cancer. Eligible subjects had experienced disease progression during or after treatment with a chemotherapy doublet in combination with bevacizumab (if eligible to receive bevacizumab) and had received no more than 2 prior systemic treatment regimens for their recurrent or metastatic disease. Subjects were treated with IV tisotumab vedotin 2.0 mg/kg 1Q3W. Imaging was obtained every 6 weeks for the first 30 weeks and then every 12 weeks thereafter, continued until the subject experiences IRC verified disease progression, began a new anti-cancer therapy, withdrew from the trial, or had died, whichever came first. For subjects who achieved a response, a repeat scan was obtained no earlier than 4 weeks (28 days) after the first scan to confirm the response. Survival status was assessed every 60 days (± 7 days), beginning from the day of last IMP dose, or more frequently around the time of a database lock. The study schema is shown in [Figure 7](#).

Figure 7: GCT1015-04 Study Schema



a: Administration of tisotumab vedotin 2.0 mg/kg on day 1 of each cycle. Each treatment cycle is 3 weeks (Q3W).

b: CT or MRI scan every 6 weeks (± 7 days) for the first 30 weeks and every 12 weeks (± 7 days) thereafter.

c: Optional

d: Survival follow-up should be performed every 60 days (± 7 days) or more frequently around the time of database lock.

Trial Location

This trial was conducted across 36 sites in the EU and the United States.

Choice of Control Group

This was an open-label, single-arm trial with no control group.

Diagnostic Criteria and Main Eligibility Criteria

Main inclusion criteria included subjects 18 years of age or older with extra-pelvic metastatic or recurrent cervical cancer of squamous cell, adenocarcinoma, or adeno-squamous histology with disease progression during or after treatment with a doublet chemotherapeutic regimen of paclitaxel + cisplatin/carboplatin or paclitaxel + topotecan, in combination with bevacizumab (if eligible), and ECOG performance status of 0 or 1. Subjects must have received no more than 2 prior lines of recurrent or metastatic cancer therapy. Key exclusion criteria included the presence of baseline neuropathy $\geq$ grade 2 and presence of baseline ocular surface disease. Complete inclusion and exclusion criteria are provided in the protocol and CSR.

Dose Selection

The RP2D was identified as 2.0 mg/kg 1Q3W in GEN701.

Study Treatments

Tisotumab vedotin was administered as an IV infusion at 2.0 mg/kg over a minimum of 30 minutes on day 1 of each treatment cycle (one treatment cycle is 21 days). Each subject's dose was calculated based on the subject's weight rounded to the nearest kilogram, ie,

2.0 mg/kg × body weight in kg. For subjects who weigh >100 kg, the calculation of IMP dose was normalized to 100 kg (ie, 2.0 mg/kg × 100 kg = 200 mg).

Blinding

This is a single-arm, open-label trial and therefore there was no blinding.

Administrative Structure

A DMC was to be consulted on an ad hoc basis in the event of any new significant safety signal, or for significant changes in the established safety profile for tisotumab vedotin. No DMC meetings were held.

Procedures and Schedule

A list of all assessments and visits is provided in Table 1-1 of the GCT1015-04 protocol and timing of PK samplings in Table 1-2. CT or MRI scans were performed every 6 weeks (±7 days) for the first 30 weeks and every 12 weeks (±7 days) thereafter, calculated from the date of first IMP dosing. All subjects were required to have a baseline ophthalmological evaluation, during screening. Subject were referred to an ophthalmologist for prompt review (preferably within 72 hours and no later than within 1 week) if ocular symptoms arose at any time during trial and/or abnormal findings were noted during the eye examination performed by the treating physician. PK assessments were performed on Days 1, 4 (±1 day), and 8 (±2 days) during Cycle 1 and on Day 1 (±3 days) of Cycle 2. Unscheduled assessments could be performed to mitigate AEs throughout the study.

The FDA's Assessment:

FDA agrees with the Applicant's description of the study protocol and has the following additions/clarifications:

- Regarding eligibility criteria:
 - Patients could not be candidates for curative treatment of any kind, including pelvic exenteration surgery or radiation.
 - Patients must have had measurable disease as per RECIST v1.1 as determined by the IRC.
 - For determination of study eligibility, neoadjuvant or adjuvant chemotherapy or chemotherapy received in combination with radiation therapy did not count as a prior line of systemic treatment.

Study Endpoints

The Applicant's Description:

The primary endpoint was confirmed ORR based upon RECIST v1.1, assessed by the IRC. Secondary efficacy endpoints included confirmed ORR assessed by investigator, DOR assessed by IRC and investigator, TTR assessed by IRC and investigator, PFS assessed by IRC and investigator, and OS. Other secondary endpoints included AEs and safety laboratory

parameters, PK, and ADAs of tisotumab vedotin.

Exploratory endpoints included:

- TF expression in pre-treatment and post-progression tumor biopsies, circulating TF, proteomic analyses, and genetic variations
- Circulating TF and proteomic analyses
- EORTC-QLQ-C30 and EORTC-QLQ-CX24

The FDA's Assessment:

FDA agrees with the Applicant's description of study endpoints.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The current version of the statistical analysis plan (SAP), version 7.0, was finalized on 17 Jun 2019, prior to the database lock. There were no changes to the analysis of the primary endpoint (confirmed ORR per IRC). The trial was designed such that by applying a one-sided exact binomial test at the 0.025 significance level, the planned sample size of 100 subjects provided $\geq 80\%$ power to reject an ORR of 11%, the combined ORR for available second-line therapies, or less for true ORRs in the range 21% - 25%, representing clinically relevant improvements over available second-line treatments.

Key analysis populations defined include:

- The Full Analysis Set (FAS) and Safety Set, which included all subjects who received at least one dose of tisotumab vedotin. Since the FAS and the Safety set are identical, all safety analyses used the term FAS as the analysis population.

Primary analysis on confirmed ORR was performed on the FAS so that any treated subjects with missing information regarding response to treatment were counted as non-responders. ORR including unconfirmed responders was also analyzed, and confirmed ORR was analyzed by subgroup using a forest plot. Further, confirmed ORR as well as confirmed and unconfirmed ORR, as assessed by the investigator, were analyzed and summarized in the same way.

DOR (months) was listed for all subjects in the FAS with a confirmed best overall response of CR or PR and presented graphically as well as summarized using survival analysis methods. Six-month DOR rate (ie, percentage of subjects with DOR ≥ 6 months) and 95% CI were summarized using Kaplan-Meier estimates. TTR was summarized in the FAS population restricted to subjects with a confirmed response using descriptive statistics. PFS and OS were analyzed in the FAS population and presented graphically as well as summarized using Kaplan Meier curves and Kaplan-Meier estimates of the median time, the first and third quartiles, along with approximate 95% confidence interval of the median.

Subgroup analyses:

Subgroup analyses were performed for the primary endpoint of ORR. Prespecified subgroups included:

- Histology (squamous or non-squamous)

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- Prior cisplatin +radiation (Yes or No)
- Prior lines of systemic regimen (1 or 2); systemic regimen refers to systemic regimen administered in the extra-pelvic metastatic or recurrent setting in this document.
- Response to last systemic regimen (Yes or No)
- Prior first line combination of Paclitaxel + Cisplatin/Carboplatin + Bevacizumab or Paclitaxel + Topotecan + Bevacizumab (Yes or No)
- ECOG (0 or 1)
- Age (<65 or ≥65)
- Region (EU or US)
- Site of disease (non-visceral or visceral) [ad hoc subgroup analysis post-DBL]

Interim Analyses: No formal interim analyses were planned.

The FDA’s Assessment:

FDA does not use inferential procedures (testing procedures, performance goals, type I error control, etc.) to evaluate single-arm trial results. Therefore, FDA efficacy evaluation is based on the estimated magnitude of ORR and adequate duration of response. Additionally, we note that time-to-event endpoints are uninterpretable without a comparator arm.

Protocol Amendments

The Applicant’s Description:

[Table 8](#) describes the key changes in each amendment. The sponsors do not believe that any of the amendments impacted the integrity of the trial or the interpretation of the results.

Table 8: Summary of Key Changes in Protocol Amendments, GCT1015-04

Amendment Number	Date	Key Changes	Rationale
0	09-Nov-2017	Not applicable (original protocol)	Not applicable (original protocol)
1	22-Jan-2018	Justifications for trial design and statistical assumptions were added. Exclusion criteria were amended based on risks identified in the IB. Addition of a post-treatment observation was added.	Voluntary harmonisation procedure (VHP) recommendation
2	09-Feb-2018	To clarify the statistical power for ORRs in the range 21-25%.	VHP recommendation
3	12-Feb-2018	The plan for mitigating ocular AEs was revised. To specify that all ocular AEs, independent of grading, should be reported to the safety CRO within 24 hours.	FDA recommended revising the plan for mitigating and reporting ocular AEs
4	01-Nov-2018	Updated safety reporting requirements.	To align safety reporting requirements across the tisotumab vedotin program.

Amendment Number	Date	Key Changes	Rationale
5	17-Jun-2019	The timing of the primary analysis of the trial was changed to ensure that all responders were followed for ≥ 6 months.	Recommendation from the FDA.

The FDA's Assessment:

FDA agrees with the Applicant's description of protocol amendments.

8.1.2 Study Results

Compliance with Good Clinical Practices

Data:

Investigator sites and service provider audits were conducted by Genmab A/S to assess compliance with Good Clinical Practice (GCP) and the GCT1015-04 protocol. A consolidated audit certificate is included in Appendix 16.1.8 of the protocol.

The Applicant's Position:

The protocol for this study was designed in accordance with the general ethical principles outlined in the Declaration of Helsinki (World Medical Association 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 that this study was conducted in compliance with principles outlined in the Declaration of Helsinki, ICH GCP, and other local guidelines.

Financial Disclosure

Data:

No investigators had significant equity interests (eg, stock and/or stock options) in Genmab A/S or Seagen Inc. as defined in 21 the Code of Federal Regulations (CFR) 54.2b.

The Applicant's Position:

No financial interests were disclosed by the investigators. Additionally, the potential impact of financial interests is minimized by multi-center study design, assessment of the primary endpoint of ORR by IRC, and safety review by the DMC.

The FDA's Assessment:

FDA agrees with the Applicant that no financial interests were disclosed by investigators and that financial interests were unlikely to impact GCT1015-04. See details in Appendix 19.2.

Patient Disposition

Data:

At the GCT1015-04 data cutoff, 96.0% of subjects had discontinued from treatment (Table 9).

Table 9: Subject Disposition

	Tisotumab Vedotin 2.0 mg/kg 1Q3W (N=101)
Subjects with ongoing treatment	4 (4.0%)
Subjects who discontinued tisotumab vedotin	97 (96.0%)
Primary reason for discontinuation of tisotumab vedotin:	
Radiographic disease progression	66 (65.3%)
Adverse event(s)	13 (12.9%)
Clinical progression	8 (7.9%)
Withdrawal of consent/Subject request	5 (5.0%)
Death	4 (4.0%)
Investigator decision	1 (1.0%)
Subjects ongoing in the trial	37 (36.6%)
Subjects who discontinued from the trial	64 (63.4%)
Primary reason for discontinuation from trial:	
Death	58 (57.4%)
Withdrawal of consent	4 (4.0%)
Lost to follow-up	2 (2.0%)

Source: GCT1015-04 CSR Tables 14.01.01 and 14.01.02

The Applicant’s Position:

As of the data cutoff, the majority of subjects had discontinued treatment, with disease progression (65.3%) being the primary reason. Study discontinuation due to AE(s) was reported in 12.9% of subjects in the pivotal GCT1015-04 trial. Discontinuation due to consent withdrawal, death, or Investigator decision occurred infrequently.

The FDA’s Assessment:

FDA agrees with Applicant’s assessment of patient disposition.

Protocol Violations/Deviations

Data:

Important protocol deviations (IPDs) are the subset of protocol deviations that could have a significant effect on the integrity of study data, or on a subject’s rights, safety, or welfare. [Table 10](#) summarizes IPDs.

Table 10: Summary of Protocol Deviations, GCT1015-04

	Tisotumab Vedotin 2.0 mg/kg 1Q3W (N=101)
Number of subjects with important protocol deviations	14 (13.9%)
Reason	
Trial drug administration	11 (10.9%)
Concomitant medications	1 (1.0%)
Trial conduct	2 (2.0%)
Informed consent	1 (1.0%)

Source: GCT1015-04 CSR Table 14.01.03.02

The Applicant’s Position:

The deviations that occurred in the GCT1015-04 trial were assessed to have negligible impact

on the overall interpretation of the trial results.

The FDA's Assessment:

FDA agrees with the Applicant's assessment that the important protocol deviations were unlikely to have a large impact on interpretation of study results.

Table of Demographic Characteristics

Data:

Demographics and baseline subject characteristics in are summarized in [Table 11](#).

Table 11: Demographic and Baseline Subject Characteristics

	GCT1015-04 (N=101)
Age (years)	
Median (Range)	50.0 (31; 78)
Age category	
< 65 years	88 (87.1%)
≥ 65 years	13 (12.9%)
Region	
EU	86 (85.1%)
US	15 (14.9%)
Race	
White	96 (95.0%)
Black or African American	1 (1.0%)
Asian	2 (2.0%)
Other	2 (2.0%)
Missing	0
Ethnicity	
Hispanic or Latino	6 (5.9%)
Not Hispanic or Latino	95 (94.1%)
Missing	0
Weight (kg)	
Median (range)	65.0 (33; 110)

Source: SCE Table 14.01.03

The Applicant's Position:

Overall, the demographics of subjects in GCT1015-04 are representative of the population of subjects with previously treated, recurrent or metastatic cervical cancer.

The FDA's Assessment:

FDA agrees with Applicant's summary of demographic and baseline characteristics for patients included in the study population and generally the patient population is representative of those who will receive this treatment post-approval. FDA disagrees with the Applicant's statement that the study population, in which 95% of the patients were white, is completely representative of a US-based population with previously treated, recurrent or metastatic cervical cancer. Only a small number of Hispanic or Latino patients were enrolled to this study and only one Black patient was enrolled to this study. This is in contrast to the demographics of

patients with metastatic cervical cancer in the US, where there is an increased incidence of advanced and metastatic cervical cancer in Hispanic or Latino patients and Black patients in the US, as compared to the incidence in White patients. Despite this, there is no evidence from the data submitted, to conclude that the safety or efficacy for tisotumab vedotin differs by race, such that the results cannot be applied to a broader, more diverse, population of cervical cancer patients in the US, post-approval. Therefore, the review team finds the demographics and characteristics of patients enrolled to be acceptable to demonstrate the safety and efficacy of tisotumab vedotin in a broad US population.

Other Baseline Characteristics (eg, disease characteristics, important concomitant drugs)

Data:

Baseline disease characteristics are summarized in Table 12.

Table 12: Baseline Disease Characteristics

	Tisotumab vedotin 2.0 mg/kg 1Q3W (N=101)
Histology type	
Squamous cell carcinoma	69 (68.3%)
Adenocarcinoma	27 (26.7%)
Adenosquamous carcinoma	5 (5.0%)
ECOG performance status at baseline	
0	59 (58.4%)
1	42 (41.6%)
Metastatic disease at screening	
Yes	95 (94.1%)
No	6 (5.9%)
Prior cisplatin + radiation	
Yes	55 (54.5%)
No	46 (45.5%)
Previous adjuvant/neoadjuvant therapy	
Yes	11 (10.9%)
No	90 (89.1%)
Prior lines of systemic therapy in the recurrent or metastatic setting	
1 line	71 (70.3%)
2 lines	30 (29.7%)
Prior bevacizumab	
Yes	70 (69.3%)
No	31 (30.7%)
Bevacizumab in combination with chemotherapy doublet as first-line systemic regimen	
Yes	64 (63.4%)
No	37 (36.6%)
Response to last systemic regimen	
Yes	38 (37.6%)
No	57 (56.4%)
Missing	6 (5.9%)

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Adapted from GCT1015-04 CSR Table 14.01.04.

The Applicant's Position:

The distribution of histology subtypes in GCT1015-04 was representative of the natural distribution of subtypes in a second-line and later population of patients with recurrent or metastatic cervical cancer (NCI, 2020) and included squamous cell carcinoma (68.3%), adenocarcinoma (26.7%), and adenosquamous carcinoma (5.0%).

GCT1015-04 enrolled 14.9% of subjects in the US. All other subjects were enrolled in Europe. As the treatment guidelines for recurrent or metastatic cervical cancer and ethnic diversity are generally similar in these regions, the trial population is considered representative of the US patient population.

The majority of subjects (69.3%) had previously been treated with bevacizumab in GCT1015-04. This is higher than health claims data indicating that approximately half of all US patients with recurrent or metastatic cervical cancer receive bevacizumab as part of a first-line treatment regimen (Kantar Health 2020). The inclusion of an appropriate number of subjects previously treated with bevacizumab, an expected histologic distribution, and the fact that biomarker (TF) enrichment was not required demonstrates that the GCT1015-04 trial population is representative of the US patient population.

The FDA's Assessment:

FDA notes additional baseline disease characteristics of the study population in Table 13 below:

Table 13: Additional Baseline Disease Characteristics of Patients enrolled to GCT1015-04

	Tisotumab vedotin 2.0 mg/kg 1Q3W (N=101)
Prior radiation	
Yes	82 (81.2)
No	19 (18.8)
FIGO Stage at diagnosis	
1A	2 (2.0)
1B	24 (23.8)
2A	5 (5.0)
2B	25 (24.8)
3B	11 (10.9)
4A	6 (5.9)
4B	25 (24.8)
Not known	3 (3.0)
Visceral disease at study entry	
Yes	48 (47.5%)
No	53 (52.5%)

[Source: GCT1015-04: adam- ads]

FDA agrees with the Applicant that, with respect to disease characteristics and prior therapies,

the study population is reflective of a US-based population with cervical cancer.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

N/A

The Applicant's Position:

Compliance was assessed on a subject-by-subject basis. To ensure treatment compliance according to the study protocol, dose modifications were documented in the clinical database and concomitant therapies were recorded in the eCRF.

The FDA's Assessment:

FDA agrees with the Applicant's description. For discussion of concomitant medications and rescue medications used for prophylaxis and treatment of TEAEs, refer to Section 8.2: Review of Safety.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Individual trial results for GCT1015-04 are presented side by side with GEN701/GCT1015-03 in Section 8.1.4. These results are also summarized below.

The primary endpoint, confirmed ORR assessed by IRC per RECIST v1.1, was 23.8% (95% CI: 15.9%–33.3%), including 7 (6.9%) CRs and 17 (16.8%) PRs (GCT1015-04 CSR, Table 14.02.01.01.01). The 95% CI excluded the reference ORR of 11% (P=0.0002) (GCT1015-04 clinical study report [CSR] Table 14.02.01.01.01). Disease control rate (DCR) was 72.3%, which included 7 (6.9%) CRs, 17 (16.8%) PRs and 49 subjects (48.5%) with a best overall response of SD. Among the 101 subjects, 77 subjects (76.2%) had target lesion reductions. Excluding 4 subjects, who did not have a postbaseline scan, resulted in 77/97 (79.4%) with a target lesion reduction.

Subgroup Analysis of ORR per IRC

Response rates were generally consistent across subgroups including region, prior treatment with bevacizumab, and ECOG score, with 95% confidence intervals overlapping with the confirmed ORR of the overall trial population (GCT1015-04 CSR Graph 14.02.01.01).

ORR Assessed by Investigator

In general, investigator assessments of efficacy were similar to IRC assessments (m2.7.3, Section 3.2.6). Confirmed ORR as assessed by investigator was 20.8% (95% CI: 13.4%, 30.0%), which included 5 CRs (5.0%) and 16 PRs (15.8%) (GCT1015-04 CSR Table 14.02.01.01.02). DCR was 83.2% (95% CI: 74.4%, 89.9%), which included responders as well as 63 subjects with SD (62.4%). The concordance rate between confirmed response assessments per IRC and responses per investigator was 85.1% (GCT1015-04 CSR Table 14.02.05).

The Applicant's Position:

Treatment with tisotumab vedotin 2.0 mg/kg 1Q3W resulted in clinically meaningful and durable responses in subjects with recurrent or metastatic cervical cancer with disease progression on or after doublet chemotherapy with bevacizumab (if eligible). Confirmed ORR of 23.8% was generally consistent across subgroups, with 95% CIs overlapping with the confirmed ORR of the overall trial population. Importantly, confirmed ORR was consistent across histologies, prior vs no prior bevacizumab as part of frontline treatment.

The FDA's Assessment:

FDA conducted an independent analysis of ORR. The confirmed ORR assessed by IRC was 23.8% (95% CI: 15.9%, 33.3%) out of 101 patients, including 7 (6.9%) CRs and 17 (16.8%) PRs, while the confirmed ORR assessed by investigator was 20.8% (95% CI: 13.4%, 30.0%), including 5 (5.0%) CRs and 16 (15.8%) PRs. Characteristics of patients who experienced responses on GCT1015-04 are shown in Table 14.

Table 14: Characteristics of patients experiencing a tumor response by IRC on GCT1015-04

Patient ID	Tumor Membrane TF: H-score; % cells positive	Tumor Cytoplasm TF: H-score; % cells positive	Target lesions by IRC	Non-target lesions by IRC	DOR In months	Best overall response and data by IRC
1	(b) (6) 0; 0	0; 0	1. 32 mm lesion Sum of diameters: 32 mm	1	2.9	PR (b) (6) Day 39
2	200; 90	120; 80	1. 37 mm Sum of diameters: 37 mm	0	4.1	CR (b) (6) Day 83
3	Not available	Not available	1. 26 mm Sum of diameters: 26 mm	1	1.4	PR (b) (6) Day 39
4	100; 50	115; 80	1. 19 mm Sum of	2	3.1	PR (b) (6) Day 42

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	(b) (6)			diameters: 19 mm			
5	40; 30	20; 15		1. 10 mm 2. 20 mm Sum of diameters: 30 mm	0	2.8	PR (b) (6) Day 40
6	100; 70	45; 30		1. 15 mm Sum of diameters: 15 mm	3	2.9	PR (b) (6) Day 43
7	75; 45	25; 20		1. 24 mm 2. 17 mm Sum of diameters: 41	2	1.6	PR (b) (6) Day 44
8	9; 5	11; 10		1. 16 mm Sum of diameters: 16 mm	1	6.6	PR (b) (6) Day 98
9	260; 100	260; 100		1. 30 mm Sum of diameters: 30 mm	3	8.1	PR (b) (6) Day 49
10	Not evaluable	No evaluable.		1. 13 mm Sum of diameters: 13 mm	1	4.1	PR (b) (6) Day 35
11	220; 100	175; 90		1. 24 mm 2. 18 mm Sum of diameters: 42 mm	1	4.2	PR (b) (6) Day 125
12	11; 5	11; 5		1. 24 mm	2	8.5	CR

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	(b) (6)			Sum of diameters: 24 mm			(b) (6) Day 85
13	Not available	Not available	1. 18 mm Sum of diameters: 18 mm	1	10.8	CR (b) (6) Day 44	
14	175; 85	170; 90	1. 15 mm Sum of diameters: 15 mm	1	8.2	CR (b) (6) Day 41	
15	Not available	Not available	1. 19 mm 2. 29 mm Sum of diameters: 48 mm	1	4.3	PR (b) (6) Day 38	
16	230; 100	190; 100	1. 16 mm 2. 15 mm Sum of diameters: 31 mm	0	11.0	PR (b) (6) Day 40	
17	4; 3	4; 3	1. 28 mm 2. 14 mm 3. 27 mm 4. 65 mm Sum of diameters: 134 mm	0	6.9	PR (b) (6) Day 88	
18	165; 85	140; 30	1. 44 mm Sum of diameters: 44 mm	0	5.9	CR (b) (6) Day 36	
19	185; 90	170; 90	1. 15 mm	0	10.9	CR (b) (6)	

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	(b) (6)			Sum of diameters: 15 mm			Day 43
20		185; 90	170; 90	1. 32 mm Sum of diameters: 32 mm	1	3.7	PR (b) (6) Day 42
21		200; 100	180; 100	1. 19 mm Sum of diameters: 19 mm	0	2.1	PR (b) (6) Day 155
22		190; 90	110; 90	1. 20 mm 2. 19 mm Sum of diameters: 39 mm	1	8.3	PR (b) (6) Day 43
23		45; 25	25; 20	1. 26 mm 2. 18 mm Sum of diameters: 44 mm	4	6.2	CR (b) (6) Day 83
24		265; 95	225; 95	1. 43 mm Sum of diameters: 43 mm	2	8.8	PR (b) (6) Day 40

[Source: GCT1015-04 adam-adtte, adam-adtf, adam-adrs]

Overall, the disease burden in patients experiencing tumor responses was low. Only one patient experiencing a response had tumor sum of diameters >5 cm in diameter, and no patients experiencing a response had bulky metastatic disease. However, based upon the mechanism of action of tisotumab, as an antibody-drug conjugate, there does not seem to be reason to expect that patients with bulkier disease may not respond to therapy with tisotumab vedotin, and the results observed in Study GCT1015-104 may have been due to a small sample size or chance. The review team did not think that restrictions on use of tisotumab vedotin, according to disease burden, were warranted.

The concordance rate between confirmed response assessed by IRC and investigator was 85.1%. A summary of concordance between specific tumor response by IRC and Investigator is shown in Table 15.

Table 15: Concordance in Patient Responses between IRC and Investigator Assessment, N

		By Investigator, N					
		CR	PR	SD	PD	NE	Total
By Central Review, N	CR	3	3	1	0	0	7
	PR	2	7	8	0	0	17
	SD	0	6	41	2	0	49
	PD	0	0	13	11	0	24
	NE	0	0	0	0	4	4
	Total	5	16	63	13	4	101

[Source: GCT1015-04: adam-adrs]

Data Quality and Integrity

Data:

N/A

The Applicant's Position:

Steps taken to ensure the accuracy and reliability of data included selection of qualified trial sites and investigators, GCP training of trial personnel, and protocol training before initiation of the trial. In addition, site monitoring visits to review source documents against the eCRF were performed by the contract research organization (CRO), with sponsor oversight of CRO's duties as per standard operating procedure. Investigators were updated on an ongoing basis on trial progress, important trial milestones, and specific protocol specified requirements via newsletters and flash letters. Data collected by external vendors (eg, laboratory results, ECG results etc. excluding central imaging data) were transferred to the sponsor on an ongoing basis and reviewed, together with other data, for accuracy and completeness. Any discrepancies were resolved with the trial site. In addition, prior to locking the database a thorough review was performed to enhance the quality and ensure completeness.

The sponsor was blinded to the IRC data with the exception of a limited number of personnel, according to the protocol-specific blinding plan, who were unblinded when preparing for database lock in order to ensure data quality and completeness of the IRC dataset.

Audits were conducted undertaking a risk-based approach. Five sites (IT03, ES01, US11, US13, and CZ01) were audited. In addition, vendors and central laboratories (b) (6) were audited.

The FDA's Assessment:

FDA OSI conducted clinical inspections and did not identify issues with data quality or integrity. Please see Section 4.1 for additional information.

Efficacy Results – Secondary and other relevant endpoints

Data

Individual trial results for GCT1015-04 are presented side by side with GEN701/GCT1015-03 in Section 8.1.4 for the secondary endpoints of confirmed ORR assessed by investigator, DOR assessed by IRC and investigator, TTR assessed by IRC and investigator, PFS assessed by IRC and investigator, and OS. These results are summarized below.

Duration of Response

Confirmed responses to tisotumab vedotin were durable, with a median DOR of 8.3 months (95% CI: 4.2 months to NR) as assessed by IRC. An estimated 62.4% of confirmed responders had a DOR of 6 months or longer (95% CI: 36.7%, 80.1%) (GCT1015-04 CSR Table 14.02.02.01).

Time to Response as Assessed by IRC

Responses occurred early in treatment, with a median TTR of 1.4 months (range, 1.1 to 5.1 months) (GCT1015-04 CSR Table 14.02.02.01). Most responders (19/24, 79.2%) recorded their first radiologic response at the first postbaseline scan.

Progression-Free Survival as Assessed by IRC

Seventy-four subjects (73.3%) experienced a PFS event (progression or death), as assessed by IRC. The median PFS was 4.2 months (95% CI: 3.0, 4.4 months). The estimated PFS rate at 6 months was 30.2% (95% CI: 20.8%, 40.1%) (GCT1015-04 CSR Table 14.02.03.01).

Overall Survival

As of the data cutoff date, 58 subjects (57.4%) had died. Median OS was 12.1 months (95% CI: 9.6, 13.9 months) (GCT1015-04 CSR Table 14.02.04).

The Applicant's Position:

Responses to tisotumab vedotin were durable, with a median DOR of 8.3 months (95% CI 4.2 months- NR) as assessed by IRC. An estimated 62% subjects had a DOR of 6 months or longer. Responses occurred early in treatment, with a median TTR by IRC of 1.4 months (range, 1.1 to 5.1 months). Median PFS by IRC was 4.2 months (95% CI 3.0 to 4.4 months) and the estimated PFS rate at 6 months was 30% (95% CI 20.8% to 40.1%). PFS data are supportive of ORR and DOR data. The median OS was 12.1 months (95% CI 9.6 to 13.9 months). OS data are supportive of the ORR and DOR data.

The FDA's Assessment:

FDA conducted an independent analysis of ORR and DOR. Among the 24 confirmed responders, 10 had progressed and 14 were still in response at the data cutoff date of February 6, 2020. The median DOR was 8.3 months (95% CI: 4.2 month, NR), and the DOR was ranged from 1.4 months to 11.0 months. An estimated 62.4% of confirmed responders had a DOR of 6 months or longer (95% CI: 36.7%, 80.1%).

Time-to-event endpoints such as time-to-response, PFS, and OS are not interpretable for single-

arm studies and do not factor into the benefit/risk determination for this application.

Dose/Dose Response

Data:

N/A

The Applicant's Position:

N/A

The FDA's Assessment:

Refer to Section 6.2.2.1 for information regarding dose/dose response.

Durability of Response

Data:

DOR is presented as a secondary endpoint. See Section 8.1.2 for the secondary endpoints.

The Applicant's Position:

N/A

The FDA's Assessment:

There are not data on durability of response beyond what is presented regarding DOR in Section 8.1.2. No additional analysis was performed by FDA.

Persistence of Effect

Data:

The persistence of efficacy of tisotumab vedotin is demonstrated by the durability of response observed in subjects with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy. See Section 8.1.2 for the secondary endpoints.

The Applicant's Position:

N/A

The FDA's Assessment:

There are no efficacy data beyond what is presented in the preceding portion of the assessment aid. No additional analysis was performed by FDA.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:

In the single arm trial GCT1015-04, HRQOL was assessed by collection of data from 2 validated questionnaires completed by trial subjects at screening visit (baseline), Cycle 2 (D1), Cycle 4 (D1), and treatment discontinuation; EORTC-QLQ-C30 and EORTC-QLQ-CX24.

The compliance and completion rates of EORTC-QLQ-C30 and EORTC-QLQ-CX24 at screening visit (baseline), Cycle 2 (D1), Cycle 4 (D1), and treatment discontinuation were reported (GCT1015-04 CSR Table 14.04.03.02).

In terms of HRQOL findings, in general, scores in most EORTC-QLQ-C30 domains numerically declined between the screening visit (baseline) and Cycle 4 (D1), as well as treatment

discontinuation (GCT1015-04 CSR Table 14.04.03.01). Scores in most EORTC-QLQ-CX24 domains generally remained stable between the screening visit (baseline) and Cycle 4 (D1) (GCT1015-04 CSR Table 14.04.04.01).

The Applicant's Position:

HRQOL was in general maintained or showed small but not clinically meaningful decreases on most domains between baseline and Cycle 4. The larger decreases in some domains/items at time of treatment discontinuation are expected as most subjects at the timepoint experienced progressive disease or discontinuation of trial drug due to ongoing AEs.

Given the single-arm trial design, limited data collected, lack of published data on HRQOL in cervical cancer, the clinical meaningfulness of these declines is hard to interpret.

The FDA's Assessment:

FDA agrees with the Applicant that it is difficult to interpret PROs, given the lack of a control arm and the small sample size.

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 FDA Assessment in Section 8.1.5.

8.1.4 Assessment of Efficacy Across Trials

Primary Endpoints

Data:

The confirmed ORR as assessed by IRC was clinically meaningful and similar across 2 independent trials at 23.8% (95% CI 15.9% - 33.3%) in GCT1015-04 and 22.0% (95% CI 11.5% - 36.0%) in GEN701/GCT1015-03. In GCT1015-04, there were 7 CRs (6.9%) and 17 PRs (16.8%). In GEN701/GCT1015-03, there was 1 CR (2.0%) and 10 PRs (20.0%) (Table 16). The DCR (CR+PR+SD) was 72.3% (95% CI 62.5% - 80.7%) and 60.0% (95% CI 45.2% - 73.6%), respectively.

Table 16: Confirmed Objective Response Rate Assessed by IRC per RECIST 1.1

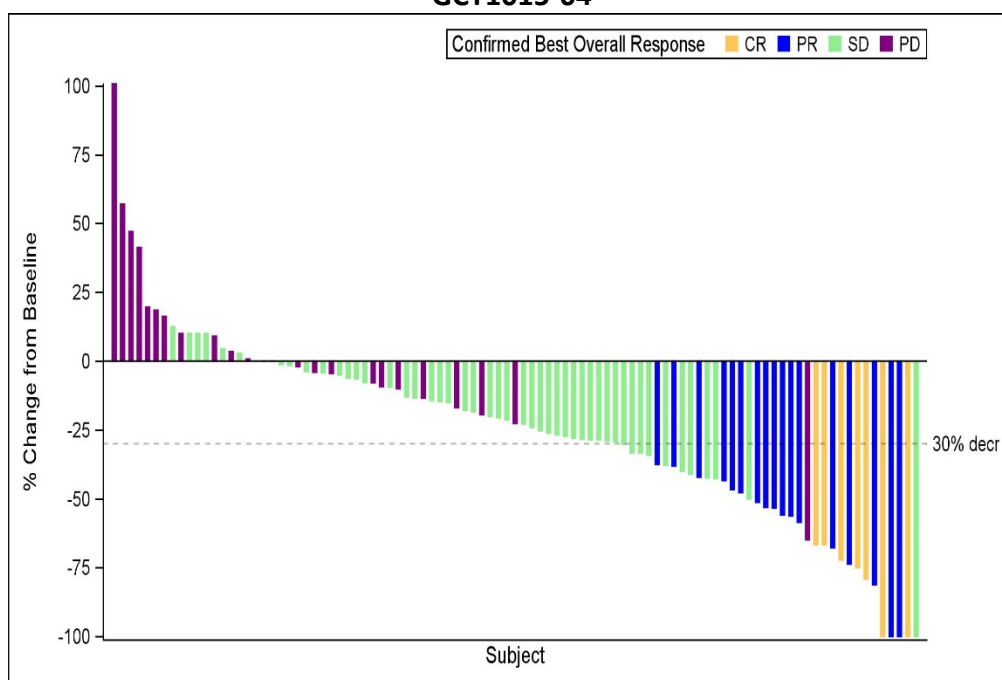
	GCT1015-04 (N=101)	GEN701/GCT1015-03 (N=50)
Confirmed best objective response		
Complete response	7 (6.9%)	1 (2.0%)
Partial response	17 (16.8%)	10 (20.0%)
Stable disease	49 (48.5%)	19 (38.0%)

	GCT1015-04 (N=101)	GEN701/GCT1015-03 (N=50)
Progressive disease	24 (23.8%)	16 (32.0%)
Not evaluable	4 (4.0)	4 (8.0%)
Confirmed objective response (CR+PR) rate	24 (23.8%)	11 (22.0%)
95% CI	(15.9%; 33.3%)	(11.5%; 36.0%)
Confirmed disease control (CR+PR+SD) rate	73 (72.3%)	30 (60.0%)
95% CI	(62.5%; 80.7%)	(45.2%; 73.6%)

Source: SCE Table 14.02.01.01

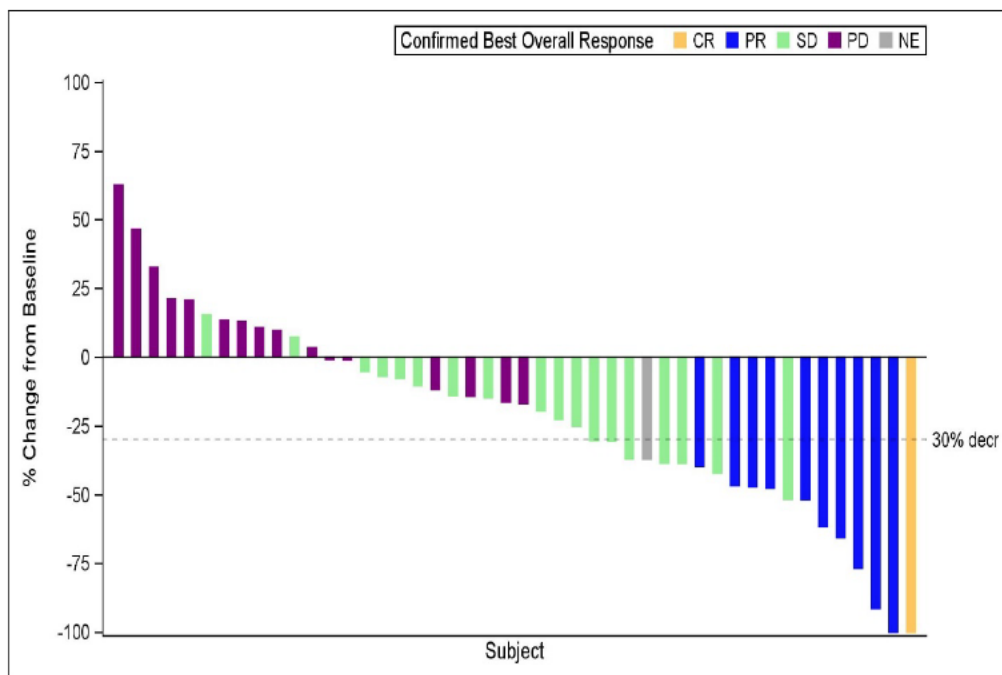
The maximum percent reduction from baseline in the sum of diameters of target lesions per IRC is shown [Figure 8](#). The majority of subjects had tumor regression.

Figure 8: Maximum Percent Change in Target Lesions Assessed by IRC per RECIST 1.1
GCT1015-04



GEN701/GCT1015-03

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Source: SCE Graph 14.02.04.01

The Applicant's Position:

Tisotumab vedotin resulted in clinically meaningful confirmed ORR per IRC of 23.8% (95% CI 15.9% - 33.3%) in subjects with previously treated recurrent or metastatic cervical cancer. The confirmed ORR as assessed by IRC was consistent across GCT1015-04 and GEN701/GCT1015-03 (SCE Table 14.02.01.01).

The FDA's Assessment:

FDA primarily based the efficacy assessment for tisotumab vedotin on results from GCT1015-04. FDA did not replicate the Applicant's analyses from GEN701/GCT-1015-03 given the small sample size.

Secondary and Other Endpoints

Data:

DOR and TTR by IRC:

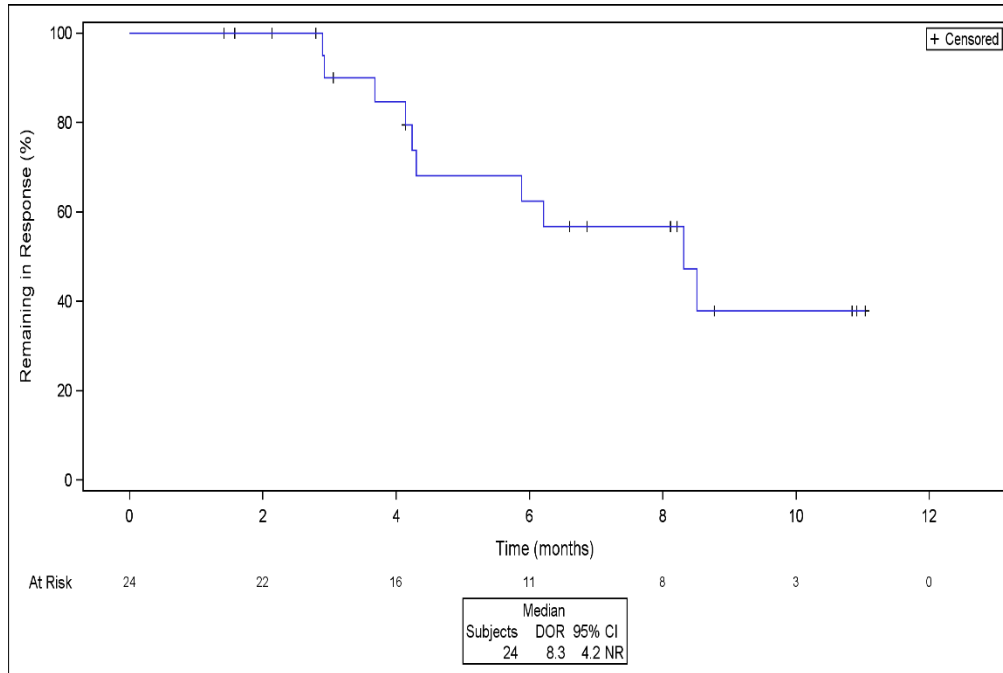
Confirmed responses to tisotumab vedotin were durable, with a median DOR of 8.3 months (95% CI 4.2 months – NR) in GCT1015-04 and 5.1 months (95% CI 3.0 months – 9.7 months) in GEN701/GCT1015-03 (Table 17 and Figure 9). Reasons for the observed difference in median DOR across trials remain to be elucidated; however, it is noted that more comprehensive safety management guidelines may have enabled subjects to stay on therapy longer in GCT1015-04, and that GCT1015-04 also enrolled a population with generally better prognostic factors. An estimated 62% of confirmed responders had a DOR of 6 months or longer in GCT1015-04.

Responses occurred early in treatment, with a median TTR of 1.4 months in GCT1015-04 and 2.8 months in GEN701/GCT1015-03 (Table 17 and Figure 10).

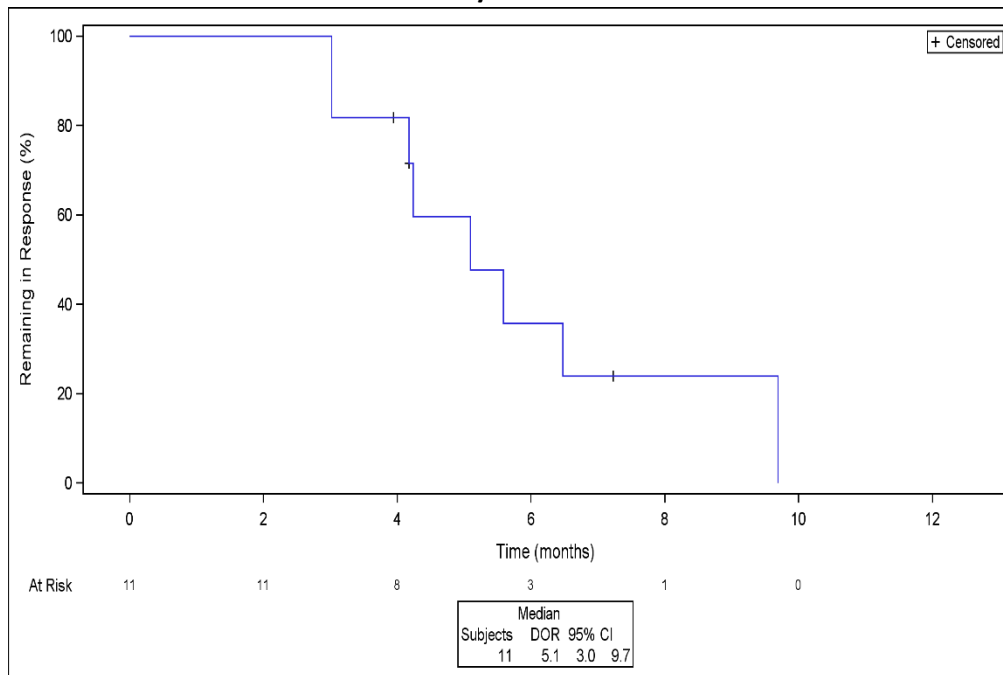
Table 17: Duration and Time to Confirmed Response Assessed by IRC per RECIST 1.1

	GCT1015-04	GEN701/GCT1015-03
	(N=24)	(N=11)
Duration of response		
Number of events	10 (41.7%)	8 (72.7%)
Number censored	14 (58.3%)	3 (27.3%)
Median DOR (months)	8.3	5.1
95% CI	(4.2; NR)	(3.0; 9.7)
25% quantile DOR (months)	4.2	4.2
75% quantile DOR (months)	NR	6.5
Range of DOR (months)	1.4+;11.0+	3.0; 9.7
Kaplan-Meier estimate, % of subjects with DOR ≥6 months	62.4%	35.8%
95% CI	(36.7%; 80.1%)	(8.8%; 64.8%)
Time to response (months)		
Mean (STD)	1.8 (1.0)	2.6 (1.4)
Median (range)	1.4 (1.1; 5.1)	2.8 (1.1; 4.6)
Source: SCE Table 14.02.02.01		

Figure 9: Duration of Confirmed Response Assessed by IRC per RECIST 1.1
GCT1015-04

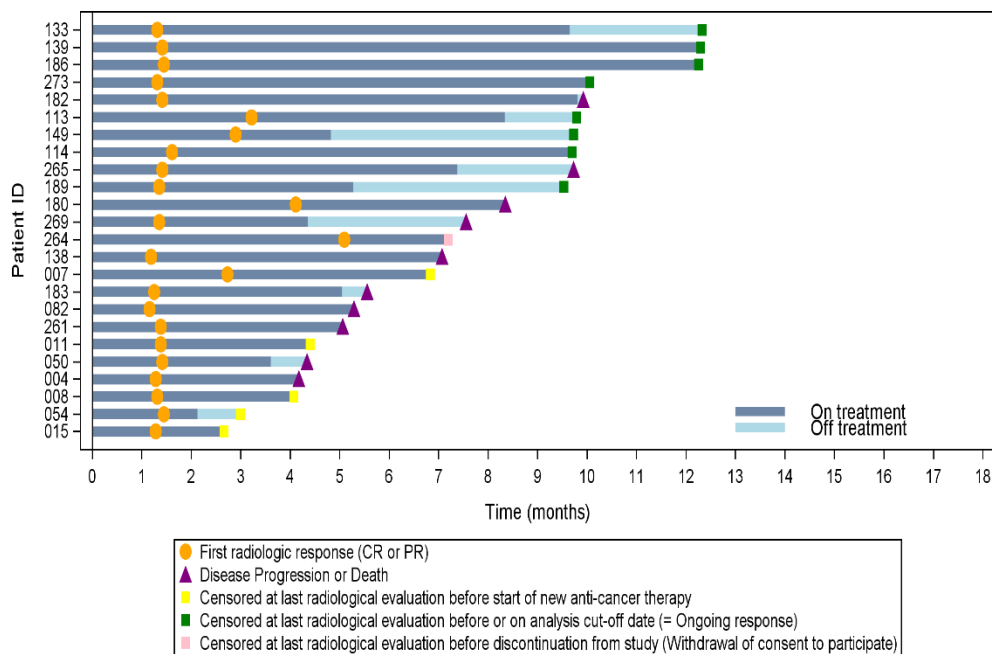


GEN701/GCT1015-03

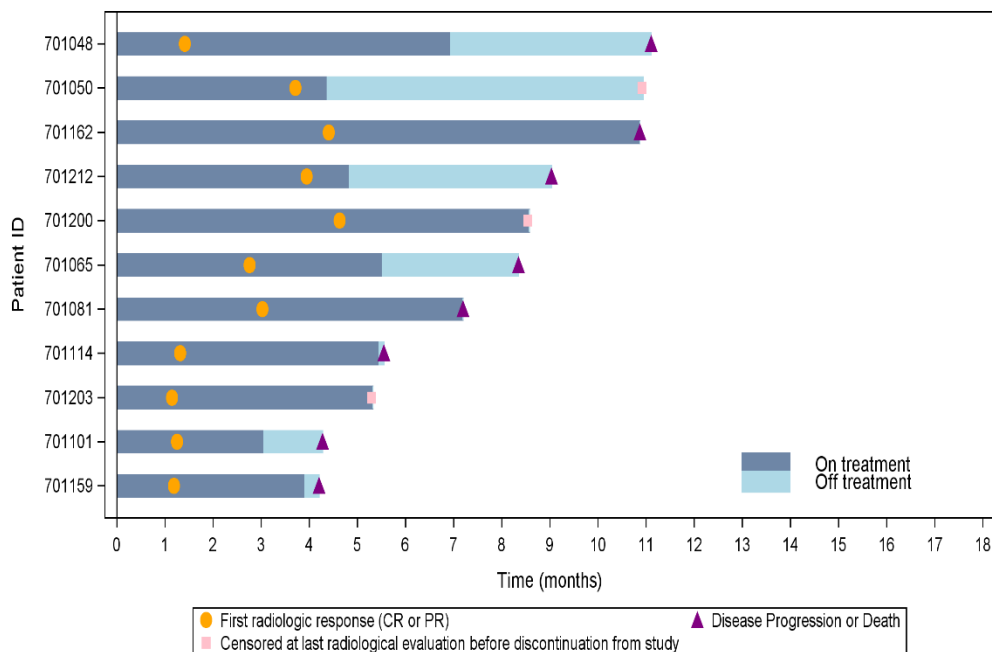


Source: SCE Graph 14.02.02.01

**Figure 10: TTR and DOR in Subjects Achieving a Confirmed Response per IRC
 GCT1015-04**



GEN701/GCT1015-03



Source: SCE Graph 14.02.06

PFS by IRC:

Median PFS per IRC was consistent across trials, at 4.2 and 4.1 months in GCT1015-04 and GEN701/GCT1015-03, respectively (Table 18 and Figure 11). The estimated PFS rate at

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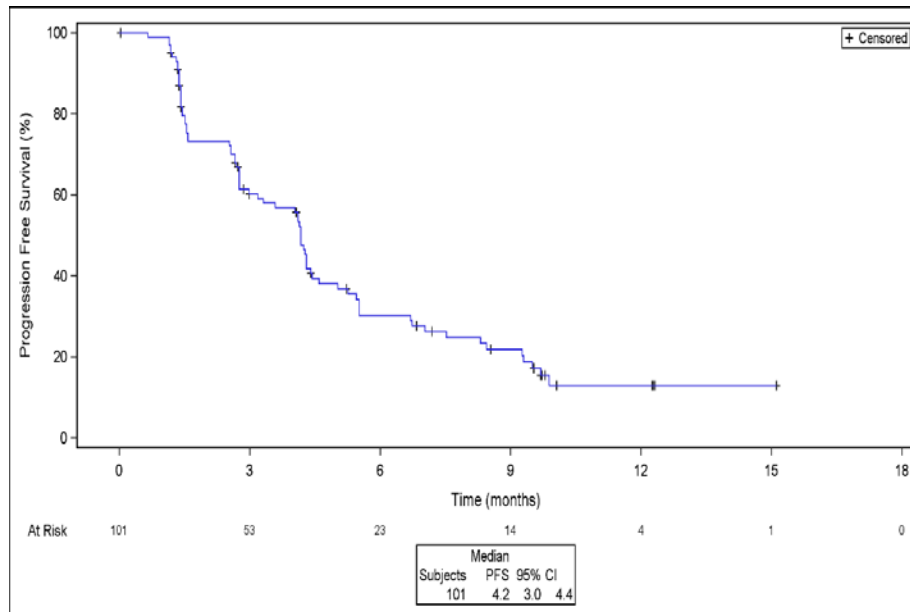
6 months was 30.2% and 33.5% in GCT1015-04 and GEN701/GCT1015-03, respectively.

Table 18: Progression-Free Survival Assessed by IRC per RECIST 1.1

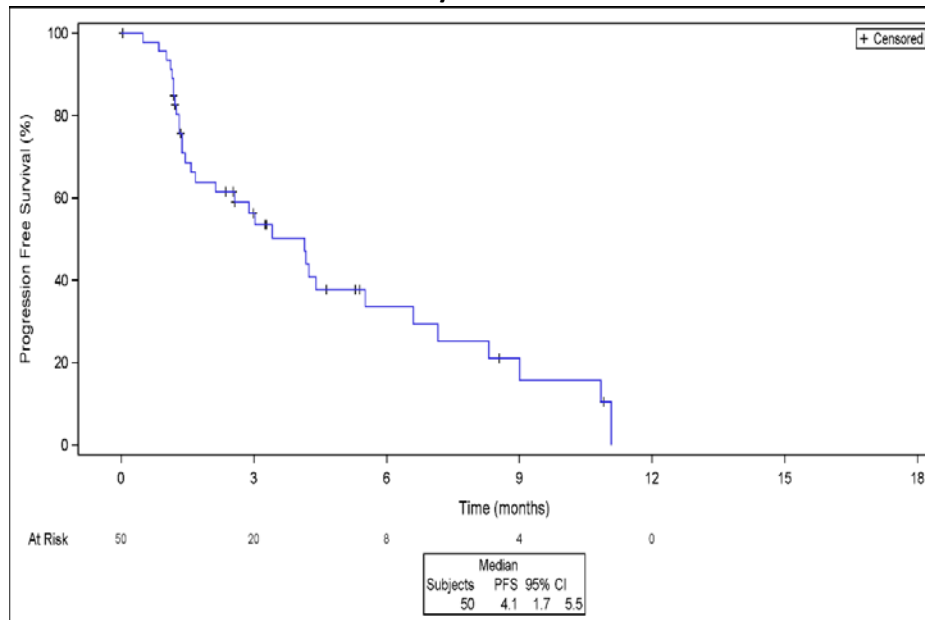
	GCT1015-04 (N=101)	GEN701/GCT1015-03 (N=50)
Number of events	74 (73.3%)	32 (64.0%)
Progression	68 (67.3%)	30 (60.0%)
Death	6 (5.9%)	2 (4.0%)
Number censored	27 (26.7%)	18 (36.0%)
Median PFS (months)	4.2	4.1
95% CI	(3.0; 4.4)	(1.7; 5.5)
25% quantile PFS (months)	1.6	1.4
75% quantile PFS (months)	7.5	8.3
Range (months)	0.0+;15.1+	0.0+; 11.1
Kaplan-Meier estimates		
% of subjects with PFS ≥ 3 months	60.2%	56.2%
95% CI	(49.7%; 69.3%)	(40.1%; 69.6%)
% of subjects with PFS ≥ 6 months	30.2%	33.5%
95% CI	(20.8%; 40.1%)	(18.4%; 49.4%)

Source: SCE Table 14.02.03.01

**Figure 11: Progression-free Survival Assessed by IRC per RECIST 1.1
GCT1015-04**



GEN701/GCT1015-03



Source: SCE Graph 14.02.03.01

Overall Survival:

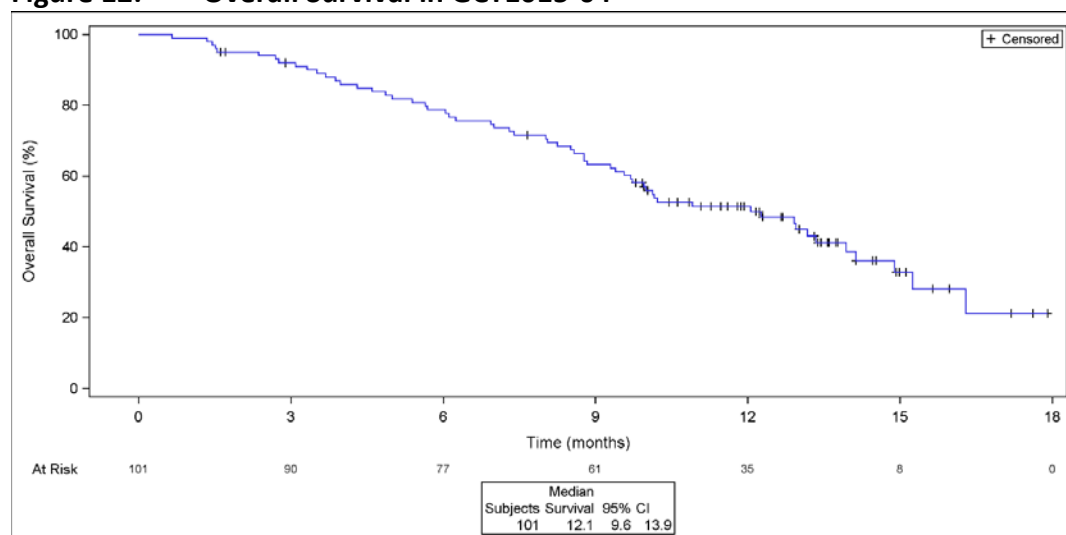
Analysis of OS is based on data from GCT1015-04 as long-term survival data were not collected in GEN701/GCT1015-03. In GCT1015-04, the median OS was 12.1 months (95% CI: 9.6; 13.9) (Table 19 and Figure 12).

Table 19: Overall Survival in GCT1015-04

	GCT1015-04 (N=101)
Number of events	58 (57.4%)
Number censored	43 (42.6%)
Median OS (range) (months)	12.1 (0.7; 17.9+)
95% CI	(9.6; 13.9)
Kaplan-Meier estimate, % of subjects alive at 6 months	78.7%
95% CI	(69.3%; 85.6%)
Kaplan-Meier estimate, % of subjects alive at 12 months	51.4%
95% CI	(40.9; 60.8%)

Source: GCT1015-04 CSR Table 14.2.04

Figure 12: Overall Survival in GCT1015-04



Source: GCT1015-04 CSR Figure 14.02.04

Efficacy Endpoints Assessed by Investigator:

In general, investigator assessments of efficacy were similar to IRC assessments (Table 20). The concordance rate between confirmed response assessments per IRC and responses per investigator was 85.1% in GCT1015-04 and 96.0% in GEN701/GCT1015-03.

Table 20: Efficacy Assessments by IRC vs Investigator

	GCT1015-04 (N=101)		GEN701/GCT1015-03 (N=50)	
	IRC	Inv	IRC	Inv
Confirmed best objective response				
Complete response	7 (6.9%)	5 (5.0%)	1 (2.0%)	0
Partial response	17 (16.8%)	16 (15.8%)	10 (20.0%)	11 (22.0%)
Stable disease	49 (48.5%)	63 (62.4%)	19 (38.0%)	19 (38.0%)
Progressive disease	24 (23.8%)	13 (12.9%)	16 (32.0%)	17 (34.0%)
Not evaluable	4 (4.0)	4 (4.0%)	4 (8.0%)	3 (6.0%)
Confirmed objective response (CR+PR)	24 (23.8%)	21 (20.8%)	11 (22.0%)	11 (22.0%)
95% CI	(15.9%; 33.3%)	(13.4%; 30.0%)	(11.5%; 36.0%)	(11.5%; 36.0%)
Confirmed disease control (CR+PR+SD)	73 (72.3%)	84 (83.2%)	30 (60.0%)	30 (60.0%)
95% CI	(62.5%; 80.7%)	(74.4%; 89.9%)	(45.2%; 73.6%)	(45.2%; 73.6%)
Median DOR (months)	8.3	8.2	5.1	5.6
95% CI	(4.2; NR)	(3.7; 11.1)	(3.0; 9.7)	(3.0; 9.7)
Time to response (months)				
Median (range)	1.4 (1.1; 5.1)	1.4 (1.1; 4.5)	2.8 (1.1; 4.6)	1.4 (1.1; 3.9)
Median PFS (months)	4.2	4.1	4.1	4.1
95% CI	(3.0; 4.4)	(3.3; 4.6)	(1.7; 5.5)	(2.1; 4.4)

Source: SCE Table 14.02.01.01, Table 14.02.01.02, Table 14.02.02.01, Table 14.02.02.02, Table 14.02.03.01, Table 14.02.03.02

The Applicant's Position:

Responses to tisotumab vedotin were durable, with a median DOR of 8.3 months (95% CI 4.2 months- NR) as assessed by IRC. An estimated 62.4% subjects had a DOR of 6 months or longer. Responses occurred early in treatment, with a median TTR by IRC of 1.4 months (range, 1.1 to 5.1 months). Median PFS by IRC was 4.2 months (95% CI 3.0 to 4.4 months) and the estimated PFS rate at 6 months was 30.2% (95% CI 20.8% to 40.1%). PFS data are supportive of ORR and DOR data. The median OS was 12.1 months (95% CI 9.6 to 13.9 months). OS data are supportive of ORR and DOR data.

The FDA's Assessment:

As previously stated, FDA's primary efficacy assessment is based on results from GCT1015-04. Please refer to Section 8.1.2 for FDA's assessment of DOR on GCT1015-04. FDA did not replicate the Applicant's analyses from GEN701/GCT-1015-03 due to the small sample size.

FDA does not consider PFS and OS data interpretable due to the lack of a comparator arm in a single arm trial.

Subpopulations

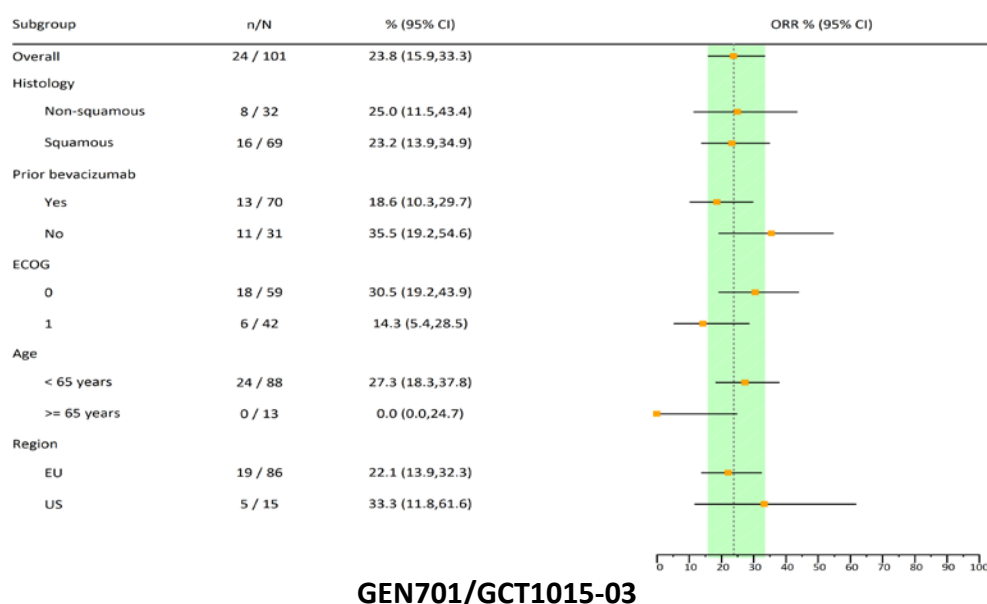
Data:

In both GCT1015-04 and GEN701/GCT1015-03, confirmed ORR were generally consistent across subgroups including region, prior treatment with bevacizumab, and ECOG score, with 95% CIs overlapping with the confirmed ORR of the overall trial population (Figure 13).

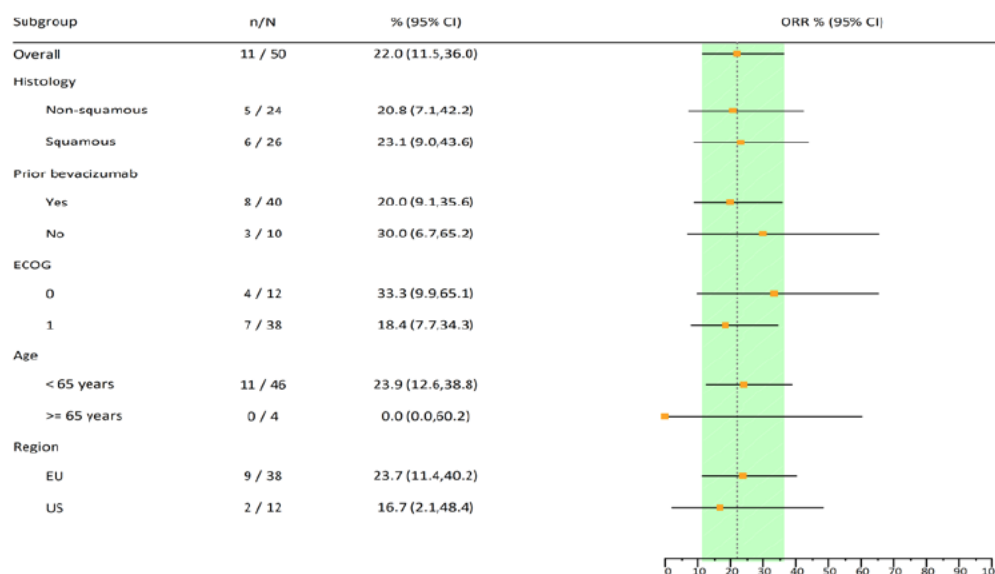
While GEN701/GCT1015-03 enrolled a higher percentage of subjects with adenocarcinoma or adenosquamous histologies compared to GCT1015-04, ORRs were similar in squamous and non-squamous histologies across the trials. These data indicate that tisotumab vedotin treatment provides clinical benefit to a broad population regardless of histology subtype.

While no confirmed responses were observed in either trial for the subgroup of subjects who were age 65 years or older, the number of subjects in this subgroup was small and there is a wide confidence interval that overlaps that of the overall trial population. At this time, there is no biological rationale suggesting that treatment with tisotumab vedotin would be less efficacious in subjects over 65 years of age.

Figure 13: Confirmed ORR Assessed by IRC per RECIST 1.1 by Subgroup GCT1015-04



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{tisotumab vedotin}



Source: SCE Graph 14.02.01.01

Tissue Factor Expression and Objective Response:

Biomarker-based subject selection was not required in GCT1015-04. Tumor TF expression was retrospectively assessed using a validated immunohistochemistry (IHC) assay in tumor biopsies from subjects with second line or greater recurrent or metastatic cervical cancer. TF expression was evaluable in 80/100 (80%) of tumor biopsies collected, and the majority of these were archival and collected prior to last systemic therapy (82.5% [66/80]).

Membrane TF expression ($\geq 1\%$ of tumor cells with TF staining) was observed in 96% of subjects with an evaluable biopsy. Responses to tisotumab vedotin were observed over a wide range of membrane TF expression levels in GCT1015-04, and comparable distribution of TF expression was observed in the IRC-assessed confirmed best overall response categories (m5.3.5.2/GCT1015-04/sec11.11.1). These data suggest that tisotumab vedotin (2.0 mg/kg 1Q3W) is a potential treatment option for patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy, regardless of TF expression levels via IHC.

The Applicant's Position:

Results of subgroup analyses were consistent across trials, with no meaningful differences in confirmed ORR observed for any of the subgroups assessed. The population for efficacy analyses was an all-comers population; that is, TF expression was not required for enrollment. In GCT1015-04, TF was expressed in the majority of subjects with cervical cancer tumors (96.3%) and responses were observed regardless of TF expression levels.

The FDA's Assessment:

Subgroup Analyses

FDA considers all subgroup analyses of ORR exploratory. In general, these analyses were supportive of primary ORR results. However, none of the 13 patients ≥ 65 years enrolled to

GCT1015-04 experienced a tumor response. The reasons for this finding are unclear and the ability to draw conclusions is limited by the small sample size of patients over 65. It is possible that the tisotumab vedotin may be less tolerable to patients ≥ 65 years of age, and this could negatively impact the chance for efficacy.

FDA also evaluated ORR by IRC in additional subgroups in GCT1015-04 as shown in Table 21 and these analyses were supportive of primary ORR results.

Table 21: Additional ORR by IRC Subgroup Analyses (GCT1015-04)

	ORR, % (n) [95% CI]
Prior lines of systemic therapy	
1	28.2% (20/71) [18.1, 40.1]
2	13.3% (4/30) [3.8, 30.7]
Response to last therapy	
Yes	26.3% (10/38) [13.4, 43.1]
No	21.1% (12/57) [11.4, 33.9]
Missing	33.3% (2/6) [4.3, 77.7]
Bevacizumab in combination with chemotherapy doublet as first-line systemic regimen	
Yes	18.8% (12/64) [10.1, 30.5]
No	32.4% (12/37) [18.0, 49.8]
Site of disease	
Visceral	22.9% (11/48) [12.0, 37.3]
Non-visceral	24.5% (13/53) [13.8, 38.3]
Metastatic at diagnosis	
Stage IVB	12.0% (3/25) [2.5, 31.2]
All other stages	27.6% (21/76) [18.0, 39.1]

Prior Bevacizumab

The Applicant’s subgroup analyses included an analysis of patients who received/did not receive bevacizumab (Figure 13). FDA reviewed these data and also did a subgroup analysis of patients who received/did not receive bevacizumab in combination with a chemotherapy doublet as first-line systemic treatment (Table 21). In both analyses, which include a small number of patients and are exploratory, ORR was higher in patients who had not received prior bevacizumab. The reasons for this are unclear.

Tissue Factor

To assess tumor TF expression, the Applicant considered both membrane TF expression and cytoplasm TF expression as % of cells staining positive and also calculated membrane TF H-

score and cytoplasm TF H-score. Cytoplasmic and membrane tissue were first graded for TF expression intensity (0=absent, 1=low, 2=intermediate, and 3=high). Then, a separate H-score was calculated for cytoplasm and for membrane for each evaluable tumor sample. H-scores for cytoplasmic and membrane TF expression were calculated using this equation:
 $H\text{-score} = [1 \times (\% \text{cells with } 1+)] + [2 \times (\% \text{cells with } 2+)] + [3 \times (\% \text{cells with } 3+)]$.

FDA assessed baseline tissue factor (TF) expression in patients enrolled to GCT1015-04. Out of 101 patients, 100 patients had biopsy tissue available. Out of the 100 patients with biopsies, 88 patients had tumor samples evaluated for TF expression with data reported, however the Applicant only considered 80 patients to have tumor samples evaluable for TF expression. This was clarified in an information request to the Applicant sent on April 21, 2021 in which the Applicant stated that there were issues with the quality of IHC for 8 of the 88 samples.

Of the 80 patients with assessable tumor samples, there was one patient with 0% membrane and cytoplasm TF positive tumor who experienced a tumor response and 4 patients not evaluable for response. The Applicant additionally conducted analyses examining tumor response by TF expression as characterized by membrane and cytoplasm H-scores. The Applicant did not find an association between TF expression and tumor response and FDA agrees with this assessment, although noting that data are available from a relatively small number of patients (n=76). Refer to Applicant and FDA assessments in Section 6.3.2 for more information.

Based on the data available, a companion diagnostic is not needed to select patients for treatment with tisotumab vedotin.

Additional Efficacy Considerations

The FDA's Assessment:

No additional considerations.

8.1.5 Integrated Assessment of Effectiveness

Data:

Results are based on a median follow-up time of 10.0 and 4.0 months in GCT1015-04 and GEN701/GCT1015-03, respectively. The follow-up time is longer in GCT1015-04 as long-term survival data were not collected in GEN701/GCT1015-03. The GCT1015-04 primary analysis data cutoff ensured that all responders were followed for a minimum of 6 months. Efficacy in GCT1015-04 as well as GEN701 are described in Section 8.1.4 demonstrating consistency of results in terms of ORR by IRC and PFS. The median OS was 12.1 months (95% CI 9.6-13.9 mos) for subjects treated in GCT1015-04 and was not measured in GEN701.

The Applicant's Position:

In pivotal trial GCT1015-04 (n=101), treatment with tisotumab vedotin resulted in a confirmed ORR of 23.8% (95% CI: 15.9%; 33.3%) by IRC assessment. Responses included 6.9% of subjects with a CR, 16.8% with a PR, and 48.5% with SD, for a DCR of 72.3%. Confirmed responses to tisotumab vedotin were durable, with a median DOR of 8.3 months (95% CI: 4.2; NR) as assessed by IRC and an estimated 62.4% of confirmed responders having a DOR of 6 months or longer in GCT1015-04.

Responses occurred early in treatment and were generally consistent across subgroups, with 95% confidence intervals overlapping with the confirmed ORR of the overall trial population. These results are supported by data from the GEN701 trial.

Benefit was consistently observed across subgroups including histology, ECOG score, region, and in subjects with or without prior treatment with bevacizumab. In addition, responses to tisotumab vedotin were observed regardless of TF expression level in tumor biopsies.

Favorable response data for tisotumab vedotin are further supported by encouraging PFS and OS data. In GCT1015-04, the median PFS by IRC was 4.2 months (range: 0.0+ - 15.1+ months) and median OS was 12.1 months (range: 0.7-17.9+ months).

Overall, the data demonstrate that treatment with tisotumab vedotin resulted in clinically meaningful efficacy in subjects with previously treated recurrent or metastatic cervical cancer, a serious and life-threatening disease with a high unmet need.

The FDA's Assessment:

FDA's conclusions regarding efficacy are primarily based on results from GCT1015-04, a multicenter, single arm trial. FDA did not replicate the Applicant's integrated assessment of efficacy including study GEN701/GCT1015-03 as noted in previous sections. For Study GCT1015-04, the IRC-confirmed ORR in 101 patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy was 23.8% (95% CI: 15.9, 33.3). Median DOR was 8.3 months (95% CI: 4.2, NR). ORR results were generally consistent across subgroups, with the exception of patients ≥ 65 years old. No patients in this age group experienced a tumor response, however FDA notes that only 13 patients ≥ 65 years were enrolled to the trial. Additionally, 63% of patients enrolled on GCT1015-04 had received prior bevacizumab, including 13 of the 24 responders (54%) to tisotumab vedotin. Since doublet chemotherapy in combination with bevacizumab is considered to be the standard of care regimen for first-line metastatic cervical cancer in the US, this factor indicates that the study population enrolled on GCT1015-04 is overall reflective of the general population of patients with cervical cancer in the US. Finally, FDA did not consider PFS and OS results in the efficacy assessment as these time-to-event endpoints are uninterpretable due to the lack of a comparator arm in a single-arm trial.

Patients with advanced cervical cancer who progress following chemotherapy in the recurrent or metastatic setting represent an area of unmet medical need and treatment options are

limited to single agent chemotherapies, with response rates generally ranging 5-21%. As mentioned, the majority of patients enrolled to GCT1015-04 had received prior treatment with a chemotherapy doublet with bevacizumab. Data on the efficacy of commonly used single agent chemotherapies in the post-bevacizumab setting is lacking but is likely to be similar to or worse than the efficacy of the same agents in patients who had not received prior bevacizumab in the same setting. Given the data from GCT1015-04, and considering the current therapeutic landscape of metastatic cervical cancer, FDA considers the ORR of 24% with a median DOR of 8.3 months to be an improvement over available therapies. Therefore, the review team concludes that these results are reasonably likely to predict the clinical benefit of tisotumab in patients with recurrent or metastatic cervical cancer following chemotherapy and recommends the current BLA for accelerated approval Confirmation of clinical benefit will be based on results from the ongoing randomized clinical trial, innovaTV 301, which is comparing tisotumab vedotin to investigator's choice chemotherapy.

8.2 Review of Safety

8.2.1 Safety Review Approach

Data:

The safety profile summarized in this application consists of data from 4 clinical trials of tisotumab vedotin monotherapy including 272 unique subjects. All subjects received the recommended starting dose of 2.0 mg/kg of tisotumab vedotin 1Q3W. The number of subjects in each of the 4 safety analysis groups is described below.

The data from these trials are grouped into 4 safety analysis sets:

- The GCT1015-04 group includes the 101 subjects with cervical cancer from the pivotal trial.
- Pool 1 (Supportive Cervical) includes 57 subjects with cervical cancer tumor types from the GEN701 Cohort Expansion part, GEN702 Cohort Expansion part, and GCT1015-03 trials. This pool evaluates safety in subjects with cervical cancer included in trials of tisotumab vedotin other than GCT1015-04.
- Pool 2 (All Cervical) combines GCT1015-04 with Pool 1 for a total of 158 subjects with cervical cancer.
- Pool 3 (All Tumor Types) adds the 114 subjects with non-cervical tumor types from GEN701 and GEN702 to the All Cervical cohort for a total of 272 subjects. This population is intended to represent the safety profile of tisotumab vedotin in the largest possible group of subjects who received the RP2D. Inclusion of Pool 3 allows assessments of safety in subjects with a diverse set of tumor types and increases the total number of subjects.

The primary evidence of safety is derived from the GCT1015-04 data as the subjects represent a more homogeneous patient population than the pooled data. In addition, all subjects in GCT1015-04 received the same protocol-specified mitigation measures and dose modification

requirements for safety. Other key features in this pivotal trial compared to the pooled analysis data sets that incorporate data from other trials include:

- Limitations in the number of prior therapies received (no more than 2 prior lines)
- Exclusion of subjects who were refractory to their primary therapies and/or did not receive a first-line standard-of-care therapy for recurrent or metastatic cervical cancer
- Treatment of all subjects with comprehensive and current protocol-defined AE management guidelines, including the most up to date recommended dose modifications for ocular AEs and peripheral neuropathy.

Thus, the pivotal trial data from GCT1015-04 represent the core safety population relevant to the proposed indication.

Safety data from GCT1015-04 are presented side-by-side in tabular format with the 3 pooled safety analysis sets. Safety data for each individual trial are presented in their respective individual CSRs in (m5.3.5).

Additional SAE data from the Global Safety Database for ongoing trials GCT1015-04 and SGNTV-001 from the CSR data cutoff dates through 16 August 2020 are provided with the respective CSRs in (m5.3.5.2) as SAE listings. Cumulative SAE listings from the Global Safety Database for ongoing trials GCT1015-05, GCT1015-06, and SGNTV-002 through 16 August 2020 are included in (m5.3.5.4). Safety data including ECG and QTcF results for SGNTV-001 through 22 August 2019 are presented in an abbreviated CSR (m5.3.5.2 SGNTV-001 CSR) and immunogenicity data (ie, ADA) from this trial also contribute to a combined population ADA analysis.

The Applicant's Position:

A comprehensive review of safety data pertinent to tisotumab vedotin was conducted across 4 clinical studies including subjects with recurrent or metastatic cervical cancer with disease progression on or after doublet chemotherapy with bevacizumab as well as other tumor types. Events of interest were well-characterized based on a thorough analysis of all available safety data in subjects, including by prior radiotherapy, bevacizumab, and prior lines of systemic regimen.

The safety data were consistent across the pooled analyses and demonstrate an acceptable safety profile of tisotumab vedotin monotherapy for the treatment of patients with recurrent and metastatic cervical cancer with disease progression on or after chemotherapy.

The FDA's Assessment:

FDA's safety analysis is primarily based on results from GCT1015-04, a single arm trial of tisotumab vedotin in 101 patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy. One reason for this is that the GCT1015-04 protocol contains the most up-to-date risk mitigation strategies and dose modification strategies for tisotumab vedotin. To assess adverse events of special interest (AESIs), FDA additionally reviewed data from the Pool 2 population which included a total of 158 patients with cervical cancer treated at the recommended dose of tisotumab vedotin across trials. FDA chose this population to assess AESIs in a slightly larger population of patients with cervical cancer. To

assess very infrequent safety events, FDA evaluated data from the Pool 3 population which included patients with other tumor types treated at the recommended dose of tisotumab vedotin across trials (n=272). FDA did not review all safety data submitted from these other trials. In the sections below, FDA notes which data were used to support safety conclusions.

FDA’s safety analysis focused on deaths, and treatment-emergent adverse events (TEAEs) including serious TEAEs, TEAEs leading to dose modifications including discontinuations, grade ≥3 TEAEs, and AESIs. AESIs for tisotumab vedotin include ocular toxicity, peripheral neuropathy, hemorrhage, infusion-related reactions, and pneumonitis.

The safety results in this section are based on data submitted with an initial data cutoff date of February 6, 2020. FDA additionally reviewed safety data from the 90-day safety update with a data cutoff date of September 25, 2020. The safety update did not include new safety signals; other key findings from the safety update are discussed in the appropriate sections below. Refer to Section 8.2.10 for FDA’s overall safety assessment.

Overall Exposure

Data:

A total of 272 subjects have received at least 1 dose of tisotumab vedotin. All subjects received the recommended dose of 2.0 mg/kg of tisotumab vedotin 1Q3W. The number of subjects in each safety analysis group is provided in Table 22.

Table 22: Integrated Safety Analysis Groups

Safety Analysis Group	Patient Population	Trials included	Total number of subjects included
GCT1015-04	Cervical cancer subjects who received 2.0 mg/kg 1Q3W tisotumab vedotin monotherapy in GCT1015-04	GCT1015-04	101
Pool 1 Supportive cervical cancer	Cervical cancer subjects who received 2.0 mg/kg 1Q3W tisotumab vedotin monotherapy in completed trials other than GCT1015-04	GEN701 expansion, GEN702 expansion, GCT1015-03	57
Pool 2 All cervical cancer	All cervical cancer subjects who received 2.0 mg/kg 1Q3W tisotumab vedotin monotherapy	GCT1015-04, GEN701 expansion, GEN702 expansion, GCT1015-03	158
Pool 3 All tumor types	Subjects with any tumor type who received 2.0 mg/kg 1Q3W tisotumab vedotin monotherapy	GCT1015-04, GEN701 expansion, GEN702 expansion, GCT1015-03	272

Tisotumab vedotin dose was calculated based on subject weight, with dosage capped at a weight equivalent of 100 kg (trial GCT1015-04) or a body mass index (BMI) of 30 kg/m² (trials

GEN701, GEN702, and GCT1015-03). In the patient populations included in these analyses the dose administered was 2.0 mg/kg 1Q3W, meaning the maximum dose per infusion was capped at 200 mg tisotumab vedotin for the GCT1015-04 trial. For trials that implemented a cap based on BMI, dose was capped at the weight that, combined with the subject’s height, would lead to a BMI of 30 kg/m².

Tisotumab vedotin administration and exposure is summarized in [Table 23](#).

Table 23: Summary of Extent of Tisotumab Vedotin Exposure

	Pivotal Cervical (GCT1015-04) (N=101)	Supportive Cervical (Pool 1) (N=57)	All Cervical (Pool 2) (N=158)	All Tumor Types (Pool 3) (N=272)
Duration of exposure to tisotumab vedotin (months)				
n	101	57	158	272
Mean (STD)	4.59 (3.07)	3.53 (2.53)	4.20 (2.92)	3.61 (2.77)
Median	4.24	3.06	3.70	2.81
Min, Max	0.7, 16.0	0.6, 10.9	0.6, 16.0	0.4, 16.0
Number of cycles received				
n	101	57	158	272
Mean (STD)	6.2 (4.2)	4.8 (3.2)	5.7 (3.9)	4.9 (3.6)
Median	6.0	4.0	5.0	4.0
Min, Max	1, 21	1, 14	1, 21	1, 21
Actual cumulative dose (mg/kg)				
n	101	57	158	272
Mean (STD)	11.6 (6.8)	9.1 (6.0)	10.7 (6.6)	9.1 (6.2)
Median	10.7	8.0	10.0	8.0
Min, Max	2, 33	1, 29	1, 33	1, 33
Relative dose intensity (RDI) (%)				
n	101	57	158	272
Mean (STD)	90.9 (12.7)	91.0 (11.9)	90.9 (12.4)	90.9 (12.5)
Median	95.9	96.2	96.1	96.6
Min, Max	44, 114	56, 107	44, 114	44, 114

Source: ISS Table 10.1.4

The Applicant’s Position:

Overall exposure is adequate to support the characterization of the safety profile of tisotumab vedotin. Median duration of treatment with tisotumab vedotin in the GCT1015-04 pivotal trial was 4.24 months (range 0.7 to 16.0 months) and median relative dose intensity was 95.9% (range, 44% to 114%). Relative dose intensity was consistent across groups (>90%) and showed that subjects generally received the drug as planned across safety analysis groups.

The FDA’s Assessment:

FDA agrees with the Applicant’s description of exposure to tisotumab vedotin on GCT1015-04. FDA did not independently verify exposure to tisotumab vedotin in the other safety populations. FDA agrees that exposure is adequate to characterize safety of tisotumab vedotin.

Relevant characteristics of the safety population:

Data:

Demographic characteristics are summarized by safety analysis group in [Table 24](#).

Table 24: Summary of Demographic Characteristics

	Pivotal Cervical (GCT1015-04) (N=101)	Supportive Cervical (Pool 1) (N=57)	All Cervical (Pool 2) (N=158)	All Tumor Types (Pool 3) (N=272)
Age (years), n	101	57	158	272
Mean (STD)	50.7 (10.7)	46.2 (11.9)	49.0 (11.3)	54.4 (12.0)
Median	50.0	46.0	48.0	56.0
Min, Max	31, 78	21, 73	21, 78	21, 79
Age Category, n (%)				
<65	88 (87.1)	53 (93.0)	141 (89.2)	209 (76.8)
>=65	13 (12.9)	4 (7.0)	17 (10.8)	63 (23.2)
Sex, n (%)				
Male	0	0	0	46 (16.9)
Female	101 (100)	57 (100)	158 (100)	226 (83.1)
Geographic Region, n (%)				
United States	15 (14.9)	12 (21.1)	27 (17.1)	40 (14.7)
Europe	86 (85.1)	45 (78.9)	131 (82.9)	232 (85.3)
Race, n (%)				
Asian	2 (2.0)	3 (5.3)	5 (3.2)	7 (2.6)
Black or African American	1 (1.0)	1 (1.8)	2 (1.3)	3 (1.1)
Native Hawaiian or Other Pacific Islander	0	0	0	1 (0.4)
White	96 (95.0)	51 (89.5)	147 (93.0)	254 (93.4)
Other	2 (2.0)	0	2 (1.3)	4 (1.5)
Missing	0	2 (3.5)	2 (1.3)	3 (1.1)
Ethnicity, n (%)				
Hispanic or Latino	6 (5.9)	0	6 (3.8)	8 (2.9)
Not Hispanic or Latino	95 (94.1)	55 (96.5)	150 (94.9)	262 (96.3)
Missing	0	2 (3.5)	2 (1.3)	2 (0.7)

Source: ISS Table 10.1.2

The baseline characteristics of the subjects in GCT1015-04 are generally representative of patients with recurrent or metastatic cervical cancer who have received at least 1 prior systemic therapy (Table 25). In the pivotal GCT1015-04 trial, 59 subjects (58.4%) had an ECOG status of 0 and 69 subjects (68.3%) had squamous cell carcinoma (Table 25).

Baseline characteristics were similar in Pool 2 (All Cervical) and there were few notable differences compared to the other pooled analysis groups. Compared to GCT1015-04, fewer subjects had an ECOG status of 0 in Pool 1 (40.4% vs 58.4%) and the proportion of subjects with squamous cell carcinoma was lower in Pool 1 (49.1% vs 68.3%). The bulk of the remaining subjects had adenocarcinoma histology, 26.7% in GCT1015-04 and 31.6% in Pool 1. Each trial enrolled the intended patient populations as defined by prior therapies.

Table 25: Summary of Baseline Disease Characteristics

	Pivotal Cervical (GCT1015-04) (N=101)	Supportive Cervical (Pool 1) (N=57)	All Cervical (Pool 2) (N=158)	All Tumor Types (Pool 3) (N=272)
Cancer Types, n (%)				
Cervix	101 (100)	57 (100)	158 (100)	158 (58.1)
Bladder	0	0	0	15 (5.5)
Endometrium	0	0	0	14 (5.1)
Esophagus	0	0	0	15 (5.5)
Lung (NSCLC)	0	0	0	15 (5.5)
Ovary	0	0	0	37 (13.6)
Prostate	0	0	0	18 (6.6)
ECOG Performance Status, n (%)				
0	59 (58.4)	23 (40.4)	82 (51.9)	129 (47.4)
1	42 (41.6)	34 (59.6)	76 (48.1)	143 (52.6)
Time from last systemic regimen to start of tisotumab vedotin (months), n	101	57	158	272
Mean (STD)	6.08 (6.75)	6.22 (9.57)	6.13 (7.86)	5.58 (6.91)
Median	3.48	3.35	3.42	3.29
Min, Max	0.9, 48.4	0.7, 65.0	0.7, 65.0	0.5, 65.0
Histology, n (%)				
Squamous Cell Carcinoma	69 (68.3)	28 (49.1)	97 (61.4)	-
Adenocarcinoma	27 (26.7)	18 (31.6)	45 (28.5)	-
Adenosquamous Carcinoma	5 (5.0)	6 (10.5)	11 (7.0)	-
Other	0	5 (8.8)	5 (3.2)	-
Prior cancer therapy, n (%)				
Any radiation therapy	82 (81.2)	44 (77.2)	126 (79.7)	174 (64.0)
Systemic therapy	101 (100)	57 (100)	158 (100)	272 (100)
Any bevacizumab	70 (69.3)	40 (70.2)	110 (69.6)	-
Any paclitaxel	101 (100)	53 (93.0)	154 (97.5)	-

Source: ISS Table 10.1.3

The Applicant’s Position:

Demographic and baseline characteristics of the subjects in GCT1015-04 are generally representative of patients with recurrent or metastatic cervical cancer who have received at least one prior systemic therapy. The demographic and baseline characteristics were similar among cervical patients across studies as indicated by Pools 1 and 2. With the exception of having more subjects over 65 years of age in Pool 3, the pooled safety analysis sets had no notable differences in demographics.

The FDA’s Assessment:

FDA agrees with the Applicant’s statement that the GCT1015-04 population is generally representative of a US-based patient with recurrent or metastatic cervical cancer with respect to disease and treatment characteristics. However, FDA notes that a relatively small number of Hispanic or Latino patients were enrolled, and only one Black patient was enrolled to GCT1015-04. This contrasts with the fact that there is an increased incidence of cervical cancer,

particularly advanced/ metastatic disease, in Hispanic or Latino patients and Black patients, as compared to white patients in the US. Despite that the study did not enroll a racially diverse population, the review team still determined that the results, based upon other important disease characteristics and prior therapies, are applicable to the cervical cancer population treated in the US, and supportive of FDA approval.

Otherwise, FDA agrees with the Applicant's description and assessment of the safety population in GCT1015-04. FDA notes that Pool 3 includes a larger proportion of patients aged 65 and older compared to the GCT1015-04 population.

Adequacy of the safety database:

Data:

The sponsor is providing safety data from a total of 272 subjects who received at least 1 dose of tisotumab vedotin 2.0 mg/kg 1Q3W. The GCT1015-04 pivotal trial evaluated tisotumab vedotin monotherapy in subjects with previously treated, recurrent or metastatic cervical cancer. All 101 subjects in this GCT1015-04 safety analysis set received tisotumab vedotin at the recommended dose of 2.0 mg/kg 1Q3W.

The Applicant's Position:

The safety database is adequate for an informed assessment of the safety profile of tisotumab vedotin monotherapy in subjects with previously treated, recurrent or metastatic cervical cancer. Additional subjects with other tumor types were included in supportive pooled analyses. The overall incidence of TEAEs was similar across the safety analysis groups and the events observed are considered to be representative of the overall safety profile.

The FDA's Assessment:

FDA agrees with the Applicant that the safety database is adequate for assessment of the tisotumab vedotin safety profile.

8.2.2 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:

Steps taken to ensure the accuracy and reliability of data in the GCT1015-04, GEN701, GEN702, and GCT1015-03 trials included selection of qualified trial sites and investigators, GCP training of trial personnel, and protocol training before initiation of the trial. In addition, site monitoring visits to review source documents against the eCRF were performed by the CRO for each trial, with sponsor oversight of the CRO's duties as per standard operating procedure. Investigators were updated on an ongoing basis on trial progress, important trial milestones, and specific protocol specified requirements via newsletters and flash letters. Data collected by external vendors (eg, laboratory results, ECG results etc. excluding central imaging data) were transferred to the sponsor on an ongoing basis and reviewed, together with other data, for

accuracy and completeness. Any discrepancies were resolved with the trial site. The sponsor was blinded to IRC data with the exception of a limited number of personnel, according to the protocol-specific blinding plan, who were unblinded when preparing for database lock in order to ensure data quality and completeness of the IRC dataset.

Prior to locking the database in the GCT1015-04 trial, a thorough review was performed to enhance the quality and ensure completeness. The database for the Expansion Part of the GEN701 trial was locked 20-Jan-2020. The database was reopened and relocked on 26-Mar-2020 for inclusion of corrected data on ADAs. The database was reopened and relocked on 25-Nov-2020 based on a data review that resulted in data queries to sites and subsequent data changes.

Site audits were conducted in all trials as outlined in the respective CSRs.

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:

FDA agrees with the Applicant's assessment of data integrity based on our own review and clinical inspections from the FDA Office of Scientific Investigations (OSI). Please see Section 4.1 for additional information.

Categorization of Adverse Event

Data:

N/A

The Applicant's Position:

Safety was assessed by the surveillance and recording of AEs (including SAEs and AEs of special interest [AESIs]), clinical laboratory test results, ECGs, ophthalmology examinations, and vital signs.

Adverse Events:

A treatment-emergent adverse event (TEAE) is defined as a newly occurring or worsening AE that is reported on or after the first dose of trial drug and with onset date on or before 30 days after the last dose of trial drug. TEAEs are coded to standard preferred terms and system organ classifications (SOCs) using the Medical Dictionary for Regulatory Activities (MedDRA, Version 22.1) for all trials at the integrated summary of safety (ISS) level. All AEs, including SAEs, are considered TEAEs unless otherwise specified. TEAEs that were associated with disease progression were excluded from the safety analysis (Preferred terms of disease progression, malignant neoplasm progression, metastases to CNS, oesophageal cancer metastatic, and pericardial effusion malignant). In the event that the frequencies for multiple preferred terms were numerically equal, the preferred terms were presented in alphabetical order. Sort order was determined by the GCT1015-04 column.

Treatment-related TEAEs refer to events that were assessed by the investigator as "possibly

related” or “related” to tisotumab vedotin. If a subject had multiple events occurring in the same SOC or preferred term, it was counted as a related event if at least 1 of the occurrences was considered to be “possibly related” or “related” to tisotumab vedotin.

TEAEs were investigator-assessed for severity grading and seriousness. If an event changed in National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE) grade or severity, the event with the worst/highest severity was counted. Missing NCI CTCAE grade was tabulated as “missing.”

TEAE grades are based on the NCI CTCAE grades as reported in each trial. NCI CTCAE version 4.03 was used in GEN701, GEN702, GCT1015-03 and version 5.0 was used in GCT1015-04. In TEAE summary tables, a subject was counted only once for each preferred term at maximum grade.

Adverse Events of Special Interest:

AESIs have been identified for tisotumab vedotin based on potential or theoretical risk to patients from the mechanism of action of tisotumab vedotin, known biology or tissue factor, and observed findings in clinical trial data. Three AESIs have been identified: ocular AEs, peripheral neuropathy, and bleeding AEs.

Search criteria for these AESIs are based on standardized MedDRA queries (SMQs), whenever possible, or the most relevant level of the MedDRA hierarchy that most suitably and completely characterizes the event at issue.

Ophthalmological Examinations:

Baseline ophthalmology examinations were to be performed by qualified ophthalmologists during screening. Such examinations were implemented from the start in pivotal trial GCT1015-04 and were incorporated later through amendments to other trials, eg, GEN701 Protocol Amendment 12 (22 December 2016). In addition, subjects were to be referred for additional ophthalmological examinations if ocular symptoms occurred or in the case of objective findings from scheduled eye exams at the site, if performed.

In addition to baseline and unscheduled exams, some trials included prespecified ophthalmological exams on trial. These included GEN701 (exams on Day 8 of every other cycle and at end of trial) and GEN702 (exams in Cycles 1 to 9 and at end of treatment). Assessments performed included visual acuity, Schirmer’s test, slit lamp, inspections of the conjunctivas and corneas including staining, intraocular pressure, and funduscopy. Further details on ophthalmological exams are provided in the trial protocols.

Electrocardiograms:

ECG variables were summarized using mean, standard deviation (STD), minimum, maximum, and median for each analysis group at 2 time points: baseline and end of treatment or safety follow up visit, including changes from baseline.

Central reviewer assessed the 12 lead ECG to summarize the number and percentage of subjects with normal, not clinically significant abnormal, and clinically significant abnormal

results for each time point. Calculation of QT, PR, RR, and QRS intervals was conducted in trials GCT1015-04 and SGNTV001. Further details on the ECGs can be found in the trial protocols.

The FDA's Assessment:

FDA agrees with the Applicant's description of adverse events on GCT1015-04. TEAEs were defined as AEs occurring after the first dose of tisotumab vedotin to within 30 days after the last dose. FDA's safety assessment focused on the frequency and severity of all TEAEs with particular focus on TEAEs leading to death, SAEs, grade ≥ 3 TEAEs, TEAEs leading to dose modifications, and the three AESIs identified by the Applicant: ocular toxicity, peripheral neuropathy, and bleeding/hemorrhage. FDA also considered pneumonitis an AESI given reports of pneumonitis with other "vedotin" containing products.

FDA did not consider treatment-related AEs in the safety analysis, as attribution is subjective and challenging.

Data:

N/A.

The Applicant's Position:

Baseline values for clinical laboratory tests are defined as the last measurements taken before initial trial drug administration. A comprehensive list of laboratory parameters collected in each trial can be found in the CSRs.

The following analyses were performed on the 4 safety analysis groups as part of the integrated safety analysis:

- Incidence of potentially drug-induced liver laboratory abnormalities (aspartate transaminase (AST)/alanine transaminase (ALT) $>3 \times$ upper limit of normal (ULN) + Total Bilirubin $>2 \times$ ULN)
- CTCAE grade shift from baseline to highest post-baseline for serum chemistry, hematology, and coagulation

Laboratory results were graded using NCI CTCAE (version 4.03 for GEN701 and GEN702, and version 5.0 for GCT1015-04).

The FDA's Assessment:

FDA agrees with the Applicant's description of laboratory assessments on GCT1015-04.

8.2.3 Safety Results

Deaths

Data:

TEAEs leading to death (ie, Grade 5 TEAEs) were reported in 4 subjects (4.0%) in GCT1015-04

(Table 26). Deaths were due to events of septic shock, ileus, and death due to unknown causes in 2 subjects, 1 of which is represented in Table 26 with a cause of death of “unknown” and 1 of which is represented as “other”). Both events of death due to unknown causes were reported as “death” and arose from subjects who died in a home care setting; no autopsy was performed. The event of fatal ileus was secondary to clinical disease progression and the subject died during surgical operation for this event; thus this death was considered due to deterioration of underlying cancer by the investigator. One additional grade 5 TEAE of general physical health deterioration was reported in Pool 3 (ISS Table 10.2.9).

The only death considered possibly related to tisotumab vedotin in GCT1015-04 was due to septic shock. The death involved a 64-year-old female with cervical cancer and metastases to the lung, liver and lymph nodes and no relevant medical history who was admitted to intensive care 10 days after the first dose of tisotumab vedotin with fever, general malaise, and grade 4 neutropenic sepsis. During hospitalization, the subject’s neutrophil count spontaneously improved and the event of neutropenic sepsis resolved (day 15). However, the subject was diagnosed with infectious colitis (day 12) and developed septic shock (day 17) 1 day after a colonoscopy with biopsy was performed. The subject died on the 8th day of hospitalization (day 20) despite supportive treatment with antibiotics. No autopsy was performed.

A summary of deaths within 30 days of last study treatment is provided in Table 26. In GCT1015-04, 8 subjects (7.9%) died within 30 days of last study treatment; 5 of these deaths were due to progression of underlying disease. All the deaths in Pool 1 (1 death), 6 of the 9 deaths in Pool 2, and 8 of 11 deaths in Pool 3 were due to progression of the underlying disease. Note that subjects were not followed for survival in the GEN701 and GEN702 studies.

Narrative summaries for each TEAE leading to death are provided in the respective CSRs.

In GCT1015-04, 2 subjects died due to non-TEAEs (cardiac arrest and malignant neoplasm progression) occurring >30 days after last dose and thus were not reflected in the ISS (GCT1015-04 CSR Table 14.03.14; Listing 16.02.03.04). The event of cardiac arrest was considered treatment-related by the investigator. This case concerns a 61-year-old subject with cervical cancer and metastases to the abdomen (carcinosis). Medical history included heavy smoking, asthmatic bronchitis (treated with salbutamol inhalation), and low BMI (approximately 15). Fourteen days after first dose of tisotumab vedotin, the subject started experiencing shortness of breath. A CT scan of the thorax performed at Day 21 showed several pulmonary embolisms bilaterally and treatment with anticoagulation was initiated. The subject was discharged the same day and continued anticoagulation therapy at home. The subject was followed-up as an outpatient. Planned trial imaging performed on Day 36 showed worsening of peritoneal disease, worsening ascites, and clots in both lungs. A paracentesis was planned to occur on Day 42; however, on Day 41 the subject died at home. An autopsy showed cervical cancer with direct spread to soft tissue in the small pelvis and peritoneum to be the underlying cause of death.

Table 26: Summary of Deaths within 30 Days of Last Study Treatment

	Pivotal Cervical (GCT1015-04) (N=101) n (%)	Supportive Cervical (Pool 1) (N=57) n (%)	All Cervical (Pool 2) (N=158) n (%)	All Tumor Types (Pool 3) (N=272) n (%)
Deaths within 30 days of last study treatment	8 (7.9)	1 (1.8)	9 (5.7)	11 (4.0)
Deterioration of Underlying Cancer Disease	5 (5.0)	1 (1.8)	6 (3.8)	8 (2.9)
Adverse Event	2 (2.0)	0	2 (1.3)	2 (0.7)
Septic Shock	1 (1.0)	0	1 (0.6)	1 (0.4)
Unknown Cause of Death	1 (1.0)	0	1 (0.6)	1 (0.4)
Other	1 (1.0)	0	1 (0.6)	1 (0.4)

Source: Adapted from ISS Table 10.2.71

The Applicant’s Position:

TEAEs leading to death were infrequent. Most TEAEs leading to death were considered not related to tisotumab vedotin therapy. The single case of a drug-related AE leading to death was confounded by comorbidities and underlying disease.

The FDA’s Assessment:

FDA performed an independent analysis of all patient deaths due to TEAEs and selected other patient deaths that occurred in GCT1015-04. In GCT1015-04, there were 58 patients who died, including 8 deaths on study treatment and 50 deaths post-treatment. Of the 8 deaths which occurred on study treatment, 4 were due to progression of disease, and 4 were due to an adverse event. Of the 50 deaths which occurred post-treatment, 48 were due to progression of disease, 1 was due to euthanasia due to progression of disease, and 1 was due to an adverse event. FDA reviewed narratives for all 4 deaths due to adverse events which occurred on study treatment. FDA attributes these 4 deaths from adverse events to septic shock related to tisotumab vedotin, pneumonitis potentially related to tisotumab vedotin, sudden death of uncertain cause, and multisystem organ failure related to ileus. These 4 deaths are included in Section 6.1 of product labeling. The narratives describing the deaths are summarized below:

Patient ID: GCT1015-04- (b) (6) Septic shock

This 64 yo woman had metastatic SCC of the cervix involving liver, lung, and pelvic and extra-pelvic lymph nodes at study entry. She received the first cycle of tisotumab vedotin. On study day 10, she was admitted to the ICU with neutropenic sepsis and received antibiotics and antifungal treatment. CT showed signs of colitis and she underwent colonoscopy on Day 12 and Day 16. Pathologic samples from each colonoscopy confirmed diagnosis of colitis. On study day 17, patient developed septic shock, and on day 20 she died. FDA agrees with the investigator and Sponsor that cause of death was septic shock related to tisotumab vedotin.

Patient ID: GCT1015-04- (b) (6) Sudden death

This 59 yo woman with history of atrial fibrillation and hypothyroidism had metastatic SCC of the cervix involving the cervix, peritoneum, and extra-pelvic lymph nodes at study entry. She

received three cycles of tisotumab vedotin. On study day 43, CT showed stable disease. On study day 47, she died at home after reporting “feeling weak” for the past 2 or 3 days. There was no autopsy performed and cause of death was reported as unknown. The investigator and Sponsor state that death was not related to tisotumab vedotin. FDA considers it impossible to make a determination and cannot make a more specific determination regarding cause of death beyond sudden death.

Patient ID: GCT1015-04- (b) (6) Pneumonitis

This 70 yo woman with history of type 2 diabetes mellitus had metastatic SCC of the cervix involving lungs, bone, rectum, and pelvis. She received two cycles of tisotumab vedotin. On study day 27, she was admitted to the hospital with fever and shortness of breath and was diagnosed with pneumonitis based on chest CT. CT also showed lung metastases and a L-sided pleural effusion, size unspecified. She received treatments with antibiotics, prednisone, and furosemide. The narrative states that the patient was believed to be at the end-of-life and was discharged from the hospital. It is not clear if she was discharged to hospice, but on day 42 she received palliative sedation with morphine and on day 45 she died. FDA disagrees with the investigator and Sponsor and thinks that pneumonitis and death are possibly related to tisotumab vedotin.

Patient ID: GCT1015-04- (b) (6) Multiorgan failure and ileus

This 59 yo woman had metastatic SCC of the cervix involving the cervix, kidney, and extra-pelvic lymph nodes. She received thirteen cycles of tisotumab vedotin. On study day 271, she experienced nausea, vomiting, abdominal pain, and diarrhea, and was diagnosed with ileus. She was treated with a partial intestinal resection and during surgery, she developed multiorgan failure and circulatory instability, and died. The investigator attributed her death to deterioration of underlying cancer disease, ileus, multiorgan failure, and circulatory instability. FDA agrees with this description and attributes this patient’s death to multiorgan failure.

Serious Adverse Events

Data:

SAEs reported in $\geq 1\%$ of subjects in GCT1015-04 or $\geq 2\%$ of subjects in Pool 3 are presented in Table 27.

Table 27: Treatment Emergent SAEs Reported in ≥1% of Subjects in GCT1015-04 or ≥2% of Subjects in Pool 3 by PT

Preferred Term	Pivotal Cervical (GCT1015-04) (N=101) n (%)	Supportive Cervical (Pool 1) (N=57) n (%)	All Cervical (Pool 2) (N=158) n (%)	All Tumor Types (Pool 3) (N=272) n (%)
Subjects with any SAE	43 (42.6)	25 (43.9)	68 (43.0)	113 (41.5)
Pneumonia	4 (4.0)	0	4 (2.5)	5 (1.8)
Constipation	3 (3.0)	2 (3.5)	5 (3.2)	7 (2.6)
Pyrexia	3 (3.0)	2 (3.5)	5 (3.2)	6 (2.2)
Anaemia	2 (2.0)	1 (1.8)	3 (1.9)	5 (1.8)
Death	2 (2.0)	0	2 (1.3)	2 (0.7)
Ileus	2 (2.0)	0	2 (1.3)	2 (0.7)
Peripheral sensorimotor neuropathy	2 (2.0)	2 (3.5)	4 (2.5)	5 (1.8)
Pneumonitis	2 (2.0)	0	2 (1.3)	2 (0.7)
Septic shock	2 (2.0)	0	2 (1.3)	2 (0.7)
Urinary tract infection	2 (2.0)	2 (3.5)	4 (2.5)	6 (2.2)
Urinary tract obstruction	2 (2.0)	1 (1.8)	3 (1.9)	3 (1.1)
Vaginal haemorrhage	2 (2.0)	1 (1.8)	3 (1.9)	3 (1.1)
Abdominal pain	1 (1.0)	2 (3.5)	3 (1.9)	6 (2.2)
Vomiting	1 (1.0)	4 (7.0)	5 (3.2)	7 (2.6)

Source: Adapted from ISS Table 10.2.10

In GCT1015-04, 13 subjects (12.9%) experienced at least 1 treatment-related SAE (ISS Table 10.2.11). The rate of treatment related SAEs was similar between GCT1015-04 and all cervical cancer subjects in Pool 2, but was lower in GCT1015-04 (12.9%) than in the other pooled analysis groups (22.8% in Pool 1 and 20.2% in Pool 3).

The Applicant’s Position:

Overall, the incidence of SAEs in GCT1015-04 was similar to the pooled analysis groups; nearly half of all tisotumab vedotin treated subjects (41.5%) experienced at least 1 SAE. The incidence of serious pneumonia was less frequent in the pooled analyses compared to GCT1015-04 but otherwise the rates of SAEs were similar across all groups. Across all safety analysis groups, between 12.9% and 22.8% of subjects experienced treatment related SAEs.

The FDA’s Assessment:

FDA conducted an independent analysis of SAEs which occurred on GCT1015-04. SAEs occurred frequently, affecting 43% of patients. The most common SAEs (≥3%) in FDA’s analysis were ileus (6%), hemorrhage (5%), pneumonia (4%), sepsis (3%), constipation (3%), pyrexia (3%), and peripheral neuropathy (3%). Slight differences in the frequencies of SAEs between FDA’s analysis and the Applicant’s analysis are due to differences in grouping of preferred terms.

Ileus is a grouped term containing the following preferred terms: ileus, subileus, large intestinal obstruction, intestinal obstruction, small intestinal obstruction. Sepsis is a grouped term containing the following preferred terms: septic shock, urosepsis, and neutropenic sepsis. For grouping for hemorrhage and peripheral neuropathy, refer to the table below in “Treatment

Emergent Adverse Events and Adverse Reactions.”

FDA does not consider attribution (treatment-related versus not) in analysis of SAEs as this is a subjective assessment and determination of causality is challenging.

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

TEAEs leading to discontinuation of treatment in at least 1 subject are presented in Table 28.

Table 28: TEAEs Resulting in Treatment Discontinuation Reported in ≥1% of Subjects in GCT1015-04 by PT

Preferred Term	Pivotal Cervical (GCT1015-04) (N=101) n (%)	Supportive Cervical (Pool 1) (N=57) n (%)	All Cervical (Pool 2) (N=158) n (%)	All Tumor Types (Pool 3) (N=272) n (%)
Subjects with any event	13 (12.9)	12 (21.1)	25 (15.8)	64 (23.5)
Subjects with TR events	12 (11.9)	12 (21.1)	24 (15.2)	62 (22.8)
PTs resulting in discontinuation				
Peripheral sensorimotor neuropathy	2 (2.0)	1 (1.8)	3 (1.9)	4 (1.5)
Peripheral sensory neuropathy	2 (2.0)	1 (1.8)	3 (1.9)	8 (2.9)
Ulcerative keratitis	2 (2.0)	1 (1.8)	3 (1.9)	3 (1.1)
Conjunctivitis	1 (1.0)	3 (5.3)	4 (2.5)	9 (3.3)
Corneal scar	1 (1.0)	0	1 (0.6)	1 (0.4)
Entropion	1 (1.0)	0	1 (0.6)	1 (0.4)
Erythema	1 (1.0)	0	1 (0.6)	1 (0.4)
Keratitis	1 (1.0)	0	1 (0.6)	1 (0.4)
Nausea	1 (1.0)	0	1 (0.6)	2 (0.7)
Neuropathy peripheral	1 (1.0)	4 (7.0)	5 (3.2)	9 (3.3)
Neutropenic sepsis	1 (1.0)	0	1 (0.6)	2 (0.7)
Peripheral motor neuropathy	1 (1.0)	2 (3.5)	3 (1.9)	4 (1.5)
Small intestinal obstruction	1 (1.0)	0	1 (0.6)	1 (0.4)
Trichiasis	1 (1.0)	0	1 (0.6)	1 (0.4)
Vomiting	1 (1.0)	0	1 (0.6)	1 (0.4)

Source: Adapted from ISS Table 10.2.6.1 and ISS Table 10.2.17

The Applicant’s Position:

Fewer discontinuations occurred in GCT1015-04 than the other safety analysis pools; this may be a result of the safety-related dose modification criteria in the GCT1015-04 trial, which may have allowed subjects in GCT1015-04 to remain on treatment longer. The events and rates observed are representative of the overall safety profile. Discontinuations due to drug-related TEAEs were infrequent, with peripheral neuropathy being the most common reason.

The FDA’s Assessment:

FDA conducted an independent analysis of TEAEs leading to discontinuation in GCT1015-04. The most common TEAEs leading to treatment discontinuation (≥1%) in FDA’s analysis were peripheral neuropathy (5%), corneal adverse reactions (4%), conjunctival adverse reactions (1%), eyelid disorders (1%), ileus (1%), nausea (1%), rash (1%), sepsis (1%), and vomiting (1%).

Differences between frequencies in FDA's analysis compared to the Applicant's analysis are due to differences in grouping of preferred terms. Refer to the "Serious Adverse Events" and "Treatment Emergent Adverse Events and Adverse Reactions" sections for description of preferred terms included in the following grouped terms: peripheral neuropathy, corneal adverse reactions, conjunctival adverse reactions, eyelid disorders, ileus, rash, and sepsis.

FDA agrees that TEAEs leading to treatment discontinuation were less common in GCT1015-04 than in the other safety pools. It is unclear if this is due to protocol changes, differences in trial populations, and/or other factors.

FDA does not consider attribution (treatment-related versus not) in the analysis of TEAEs leading to discontinuation as this is a subjective assessment and determination of causality is challenging.

Dose Interruption/Reduction Due to Adverse Effects

Data:

In GCT1015-04, dose reductions occurred in more than 1 subject for ocular preferred terms, which included conjunctivitis (7 subjects), keratitis (6 subjects), dry eye (3 subjects), blepharitis (2 subjects), and punctate keratitis (2 subjects) (ISS Table 10.2.8). These dose reductions were as required by the trial protocol. Dose reductions occurred in 1 subject due to peripheral sensorimotor neuropathy and in 1 subject due to peripheral sensory neuropathy (also arising from protocol-required safety measures). The AEs leading to dose reduction in Pool 3 primarily reflect the events that occurred in the GCT1015-04 trial. Three subjects (5.3%) in Pool 1 had dose reductions due to conjunctivitis.

In GCT1015-04, 47 subjects (46.5%) had dose interruptions (ISS Table 10.2.7). The most common reasons for interruption were conjunctivitis (4 subjects), anemia (3 subjects), dry eye (3 subjects), and peripheral sensorimotor neuropathy (3 subjects). In Pool 1, 9 subjects (15.8%) had a dose interruption. The incidence of dose interruption in the safety pooled analysis data sets primarily reflects events that occurred in the GCT1015-04 trial.

The Applicant's Position:

Dose reductions in response to AESIs were implemented as important subject safety measures in GCT1015-04. In earlier trials (GEN701, GEN702), dose reductions in response to observed AESIs were added to protocols as amendments. As such, dose reductions were not used as extensively to manage AESIs, particularly ocular events, in the populations for the pooled analyses as they were for GCT1015-04.

Dose interruptions, particularly dose delays, were also an integral part of subject safety measures in the GCT1015-04 trial. Safety-related dose modification criteria in the GCT1015-04 trial may have contributed to a higher percentage of dose interruptions (46.5%) among these subjects relative to subjects in Pool 1 (15.8%), which may have allowed them to remain on treatment longer with fewer discontinuations due to TEAEs.

The FDA’s Assessment:

FDA conducted an independent analysis of dose reductions and interruptions in GCT105-04. In this trial, 23% of patients experienced TEAEs leading to dose reductions, and 47% of patients experienced TEAEs leading to dose interruptions. The most common reasons for dose reductions ($\geq 3\%$) were conjunctival adverse reactions (9%), corneal adverse reactions (8%), and dry eye (3%). The most reasons for dose interruptions ($\geq 3\%$) were peripheral neuropathy (8%), conjunctival adverse reactions (4%), hemorrhage (4%), acute kidney injury (3%), anemia (3%), dry eye (3%), and ileus (3%). Differences between FDA’s analysis and the Applicant’s analysis are due to grouping of preferred terms.

FDA agrees that one contributor to differences in frequencies of dose modifications in GCT1015-04 compared to the other safety pools could be due to protocol differences relating to implementation of dose modifications in responses to adverse events, particularly ocular adverse events.

Significant Adverse Events

Data:

For the purposes of this section, grade 3 and higher TEAEs are considered to be significant. TEAEs of grade 3 or higher, regardless of causality, are presented in [Table 29](#). Overall, the incidence of TEAEs of grade 3 and higher were similar across all analysis groups and similar proportions of subjects with anemia and fatigue TEAEs of grade 3 and higher were observed.

Table 29: TEAEs $\geq$ Grade 3 Reported in $\geq 2\%$ of Subjects in GCT1015-04 or Pool 3 by PT

Preferred Term	Pivotal Cervical (GCT1015-04) (N=101) n (%)	Supportive Cervical (Pool 1) (N=57) n (%)	All Cervical (Pool 2) (N=158) n (%)	All Tumor Types (Pool 3) (N=272) n (%)
Subjects with any event	61 (60.4)	30 (52.6)	91 (57.6)	153 (56.3)
Anaemia	8 (7.9)	7 (12.3)	15 (9.5)	20 (7.4)
Fatigue	5 (5.0)	5 (8.8)	10 (6.3)	19 (7.0)
Pneumonia	4 (4.0)	0	4 (2.5)	5 (1.8)
Hypocalcaemia	3 (3.0)	0	3 (1.9)	3 (1.1)
Neutropenia	3 (3.0)	0	3 (1.9)	6 (2.2)
Pulmonary embolism	3 (3.0)	0	3 (1.9)	4 (1.5)
Ulcerative keratitis	3 (3.0)	0	3 (1.9)	3 (1.1)
Urinary tract obstruction	3 (3.0)	1 (1.8)	4 (2.5)	4 (1.5)
Asthenia	2 (2.0)	0	2 (1.3)	3 (1.1)
Back pain	2 (2.0)	1 (1.8)	3 (1.9)	3 (1.1)
Constipation	2 (2.0)	1 (1.8)	3 (1.9)	5 (1.8)
Death	2 (2.0)	0	2 (1.3)	2 (0.7)
Hyperglycaemia	2 (2.0)	0	2 (1.3)	4 (1.5)
Hypokalaemia	2 (2.0)	3 (5.3)	5 (3.2)	9 (3.3)
Lymphocyte count decreased	2 (2.0)	1 (1.8)	3 (1.9)	5 (1.8)
Neuropathy peripheral	2 (2.0)	1 (1.8)	3 (1.9)	4 (1.5)
Peripheral motor neuropathy	2 (2.0)	1 (1.8)	3 (1.9)	3 (1.1)

Preferred Term	Pivotal Cervical (GCT1015-04) (N=101) n (%)	Supportive Cervical (Pool 1) (N=57) n (%)	All Cervical (Pool 2) (N=158) n (%)	All Tumor Types (Pool 3) (N=272) n (%)
Peripheral sensorimotor neuropathy	2 (2.0)	2 (3.5)	4 (2.5)	4 (1.5)
Peripheral sensory neuropathy	2 (2.0)	1 (1.8)	3 (1.9)	6 (2.2)
Rectal haemorrhage	2 (2.0)	0	2 (1.3)	2 (0.7)
Septic shock	2 (2.0)	0	2 (1.3)	2 (0.7)
Urinary tract infection	2 (2.0)	1 (1.8)	3 (1.9)	5 (1.8)
Vaginal haemorrhage	2 (2.0)	1 (1.8)	3 (1.9)	3 (1.1)
Vomiting	2 (2.0)	4 (7.0)	6 (3.8)	7 (2.6)
Abdominal pain	1 (1.0)	3 (5.3)	4 (2.5)	7 (2.6)

Source: ISS Table 10.2.5

The Applicant's Position:

As expected, based on underlying malignancy, anemia was the most common grade 3 and higher TEAE. The pooled analyses show similar proportions of subjects with anemia and fatigue TEAEs of grade 3 and higher. The sponsor considers the AESIs of ocular events and peripheral neuropathy to be causally associated with tisotumab vedotin and therefore also significant. These are described in later sections of this document.

The FDA's Assessment:

FDA conducted an independent analysis for Grade ≥ 3 TEAEs in GCT1015-04. Grade ≥ 3 TEAEs occurred frequently, affecting 60% of patients. The most common Grade ≥ 3 TEAEs ($\geq 3\%$) in FDA's analysis were: anemia (9%), peripheral neuropathy (7%), fatigue (7%), hemorrhage (6%), pneumonia (4%), ileus (4%), urinary tract infection (3%), urinary tract obstruction (3%), acute kidney injury (3%), pulmonary embolism (3%), hypocalcemia (3%), neutropenia (3%), and corneal adverse reactions (3%). Differences between FDA's analysis and the Applicant's analyses are due to grouping of preferred terms. FDA notes that when preferred terms are grouped, the frequencies of certain Grade ≥ 3 TEAEs including peripheral neuropathy, hemorrhage, and corneal adverse reactions are higher than reported by the Applicant.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

All subjects except 1 in Pool 3 (non-cervical tumor type) experienced at least 1 TEAE. An overall summary of TEAEs is presented for integrated safety population in [Table 30](#). The most common TEAEs (occurring in $\geq 10\%$ of subjects, regardless of causality) are presented in Table 31.

Table 30: Summary of TEAEs

	Pivotal Cervical (GCT1015-04) (N=101) n (%)	Supportive Cervical (Pool 1) (N=57) n (%)	All Cervical (Pool 2) (N=158) n (%)	All Tumor Types (Pool 3) (N=272) n (%)
Any TEAE	101 (100)	57 (100)	158 (100)	271 (99.6)
≥ Grade 3 TEAE	61 (60.4)	30 (52.6)	91 (57.6)	153 (56.3)
TE SAE	43 (42.6)	25 (43.9)	68 (43.0)	113 (41.5)
Grade 5 TEAEs	4 (4.0)	0	4 (2.5)	5 (1.8)
TEAE resulting in treatment discontinuation	13 (12.9)	12 (21.1)	25 (15.8)	64 (23.5)
TEAEs leading to dose interruption	47 (46.5)	9 (15.8)	56 (35.4)	69 (25.4)
TEAEs leading to dose reduction	23 (22.8)	8 (14.0)	31 (19.6)	46 (16.9)

Sources: ISS Table 10.2.1, Table 10.2.7, and Table 10.2.8; ISS Table 10.2.2

Table 31: TEAEs Reported in ≥10% of Subjects in GCT1015-04 by PT

Preferred Term	Pivotal Cervical (GCT1015-04) (N=101) n (%)	Supportive Cervical (Pool 1) (N=57) n (%)	All Cervical (Pool 2) (N=158) n (%)	All Tumor Types (Pool 3) (N=272) n (%)
Subjects with any event	101 (100)	57 (100)	158 (100)	271 (99.6)
Nausea	41 (40.6)	25 (43.9)	66 (41.8)	129 (47.4)
Alopecia	39 (38.6)	24 (42.1)	63 (39.9)	110 (40.4)
Epistaxis	39 (38.6)	30 (52.6)	69 (43.7)	154 (56.6)
Fatigue	35 (34.7)	31 (54.4)	66 (41.8)	132 (48.5)
Anaemia	34 (33.7)	13 (22.8)	47 (29.7)	60 (22.1)
Conjunctivitis	31 (30.7)	24 (42.1)	55 (34.8)	102 (37.5)
Dry eye	25 (24.8)	15 (26.3)	40 (25.3)	64 (23.5)
Diarrhoea	24 (23.8)	19 (33.3)	43 (27.2)	77 (28.3)
Constipation	23 (22.8)	20 (35.1)	43 (27.2)	83 (30.5)
Asthenia	18 (17.8)	1 (1.8)	19 (12.0)	24 (8.8)
Vomiting	17 (16.8)	19 (33.3)	36 (22.8)	68 (25.0)
Arthralgia	16 (15.8)	6 (10.5)	22 (13.9)	37 (13.6)
Decreased appetite	16 (15.8)	20 (35.1)	36 (22.8)	78 (28.7)
Myalgia	16 (15.8)	5 (8.8)	21 (13.3)	41 (15.1)
Pyrexia	16 (15.8)	11 (19.3)	27 (17.1)	36 (13.2)
Abdominal pain	15 (14.9)	15 (26.3)	30 (19.0)	50 (18.4)
Neuropathy peripheral	13 (12.9)	18 (31.6)	31 (19.6)	60 (22.1)
Pruritus	13 (12.9)	10 (17.5)	23 (14.6)	39 (14.3)
Rash	13 (12.9)	8 (14.0)	21 (13.3)	39 (14.3)
Pain in extremity	12 (11.9)	4 (7.0)	16 (10.1)	25 (9.2)
Weight decreased	12 (11.9)	9 (15.8)	21 (13.3)	42 (15.4)
Keratitis	11 (10.9)	3 (5.3)	14 (8.9)	17 (6.3)
Peripheral sensory neuropathy	11 (10.9)	6 (10.5)	17 (10.8)	31 (11.4)
Urinary tract infection	11 (10.9)	12 (21.1)	23 (14.6)	31 (11.4)
Vaginal haemorrhage	11 (10.9)	5 (8.8)	16 (10.1)	19 (7.0)

Source: ISS Table 10.2.4

The Applicant’s Position:

Overall incidence of TEAEs appears generally similar across groups. Rates of epistaxis and conjunctivitis were lower in the GCT1015-04 trial, and in the case of conjunctivitis may reflect the evolving management of ocular AEs as clinical development of tisotumab vedotin progressed. Generally, the events and rates observed in the pivotal trial are similar and representative of the overall safety profile.

Tisotumab vedotin has a manageable and tolerable safety profile in subjects with recurrent or metastatic cervical cancer who previously received chemotherapy doublet plus bevacizumab, if eligible. Most observed AEs were manageable with either supportive or preventative care or dose modifications.

The FDA’s Assessment:

FDA agrees with the Applicant’s summary of TEAEs, presented in Table 30. The frequency of grade ≥ 3 TEAEs is slightly higher in GCT1015-04 than in the other safety pools. The reasons for this are unclear, and FDA notes that this comparison across safety pools is limited by small sample size.

FDA conducted an independent analysis of all grade TEAEs in GCT1015-04 which is shown in Table 32. The most common TEAEs included fatigue (50%), nausea (41%), peripheral neuropathy (39%), alopecia (39%), epistaxis (39%), conjunctival adverse reactions (37%), and hemorrhage (32%). These toxicities reflect both the anti-TF target and the MMAE payload. Differences between FDA’s analysis and the Applicant’s analysis are due to grouping of preferred terms.

Table 32: Adverse Reactions ($\geq 10\%$) in Patients Who Received Tisotumab Vedotin in GCT1015-04

Adverse Reaction	Tisotumab Vedotin N=101	
	All Grades	Grade 3-4
	%	%
General		
Fatigue ¹	50	7
Pyrexia	16	1
Pruritis	13	1
Gastrointestinal disorders		

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Nausea ²	41	0
Diarrhea ³	25	2
Constipation	23	2
Abdominal Pain ⁴	23	1
Vomiting	17	2
Nervous system disorders		
Peripheral Neuropathy ⁵	39	7
Skin and subcutaneous tissue disorders		
Alopecia	39	0
Rash ⁶	25	0
Vascular disorders		
Epistaxis	39	0
Hemorrhage ⁷	32	6
Eye disorders		
Conjunctival adverse reactions ⁸	37	0
Dry eye ⁹	29	0
Corneal adverse reactions ¹⁰	21	3
Periorbital adverse reactions ¹¹	16	0
Musculoskeletal and connective tissue disorders		
Myalgia ¹²	21	0
Arthralgia	16	0
Pain in extremity ¹³	13	1
Metabolism and nutrition disorders		
Decreased appetite	16	1
Infections		

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Urinary tract infection ¹⁴	14	2
Investigations		
Weight decreased	12	0

1. Fatigue includes fatigue and asthenia
2. Nausea includes nausea and retching
3. Diarrhea includes diarrhea, gastroenteritis, and colitis
4. Abdominal pain includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal distention and abdominal discomfort
5. Peripheral neuropathy includes neuropathy peripheral, peripheral sensorimotor neuropathy, polyneuropathy, peripheral sensory neuropathy, parasthesia, hypoesthesia, burning sensation, neuralgia, sensory loss, peripheral motor neuropathy, muscular weakness, gait disturbance, and hyperesthesia
6. Rash includes rash, rash maculo-papular, rash macular, dermatitis acneiform, dermatitis allergic, and erythema
7. Hemorrhage includes vaginal hemorrhage, hematuria, rectal hemorrhage, cystitis hemorrhagic, lower gastrointestinal hemorrhage, urinary bladder hemorrhage, hematochezia, anal hemorrhage, gingival bleeding, post procedural hemorrhage, radiation associated with hemorrhage, metrorrhagia, large intestinal hemorrhage, paranasal sinus hemorrhage, and hemoptysis
8. Conjunctival adverse reactions includes conjunctivitis, conjunctival abrasion, conjunctival erosion, conjunctival hyperemia, conjunctival scar, noninfective conjunctivitis, ocular hyperemia, and conjunctival hemorrhage
9. Dry eye includes dry eye and lacrimation increased
10. Corneal adverse reactions includes keratitis, punctate keratitis, ulcerative keratitis, corneal erosion, corneal scar, keratopathy, and corneal bleeding
11. Periorbital adverse reactions includes blepharitis, meibomianitis, eye pruritus, entropion, trichiasis, chalazion, and meibomian gland dysfunction
12. Myalgia includes myalgia, musculoskeletal discomfort, and musculoskeletal pain
13. Pain in extremity includes pain in extremity and limb discomfort
14. Urinary tract infection includes urinary tract infection, urinary tract infection bacterial, and cystitis

[Source: Tisotumab vedotin USPI Section 6]

The safety profile for tisotumab vedotin contains certain unique toxicities (ocular toxicity, hemorrhage) as well toxicities more familiar to an oncology population (peripheral neuropathy, nausea, alopecia, fatigue, anemia) which require attention from patients and providers. The safety profile is manageable through labeling and routine oncologic care.

Laboratory Findings

Data:

Serum Chemistry:

Exposure to tisotumab vedotin did not meaningfully impact clinical laboratory results for serum chemistry. Across all safety analysis groups, shifts to grade 3 or 4 laboratory chemistry values were infrequent (5% or less). For this reason, only Pool 3 is described. Shift tables for serum chemistry values for GCT1015-04 are available in (ISS Table 10.4.1) and for safety analysis Pools 1 and 2 are located in (ISS Table 10.4.2) and (ISS Table 10.4.3), respectively.

Complete Blood Count:

Exposure to tisotumab vedotin did not meaningfully impact clinical laboratory results for

complete blood count. In Pool 3, the number of subjects who experienced shifts in blood count to grade 3 or 4 at any post-baseline treatment trial visit was infrequent (5% or less) with the exception of low lymphocytes (8.5% of subjects experienced shift from grade 2 to grade 3). Shift tables for blood count parameters for GCT1015-04 are available in (ISS Table 10.4.9) and for safety analysis Pools 1, 2, and 3 are located in (ISS Table 10.4.10), (ISS Table 10.4.11), and (ISS Table 10.4.12), respectively.

Drug-Induced Liver Abnormalities:

In GCT1015-04, no drug-induced liver injuries (DILI; defined as AST/ALT >3×ULN and total bilirubin >2×ULN and as AST/ALT >3×ULN, total bilirubin >2×ULN, and alkaline phosphatase <1.5XULN that occurred within 30 days of the last dose) were observed (ISS Table 10.4.13). The number of abnormal liver function tests was <1% across all trials (ie, in Pool 3). One subject (701126) in Pool 3 had AST and/or ALT elevations >3×ULN combined with bilirubin elevations >2×ULN. The subject had a high ALP level, bile duct obstruction and did not meet the criteria consistent with the event designation of DILI.

Coagulation Parameters:

In Pool 3, 2 subjects (0.7%) experienced shifts in coagulation parameters (aPTT) to grade 3 at any post-baseline treatment trial visit in Pool 3 (ISS Table 10.4.8). Shift tables for coagulation parameters for GCT1015-04 are available in (ISS Table 10.4.5) and for safety analysis Pools 1 and 2 are located in (ISS Table 10.4.6) and (ISS Table 10.4.7), respectively. Most tisotumab vedotin trials excluded subjects with a history of bleeding events or coagulation abnormalities.

The Applicant’s Position:

Exposure to tisotumab vedotin did not meaningfully impact clinical laboratory results for complete blood count or serum chemistry. Most tisotumab vedotin trials excluded subjects with a history of coagulation defects that increased the risk of bleeding as well as subjects with ongoing major bleeding (ie, symptomatic bleeding in critical area organ or bleeding causing a drop in hemoglobin level of ≥2 g/dL or that required transfusion of ≥2 units).

The FDA’s Assessment:

FDA’s laboratory analysis was based on GCT1015-04 results only and FDA conducted an independent analysis of laboratory abnormalities on this trial which is shown in Table 33. Most laboratory abnormalities were low-grade, and grade ≥3 laboratory abnormalities were infrequent. The most common Grade≥3 laboratory abnormalities were lymphocytes decreased (8%), anemia (7%), creatinine increased (4%), creatinine kinase increased (2%), magnesium decreased (2%), and aPTT prolonged (2%).

Table 33: Select laboratory abnormalities (>10%) that worsened from baseline in patients who received Tisotumab Vedotin in GCT1015-04

Laboratory Abnormality	All Grades (%)	Grade 3 or 4 (%)

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Hematology		
Hemoglobin decreased	51	7
Lymphocytes decreased	42	8
Leukocytes decreased	30	0
Neutrophils decreased	21	3
Chemistry		
Creatinine increased	29	4.1
Alanine aminotransferase increased	24	0
Lactate dehydrogenase increased	22	0
Urate increased	20	0
Glucose decreased	19	0
Aspartate aminotransferase increased	20	0
Sodium decreased	18	0
Alkaline phosphatase increased	17	0
Creatinine kinase increased	16	2.1
Magnesium decreased	17	2.1
Albumin decreased	16	0
Coagulation		
Prothrombin international normalized ratio increased	26	0

Activated partial thromboplastin time prolonged	26	2

[Source: Adapted from tisotumab vedotin USPI]

Vital Signs

Data:

Vital sign measurements, including heart rate, diastolic and systolic blood pressure, and temperature, are summarized or listed individually in each CSR for the trials included in the safety analysis groups. Any clinically significant changes were captured as AEs.

The Applicant's Position:

Tisotumab vedotin did not appear to have clinically meaningful adverse effects on vital signs during any clinical trial.

The FDA's Assessment:

FDA did not conduct an independent analysis of vital sign data and believes that any clinically significant changes would be captured as TEAEs.

Electrocardiograms (ECGs)

Data:

High-quality triplicate ECG measures were collected in studies GCT1015-04 and SGNTV-001 at a dose of 2.0 mg/kg 1Q3W. In GCT1015-04, no meaningful changes in ECG interpretation (normal vs abnormal) were observed over time. In the SGNTV-001 trial, none of the subjects had any ECG change from baseline of more than 60 ms.

The Applicant's Position:

No clinically significant changes in ECG readings were detected after treatment with tisotumab vedotin.

The FDA's Assessment:

Tisotumab vedotin treatment at 2 mg/kg Q3W does not cause large mean increases (>20 msec) in the QTc interval. Please refer to the FDA QT IRT by Nan Zheng and Christine Garnett dated 4/21/21 review for further information.

QT

Data:

The effect of tisotumab vedotin on the duration of cardiac ventricular repolarization was evaluated in GCT1015-04 and SGNTV-001. This analysis was conducted on PK and ECG data from 153 subjects with solid tumors. The relationship between ADC and MMAE concentrations and change in QTcF intervals from baseline (Δ QTcF) was explored using linear mixed effects modeling. The concentration- Δ QTcF analysis did not show a clinically relevant Δ QTcF risk at C_{max} of both ADC and MMAE following the administration of tisotumab vedotin at a dose of 2.0 mg/kg 1Q3W, as the upper bounds of one-sided 95% CI were below 10 msec for all analytes.

The Applicant's Position:

Tisotumab vedotin, administered at the recommended dose of the 2.0 mg/kg 1Q3W, does not have a clinically meaningful effect on the QTc prolongation.

The FDA's Assessment:

Based on the FDA QT IRT's analysis, tisotumab vedotin treatment at 2 mg/kg Q3W IV does not cause large mean increases (>20 msec) in the QTc interval. Please refer to the FDA QT IRT review dated 4/21/21 for further information.

Immunogenicity

Data:

Serum samples of subjects from the GCT1015-04, as well as ADA Pool 1 and ADA Pool 2, were analyzed for ADAs to tisotumab vedotin during the course of clinical development. ADA Pool 2 also included data from 56 subjects in the SGNTV-001 trial to enlarge the dataset to 305 subjects and include subjects that were a part of the PopPK analysis.

In GCT1015-04, approximately 2% of subjects were positive for ADAs at baseline. Across all ADA Pools, the percentage of subjects positive for ADAs at baseline ranged from 2.1% to 3.9% (ISS Table 10.4.14). In GCT1015-04, approximately 5% of the subjects were confirmed to have treatment emergent ADAs. 4.3% of subjects were confirmed to be positive for treatment-emergent ADA in the ADA Pool 2.

A total of 305 subjects were tested for ADA; 13 subjects (4.3%) were confirmed to be positive for ADA at any post-baseline timepoint (ISS Table 10.4.14).

The Applicant's Position:

Overall, the rate of immunogenicity to tisotumab vedotin was low. The presence of ADA had no clinically meaningful effect on tisotumab vedotin pharmacokinetics. There is no evidence of a significant safety risk associated with immunogenicity.

The FDA's Assessment:

In Study GCT1015-04, 5 of 93 (5.4%) patients who had immunogenicity assessment at baseline and at least one time point post-dose, developed treatment-emergent ADA against tisotumab vedotin. Two of these 5 patients in Study 04, tested positive for neutralizing antibodies against tisotumab vedotin. Across studies, 145 patients with cervical cancer treated at the proposed 2 mg/kg Q3W IV dosage in Studies GEN701, GEN702, 04 had immunogenicity assessment at baseline and at least one time point post-dose. Eight of 145 patients (5.5%) developed treatment-emergent ADA against tisotumab vedotin. Due the limited number of patients who were positive for ADA during treatment with tisotumab vedotin, the impact of ADA on the PK, safety and efficacy of tisotumab vedotin is not fully characterized.

8.2.4 Analysis of Submission-Specific Safety Issues

8.2.4.1 Ocular Events/Toxicity

Data:

Ocular AEs are a known safety risk of tisotumab vedotin treatment. Analyses of ocular AEs were

conducted across safety analysis populations using the following MedDRA specifications.

- Conjunctival disorders SMQ (Narrow) [20000175]
- Corneal disorders SMQ (Broad) [20000156]
- Glaucoma SMQ (Broad) [20000146]
- Lacrimal disorders SMQ (Narrow) [20000176]
- Ocular infections SMQ (Broad) [20000183]
- Optic nerve disorders SMQ (Broad) [20000148]
- Periorbital and eyelid disorders SMQ (Narrow) [20000179]
- Retinal disorders SMQ (Broad) [20000158]
- Scleral disorders SMQ (Narrow) [20000182]
- Eye Disorders SOC [10015919]

In GCT1015-04, 55 subjects (54.5%) had at least one ocular event (Table 33). Treatment-related ocular events were reported in all but one of these subjects. Most ocular AEs were confined to the ocular surface (ie, conjunctival, corneal, periorbital, and eyelid disorders). The most common ocular TEAEs ($\geq 5\%$ incidence) for subjects in the GCT1015-04 trial were conjunctivitis (30.7%), dry eye (24.8%), keratitis (10.9%), blepharitis (6.9%), and punctate keratitis (5.9%) (ISS Table 10.2.38).

In GCT1015-04, most ocular events were grade 1 (22.8%) or grade 2 (28.7%) in severity, were transient, and achieved resolution. Three subjects (3.0%) had grade 3 ocular events; all of which were ulcerative keratitis (ISS Table 10.2.42). There were no grade 4 ocular events. No subjects experienced ocular SAEs (ISS Table 10.2.39). Five subjects (5.0%) discontinued tisotumab vedotin due to ocular AEs (2 subjects due to ulcerative keratitis, 1 subject due to corneal scar, 1 subject due to conjunctivitis, and 1 subject due to keratitis, entropion, and trichiasis) (ISS Table 10.2.45).

In GCT1015-04, 72.7% of subjects with ocular events experienced complete resolution of all ocular events. All remaining subjects had improvement or resolution of at least 1 ocular event. Median time to resolution was 0.59 months (range 0.0 to 11.1 months). At the last follow-up, of the 55 subjects who experienced ocular AEs, 12 (21.8%) had ongoing ocular AEs with residual maximum grade 1, 2 (3.6%) had grade 2, and 1 subject (1.8%) had grade 3.

Overall, the incidence of ocular events was numerically lower in GCT1015-04 compared to the pooled analysis groups, with the highest rate observed in Pool 1 (70.2%). Grade 3 ocular events were similar, occurring in 1.8% to 3.3% of subjects across all safety analysis groups. Time to onset was longer, time to resolution was shorter, and a greater proportion of events resolved in GCT1015-04 compared to the pooled analysis groups (Table 33). Rates of treatment discontinuation due to ocular AEs were generally similar between pivotal trial GCT1015-04 and the pooled safety analysis groups (range 5.0% to 8.8% across all groups).

In Pool 3, symblepharon was noted in 3 subjects (1.1%) with other tumor types treated with tisotumab vedotin 2.0 mg/kg, and 2 subjects (0.7%) experienced serious conjunctivitis.

Table 34: Summary of Treatment Emergent Ocular Adverse Events

	Pivotal Cervical (GCT1015-04) (N=101)	Supportive Cervical (Pool 1) (N=57)	All Cervical (Pool 2) (N=158)	All Tumor Types (Pool 3) (N=272)
Subjects with any treatment-emergent ocular adverse events	55 (54.5%)	40 (70.2%)	95 (60.1%)	171 (62.9%)
Grade 1	23 (22.8%)	15 (26.3%)	38 (24.1%)	60 (22.2%)
Grade 2	29 (28.7%)	23 (40.4%)	52 (32.9%)	101 (37.1%)
Grade 3	3 (3.0%)	1 (1.8%)	4 (2.5%)	9 (3.3%)
Missing	0	1 (1.8%)	1 (0.6%)	1 (0.4%)
Time to onset of first event (months), n	55	40	95	171
Mean (STD)	1.42 (1.04)	1.35 (1.20)	1.39 (1.11)	1.12 (1.05)
Median	1.41	0.97	1.15	0.89
Min, Max	0.0, 3.8	0.1, 6.5	0.0, 6.5	0.0, 6.5
Subjects with all events resolved	40/55 (72.7%)	12/40 (30.0%)	52/95 (54.7%)	81/171 (47.4%)
Subjects with some events resolved or improved	15/55 (27.3%)	13/40 (32.5%)	28/95 (29.5%)	55/171 (32.2%)
Subjects with no events resolved or improved	0	15/40 (37.5%)	15/95 (15.8%)	35/171 (20.5%)
Number of events	161	98	259	458
Number of events resolved	135/161 (83.9%)	59/98 (60.2%)	194/259 (74.9%)	312/458 (68.1%)
Time to resolution (months), n	135	59	194	312
Mean (STD)	1.25 (1.64)	1.25 (1.36)	1.25 (1.56)	1.19 (1.44)
Median	0.59	0.56	0.59	0.66
Min, Max	0.0, 11.1	0.1, 6.2	0.0, 11.1	0.0, 11.1
Subjects with ongoing events at the last follow-up				
Maximum Grade 1	12/55 (21.8%)	14/40 (35.0%)	26/95 (27.4%)	45/171 (26.3%)
Maximum Grade 2	2/55 (3.6%)	13/40 (32.5%)	15/95 (15.8%)	40/171 (23.4%)
Maximum Grade 3	1/55 (1.8%)	0	1/95 (1.1%)	4/171 (2.3%)
Grade Missing	0	1/40 (2.5%)	1/95 (1.1%)	1/171 (0.6%)

Source: Adapted from ISS Table 10.2.48; Table 10.2.42; Table 10.2.43

In GCT1015-04, approximately half of subjects (47 subjects, 46.5%) had pre-existing ocular AEs at the baseline visit as assessed by an ophthalmologist. Subjects with pre-existing ocular AEs did not report an increase in ocular TEAEs while on study compared to the overall study population (Table 34) and the incidence was similar to subjects without a preexisting event.

Best corrected visual acuity (BCVA) was measured in the GCT1015-04 trial at baseline and as appropriate at the time of the ocular AE. A total of 55 subjects developed ocular TEAEs, of which 49 had both baseline and post-baseline visual acuity exam. In total, 3 subjects (3.0%) experienced visual acuity (VA) Snellen score(s) $\geq 20/50$ post-baseline. Two subjects experienced unilateral VA $\geq 20/50 \leq 20/200$ post-baseline. One subject experienced bilateral VA $\geq 20/50$ postbaseline, with unilateral VA of 20/200 (improved to 20/40 after 7 days). BCVA remained normal for the majority of subjects who had ocular AEs (see [GCT1015-04 CSR Table 14.03.29]).

Impact of Protocol-Defined OMP

Protocol-defined ocular mitigation plan (OMP) measures intended to limit the risk of ocular AEs with tisotumab vedotin administration have evolved over the course of the clinical development program. The initial version of a protocol-defined OMP for tisotumab vedotin was introduced in the GEN701 and GEN702 trials in June 2016, with additional measures added in October 2016, December 2016, July 2017, and March 2018 (see July 2019 FDA Information Amendment, submitted to IND (b) (6) Sequence # (b) (4)). Thus, ocular safety data from trials that enrolled subjects before or during the time period of OMP refinement may reflect ongoing changes. The integrated safety pooled analysis groups include subjects from GEN701 and GEN702 who were treated during this period of OMP refinement. The GCT1015-04 trial began enrollment in June 2018. The current and most comprehensive protocol-defined OMP in GCT1015-04 was implemented from initiation onward and all subjects treated in GCT1015-04 received this current OMP. It included prophylactic measures (vasoconstrictor eye drops and cold packs during infusion as well as steroid and lubricating eye drops throughout each treatment cycle), symptom-induced ophthalmological exams, and dose modifications based on low grade ocular events.

Ocular TEAEs in subjects by OMP status at Cycle 1 (per the defined measures in the GCT1015-04 protocol) are summarized in Table 35. Overall, results showed that when the current and most comprehensive OMP was implemented as per the GCT1015-04 protocol, subjects had a reduced and consistent incidence of ocular TEAEs (range 54.5% to 58.5% across groups) compared to subjects who received earlier or variable implementation of the OMP (75.0% in Pool 2 and 72.6% in Pool 3). The reduction in ocular TEAEs seen with the current OMP appeared primarily driven by the difference in reports of conjunctivitis (reported in 30.3% of subjects with GCT1015-04 protocol-defined OMP at Cycle 1 versus 53.6% of subjects without in Pool 3) (ISS Table 10.3.12). Corneal disorders were consistent across all groups and irrespective of the OMP (range 18.8% to 21.1%) with the exception of Pool 3 wherein they were reported in 3.6% of subjects who had not received the current OMP measures at Cycle 1. Preferred terms under corneal disorders included keratitis, punctate keratitis, ulcerative keratitis, and vital dye staining cornea present. In addition, a small numerical increase in dry eye was observed (range 24.5% to 26.8%) in subjects who received the OMP as per the GCT1015-04 protocol versus those subjects who did not (12.5% in Pool 2 and 21.4% in Pool 3) (ISS Table 10.3.12).

Most ocular events were grade 1 or 2 regardless of OMP status at Cycle 1 (Table 35). Subjects who received the protocol-defined OMP at Cycle 1 had a reduced frequency of grade 2 and higher ocular events (range 31.7% to 36.7%) versus subjects who did not (50.0% in Pool 2 and 48.8% in Pool 3).

The rate of treatment discontinuations due to ocular events in subjects receiving tisotumab vedotin with the current OMP was approximately half of that in subjects who received initial or earlier OMP measures (5.3% versus 9.5% in Pool 3) (Table 34). Dose reductions were more frequent in subjects who received the current OMP (range 14.4% to 19.8%) than those who did not (6.3% in Pool 2 and 6.0% in Pool 3). Dose modifications and proactive ophthalmology

consultation in response to ocular events are part of the protocol-defined OMP and may have enabled a longer duration of therapy for tisotumab vedotin.

Time to onset for any grade 2 and higher ocular AEs was longer for subjects who received the OMP in Cycle 1 in Pool 3 (ISS Table 10.3.14). Median time to onset of the first ocular event leading to treatment discontinuation in Pool 3 was longer in subjects who received the current OMP (4.42 months) compared to subjects who did not (0.90 months) (ISS Table 10.3.14).

Exposure-adjusted toxicity analysis of Pool 3 showed lower incidence of ocular TEAEs in subjects who received the OMP vs those who did not (495 vs 564 ocular AEs per 100 patient-years) (ISS Table 10.3.16). Grade 3 and higher ocular TEAEs showed a similar trend (8 vs 17 AEs per 100 patient-years with OMP vs without OMP). Additionally, the rate of discontinuations was lower for subjects who received the OMP as compared to those who did not (23 vs 39 per 100 patient-years). Subjects across all trials (ie, Pool 3) who received the current OMP at Cycle 1 as per GCT1015-04 had lower rates of conjunctivitis (132 events per 100 person-years vs 241 events) and dry eye (77 events per 100 person-years vs 82 events) (ISS Table 10.3.15).

Table 35: Summary of Treatment-Emergent Ocular Adverse Events by Cycle 1 OMP Status (Yes, No)

	Pivotal Cervical (GCT1015-04) (N=101)	Pool 2 (All Cervical)		Pool 3 (All Tumor Types)	
		Yes (N=142) n (%)	No (N=16) n (%)	Yes (N=188) n (%)	No (N=84) n (%)
Number of subjects with at least one treatment-emergent event	Yes (N=101) n (%)	Yes (N=142) n (%)	No (N=16) n (%)	Yes (N=188) n (%)	No (N=84) n (%)
Ocular AE	55 (54.5%)	83 (58.5)	12 (75.0)	110 (58.5)	61 (72.6)
Ocular AE related to Tisotumab Vedotin	54 (53.5)	80 (56.3)	12 (75.0)	107 (56.9)	58 (69.0)
Grade >=3 Ocular AE	3 (3.0)	4 (2.8)	0	5 (2.7)	4 (4.8)
Grade >=3 Ocular AE related to Tisotumab Vedotin	2 (2.0)	3 (2.1)	0	4 (2.1)	4 (4.8)
Grade >=2 Ocular AE	29 (28.7)	48 (33.8)	8 (50.0)	69 (36.7)	41 (48.8)
Grade >=2 Ocular AE related to Tisotumab Vedotin	27 (26.7)	44 (31.0)	8 (50.0)	65 (34.6)	40 (47.6)
Serious Ocular AE	0	0	0	1 (0.5)	1 (1.2)
Serious Ocular AE related to Tisotumab Vedotin	0	0	0	1 (0.5)	1 (1.2)
Ocular AE leading to treatment discontinuation	5 (5.0)	8 (5.6)	2 (12.5)	10 (5.3)	8 (9.5)
Ocular AE leading to dose reduction	20 (19.8)	25 (17.6)	1 (6.3)	27 (14.4)	5 (6.0)

Source: Adapted from ISS Table 10.3.13; Table 10.2.42; Table 10.2.43; Table 10.2.39; Table 10.2.45; Table 10.2.47

The Applicant's Position:

Most ocular events were grade 1 or 2, were transient, and achieved resolution. Three subjects (3.0%) had grade 3 ocular events in GCT1015-04 and this rate was similar across the pooled safety groups (1.8% to 3.3%). There were no grade 4 ocular events in any study with 2.0 mg/kg 1Q3W dosing and use of the protocol-defined OMP. Rates of conjunctivitis were lower in the

GCT1015-04 trial, which may result from evolving management of ocular AEs as clinical development of tisotumab vedotin progressed.

In the GCT1015-04 study, all subjects received the current, comprehensive OMP. This OMP includes preventive eye drops, cooling eye packs, prompt assessment by eye care specialists upon occurrence of ocular symptoms, and dose modifications. Time-to-onset and exposure adjusted analyses suggest that, with use of the comprehensive OMP, onset of ocular TEAEs was delayed, these events were less frequent, and fewer treatment discontinuations occurred.

The FDA's Assessment:

FDA disagrees with portions of the Applicant's statements. FDA conducted an independent analysis of ocular toxicity focusing on the GCT1015-04 and Pool 2 safety populations. FDA's search strategy for ocular toxicity relied on identifying preferred terms which connotated ocular toxicity and this strategy produced results similar to the Applicant's for overall frequency of ocular toxicity in GCT1015-04 and in Pool 2, including the frequencies of Grade 1 and Grade 2 adverse reactions.

The most common ocular toxicities in Pool 2 were: conjunctival adverse reactions (40%), dry eye (28%), and corneal adverse reactions (21%). The frequencies of these events were similar in the GCT1015-04 population. Differences in frequencies reported by the FDA and the Applicant were due to grouping of preferred terms. FDA's groupings of preferred terms are listed at the end of this section. Ocular toxicity led to discontinuation of tisotumab vedotin in 6% of patients in the Pool 2 population.

FDA disagrees with the Applicant's description of Grade 3 and Grade 4 ocular toxicity in the GCT1015-04 and Pool 2 safety populations. With respect to Grade 3 ocular toxicity, in addition to the n=3 patients with grade 3 ulcerative keratitis (b) (6) in GCT1015-04 and n=1 additional patient with grade 3 conjunctivitis in Pool 2 reported by the Applicant, there was n=1 patient who had grade 3 ulcerative keratitis (b) (6) in GCT1015-04 in the 90-day DSUR. There were also n=2 patients who developed corneal ulcers (grade 3 keratitis) >30 days after the last dose of tisotumab vedotin (b) (6) in GCT1015-04. Although these toxicities fall outside the treatment-emergent window, FDA considered these events in the overall safety assessment of tisotumab vedotin.

Additionally, in the 90-day safety update, a patient enrolled to GCT1015-04 who had unresolved grade 3 keratitis (b) (6) in her L eye with diminished vision to 20/80 experienced worsening to grade 4 keratitis. She experienced rupturing of her corneal ulcer requiring corneal transplantation.

In summary, in the FDA's analysis, there were an overall n=5 patients (5%) with a worst-grade grade 3 toxicity and n=1 (1%) patient with a worst-grade grade 4 toxicity in GCT1015-04, and n=1 additional patient with grade 3 toxicity in the Pool 2 population. The overall frequency of grade 3 toxicity and grade 4 toxicity in GCT1015-04 is 5% and 1%, and in Pool 2 is 3.8% and

0.6%. These findings underscore that tisotumab vedotin may be associated with severe ocular toxicity and the toxicity may persist and worsen even after treatment is withdrawn.

FDA disagrees with the Applicant that only 3 patients experienced visual acuity changes $\geq 20/50$ post-baseline. FDA sent the Applicant an information request on May 11, 2021 regarding changes in visual acuity for patients enrolled to GCT1015-04. FDA identified five patients with visual acuity changes to $\geq 20/50$ post-baseline, summarized in the table below. There were two patients with ongoing changes at last assessment. Patient (b) (6)'s ocular toxicity is described above. Patient (b) (6) had ongoing visual acuity changes and G2 conjunctivitis and had also been diagnosed with G1 cataracts while on trial. She also developed bilateral corneal ulcers which were not reported as a TEAE as they were discovered >30 days after the final dose of tisotumab vedotin.

Patient ID	Baseline	Worst-Post Baseline	Last Assessment	Ocular toxicities
(b) (6)	Normal	20/80 in L eye	20/80 in L eye	G3 keratitis
	Normal	20/50 in R eye, 20/50 in L eye	20/50 in R eye, 20/50 in L eye	G2 conjunctivitis
	20/30 in L eye	20/70 in L eye	Normal	G2 ambylopia, G1 blepharitis, "moderate" keratitis, not graded
	Normal	20/50 in R eye, 20/200 in L eye	Normal	G2 keratitis, G2 conjunctivitis
	20/30 in L eye	20/70 in L eye	Normal	G3 keratitis

FDA agrees with the Applicant that 55% of patients experiencing ocular toxicity in Pool 2 had resolution to baseline, and this frequency was even higher in GCT1015-04 with 73% of patients having resolution to baseline. Among the n=6 patients who developed Grade 3 ocular toxicity in Pool 2, n=4 patients experienced resolution. Data on resolution are not available for the n=2 patients with grade 3 keratitis detected in the non-treatment-emergent period in GCT105-04. The patient with Grade 4 toxicity initially had grade 3 ulcerative keratitis which worsened and required corneal transplantation. This toxicity was only considered resolved following this procedure.

FDA reviewed the protocol-defined OMP measures. FDA agrees that the frequency of ocular toxicity was lower, and more patients experienced resolution of toxicity in GCT1015-04 compared to Pool 2 and Pool 3, likely due to changes in the OMP measures. However, as noted by the FDA Ophthalmology consultant, the OMP measures also carry risk. The review team requested input from Ophthalmology and the consultant had the following (paraphrased)

comments:

OMP measures resulted in decrease of ocular TEAEs. However, the OMP measures carry risks. Ophthalmic corticosteroids can increase the development of cataracts and increases the risk of sight-threatening keratitis and corneal ulcers. [The oncology review team notes that 2 patients enrolled to GCT1015-04 developed cataracts and one patient developed herpes keratitis.] Ophthalmic corticosteroids should be used consistent with current labeling which includes a slit lamp exam prior to the initial prescription and prior to all renewals.

FDA assessed that the time to onset and time to resolution was similar across the safety populations based on the Applicant's analysis, and the impact of OMP measures on these parameters is unclear. FDA did not conduct independent exposure-adjusted toxicity analyses.

In summary, ocular toxicity occurred frequently in patients receiving tisotumab vedotin. Although most toxicities were grade 1 or 2, FDA notes that a grade 2 event indicates a moderate decrease in visual acuity and can have a significant impact on quality-of-life. Patients enrolled to GCT1015-04 received the most up-to-date OMP measures and even in this trial population, five patients experienced a grade 3 toxicity (keratitis), and one patient experienced a grade 4 toxicity (keratitis). Additionally, five patients experienced visual acuity changes $\geq 20/50$. After stopping tisotumab vedotin, the patient with grade 4 keratitis required corneal transplantation, and one patient continued to experience bilateral visual acuity changes $\geq 20/50$.

To alert providers to the potential of severe ocular toxicity in patients receiving tisotumab vedotin, ocular toxicity is included as a Boxed Warning in the USPI. FDA recommends adherence to the premedication and required eye care plan, prompt referral to an eye care professional for any new or worsening symptoms, and dose modifications if indicated.

Preferred terms

FDA grouped the following preferred terms as conjunctival adverse reactions: conjunctivitis, conjunctival abrasion, conjunctival erosion, conjunctival hyperemia, conjunctival scar, noninfective conjunctivitis, ocular hyperemia, and conjunctival hyperemia. FDA grouped the following preferred terms for dry eye: dry eye and lacrimation increased. FDA grouped the following preferred terms for corneal adverse reactions: keratitis, punctate keratitis, ulcerative keratitis, corneal erosion, corneal scar, keratopathy, corneal bleeding, cornea irritation, corneal thinning, and vital dye staining cornea present.

8.2.4.2 Peripheral Neuropathy

Data:

Peripheral neuropathy is a known safety risk of tisotumab vedotin treatment. The cytotoxic component of the tisotumab vedotin ADC, MMAE, is a microtubule-disrupting agent. Peripheral

neuropathy is associated with microtubule-disrupting ADCs, including tisotumab vedotin. The rate of treatment-emergent peripheral neuropathy reported varies depending on the MMAE ADC. Peripheral neuropathy is also associated with other anti-cancer treatments like taxanes and platinum compounds including cisplatin and carboplatin, which are commonly used in cervical cancer treatment.

In the GCT1015-04 trial, all subjects had been treated previously with systemic therapy. Prior anticancer therapy included bevacizumab (69.3%), cisplatin (86.1%), carboplatin (65.3%) and paclitaxel (100.0%) (m5.3.5.2 GCT1015-04 Table 14.01.07.02). The majority of subjects (81.2%) had received previous radiation therapy (ISS Table 10.1.3). Peripheral neuropathy events were therefore solicited in the pivotal GCT1015-04 trial and denoted as a secondary endpoint in the GEN701 and GEN702 trials, as specified in the protocols.

The safety analysis of peripheral neuropathy events in subjects treated with 2.0 mg/kg tisotumab vedotin 1Q3W focused on the broad SMQ of peripheral neuropathy (20000034).

Peripheral neuropathy TEAEs are summarized in [Table 36](#). The most common ($\geq 4.0\%$ of subjects) peripheral neuropathy preferred terms in GCT1015-04 were neuropathy peripheral (13 subjects, 12.9%), peripheral sensory neuropathy (11 subjects, 10.9%), peripheral sensorimotor neuropathy (6 subjects, 5.9%), and paraesthesia (4 subjects, 4.0%) (ISS Table 10.2.49.1).

In GCT1015-04, peripheral neuropathy AESIs were mostly grade 1 and 2 (18.8% and 11.9%, respectively), and were manageable with dose modifications and standard supportive care. Grade 3 peripheral neuropathy events were experienced by 7 subjects (6.9%) in GCT1015-04; all were considered to be treatment related. No subjects experienced grade 4 or 5 events of peripheral neuropathy. SAEs of peripheral neuropathy were reported in 3 subjects (3.0%) (peripheral sensorimotor neuropathy in 2 subjects and peripheral motor neuropathy in 1 subject (ISS Table 10.2.50.1). Narratives for SAEs can be found in the individual CSRs.

As per the GCT1015-04 protocol, events of initial or worsening of pre-existing condition to grade 2 and 3 peripheral neuropathy were to lead to dose interruption until the event had improved to grade 1 or lower. Events of grade 4 and higher peripheral neuropathy were to lead to the permanent discontinuation of tisotumab vedotin (m5.3.5.2 GCT1015-04 Protocol Section 7.2.2). Five subjects (5.0%) discontinued, none due to a grade 4 event; the most common preferred terms leading to discontinuation were peripheral sensorimotor neuropathy and peripheral sensory neuropathy (each in 2 subjects, 2.0%) (ISS Table 10.2.56.1). Eight subjects (7.9%) experienced events leading to a dose interruption and 2 subjects (2.0%) had peripheral neuropathy TEAEs that led to a dose reduction (ISS Table 10.2.57.1 and ISS Table 10.2.58.1).

In GCT1015-04, approximately half (16 subjects) experienced improvement or resolution of at least one peripheral neuropathy event within the 30-day follow-up period after end of treatment (18.4% all resolved, 23.7% some resolved or improved). Median time to resolution was 0.49 months (range 0 to 4.8 months) ([Table 36](#)). At the last follow-up, 18/38 subjects (47.4%) had ongoing events with residual maximum grade 1, 8 (21.1%) had grade 2, and 5 (13.2%) had grade 3. It should be noted that TEAEs of peripheral neuropathy were followed

only until the safety follow-up visit (30 days after last dose), which may explain the relatively high number of events that had not yet resolved at time of last follow-up.

The incidence of peripheral neuropathy events was generally similar between GCT1015-04 and Pools 2 and 3 (any grade ranged 37.6% to 43.0%, grade 3 ranged 6.9% to 10.5%). The median time to onset of grade 2 and 3 peripheral neuropathy events was longer in GCT1015-04 (4.57 months) compared to the pooled analysis groups (median range 2.68 to 3.83 months) (ISS Table 10.3.19).

Table 36: Summary of Treatment Emergent Peripheral Neuropathy

	Pivotal Cervical (GCT1015-04) (N=101)	Non-pivotal Cervical (Pool 1) (N=57)	All Cervical (Pool 2) (N=158)	All Tumor Types (Pool 3) (N=272)
Subjects with any treatment-emergent peripheral neuropathy	38/101 (38%)	28/57 (49%)	66/158 (42%)	117/272 (43%)
Grade 1	19 (18.8%)	15 (26.3%)	34 (21.5%)	57 (21.0%)
Grade 2	12 (11.9%)	7 (12.3%)	19 (12.0%)	40 (14.7%)
Grade 3	7 (6.9%)	6 (10.5%)	13 (8.2%)	20 (7.4%)
Subjects with any treatment-related treatment-emergent peripheral neuropathy adverse events	33 (32.7%)	25 (43.9%)	58 (36.7%)	107 (39.3%)
Grade 1	17 (16.8%)	13 (22.8%)	30 (19.0%)	53 (19.5%)
Grade 2	9 (8.9%)	6 (10.5%)	15 (9.5%)	35 (12.9%)
Grade 3	7 (6.9%)	6 (10.5%)	13 (8.2%)	19 (7.0%)
Time to onset of first event (months), n	38	28	66	117
Mean (STD)	3.08 (2.30)	2.99 (2.41)	3.04 (2.33)	2.56 (2.08)
Median	2.46	2.28	2.41	2.10
Min, Max	0.0, 11.3	0.1, 10.0	0.0, 11.3	0.0, 11.3
Subjects with all events resolved	7/38 (18.4%)	4/28 (14.3%)	11/66 (16.7%)	17/117 (14.5%)
Subjects with some events resolved or improved	9/38 (23.7%)	2/28 (7.1%)	11/66 (16.7%)	18/117 (15.4%)
Subjects with no events resolved or improved	22/38 (57.9%)	22/28 (78.6%)	44/66 (66.7%)	82/117 (70.1%)
Number of events	56	41	97	172
Number of events resolved	13/56 (23.2%)	8/41 (19.5%)	21/97 (21.6%)	37/172 (21.5%)
Time to resolution (months), n	13	8	21	37
Mean (STD)	0.91 (1.32)	0.88 (1.24)	0.90 (1.26)	1.25 (2.29)
Median	0.49	0.44	0.49	0.49
Min, Max	0.0, 4.8	0.0, 3.6	0.0, 4.8	0.0, 12.9
Subjects with ongoing events at the last follow-up	38	28	66	117
Maximum Grade 1	18/38 (47.4%)	12/28 (42.9%)	30/66 (45.5%)	49/117 (41.9%)
Maximum Grade 2	8/38 (21.1%)	6/28 (21.4%)	14/66 (21.2%)	35/117 (29.9%)
Maximum Grade 3	5/38 (13.2%)	6/28 (21.4%)	11/66 (16.7%)	16/117 (13.7%)

Source: Adapted from ISS Table 10.2.59; Table 10.2.54.1; Table 10.2.53.1

In GCT1015-04, 20 out of 101 subjects had pre-existing peripheral neuropathy TEAEs (ISS Table 10.3.17). Subjects with pre-existing peripheral neuropathy had a similar rate of

treatment-emergent peripheral neuropathy compared to the overall study population (Table 25) as well as those without pre-existing peripheral neuropathy.

These results from the pivotal trial were generally consistent with Pool 3 (ISS Table 10.3.17).

The Applicant's Position:

Peripheral neuropathy AEs were mostly grade 1 and 2 and were manageable with dose modifications and standard supportive care. Across pools, the most common TEAE leading to treatment discontinuation was peripheral neuropathy. Subjects with pre-existing peripheral neuropathy had a similar rate and maximum severity of treatment-emergent peripheral neuropathy as subjects without prior history.

The FDA's Assessment:

FDA conducted an independent analysis of peripheral neuropathy associated with tisotumab vedotin. FDA's analysis focused on the GCT1015-04 population and the Pool 2 population. Any instance of new or worsening peripheral neuropathy was captured as a TEAE. In the Pool 2 population, the frequency of peripheral neuropathy was 42%, with 8% of patients experiencing grade 3 events. The frequencies of all grade and grade 3 events were similar in the GCT1015-04 population. The most common peripheral neuropathy preferred terms in the Pool 2 population were neuropathy peripheral (20%), peripheral sensory neuropathy (11%), and peripheral sensorimotor neuropathy (5%).

In Pool 2, peripheral neuropathy led to dose interruption in 6% of patients, dose reduction in 1% of patients, and dose discontinuation in 8% of patients. Only 17% of patients who experienced peripheral neuropathy had complete resolution at last follow-up, and no patients who experienced grade 3 neuropathy had complete resolution. FDA does not consider time to resolution to be helpful or accurate information, given the large number of patients with ongoing peripheral neuropathy at last follow-up.

In GCT1015-04, information regarding whether patients had pre-existing peripheral neuropathy was captured. Peripheral neuropathy occurred in approximately equal frequency in patients with and without pre-existing peripheral neuropathy: 35% vs. 38%, respectively. Grade 3 neuropathy was more common in patients with pre-existing neuropathy compared to patients without pre-existing neuropathy: 15% vs. 5%, respectively. Patients with pre-existing peripheral neuropathy grade ≥ 2 were not eligible to receive tisotumab vedotin.

FDA's analysis also considered whether all observed peripheral neuropathy was axonal, or whether tisotumab vedotin may also be associated with a demyelinating neuropathy. Axonal neuropathy is characterized predominantly by sensory loss, whereas demyelinating neuropathy is autoimmune in nature and may be associated with muscle weakness. To assess for a demyelinating neuropathy signal, FDA did a focused search for preferred terms that indicated a predominantly motor neuropathy or demyelinating neuropathy. In the Pool 2 population, 3% of patients developed motor neuropathy, 3% of patients developed muscular weakness, and 1% of patients developed a demyelinating peripheral neuropathy. In addition, there was one patient

with a different tumor type in the Pool 3 population who developed Guillain-Barre syndrome.

Peripheral neuropathy is included in Section 5: Warnings and Precautions of the tisotumab vedotin USPI. FDA recommends discontinuing tisotumab vedotin for grade 3 or 4 peripheral neuropathy.

8.2.4.3 Bleeding Events

Data:

Tisotumab vedotin is an ADC-targeting tissue factor, which is the molecular initiator of the coagulation cascade after vascular injury in normal physiology. For this reason, bleeding was identified as an AESI for tisotumab vedotin. Pelvic bleeding is a well-known complication of cervical cancer because of local tumor growth in vaginal and pelvic regions. In addition, as irradiated areas of the body are more prone to bleeding, prior pelvic radiotherapy, may increase the risk of bleeding. Bleeding events have been commonly reported in trials of therapies for cervical cancer. Patients with a history of bleeding conditions or severe bleeding events were typically excluded from trials of tisotumab vedotin.

The safety analysis of bleeding AEs in subjects treated with 2.0 mg/kg tisotumab vedotin 1Q3W focused on SMQs detailed in the ISS.

Bleeding events across safety analysis groups are summarized in [Table 37](#). In GCT1015-04, bleeding events occurred in 57 subjects (56.4%) and were considered to be treatment-related in 39 subjects (38.6%). The most commonly occurring (>20%) bleeding event was epistaxis, reported in 39 subjects (38.6%) (ISS Table 10.2.60). More than 90% of all epistaxis events (36/39 subjects) were grade 1 and did not require intervention. Other common bleeding AEs were (≥5% incidence) vaginal haemorrhage (11 subjects, 10.9%) and haematuria (9 subjects 8.9%).

Six subjects (5.9%) had grade 3 bleeding events, which were mostly attributable to underlying illness. No subjects reported bleeding events of grade 4 or 5 (ISS Table 10.2.64). Bleeding SAEs were reported in 5 subjects (5.0%) and included preferred terms of vaginal haemorrhage (2 subjects), and cystitis haemorrhagic, haematuria, and rectal haemorrhage (each in 1 subject) (ISS Table 10.2.61). Narratives for SAEs can be found in the individual CSRs. No subjects in GCT1015-04 discontinued due to bleeding AEs (ISS Table 10.2.67).

In GCT1015-04, 45/57 (78.9%) experienced complete resolution of all their events and a further 6 subjects (10.5%) had improvement or resolution of at least 1 event of bleeding ([Table 37](#)). Median time to resolution was 0.33 months (range 0.0 to 6.1 months). At the last follow-up, 8/57 (14.0%) had AEs with residual maximum grade 1, 2 (3.5%) had AEs with residual maximum grade 2, and 2 (3.5%) had AEs with residual maximum grade 3.

These results from GCT1015-04 were generally consistent with Pool 2. The rate of bleeding AEs was lower in the GCT1015-04 group (56.4%) compared to subjects in Pool 1 (71.9%) and Pool 3 (70.6%). In addition, treatment-related bleeding events were slightly less frequent in the pivotal

trial compared to Pool 2 (46.2%) and lower than in the other pooled analyses (59.6% in Pool 1, and 58.1% in Pool 3). While no subjects with cervical cancer discontinued due to bleeding AEs, 2 subjects (0.7%) with other tumor types included in Pool 3 were discontinued due to bleeding events (epistaxis and haemoptysis in 1 subject and gastrointestinal hemorrhage in 1 subject) (ISS Table 10.2.67). Other differences included the median time to first onset of other bleeding events excluding epistaxis, which occurred later in subjects in GCT1015-04 compared to the pooled groups (median of 0.76 months vs 0.26, 0.46, and 0.30 months in Pools 1, 2, and 3, respectively) (ISS Table 10.3.4).

Table 37: Summary of Treatment Emergent Bleeding Adverse Events

	Pivotal Cervical (GCT1015-04) (N=101)	Supportive Cervical (Pool 1) (N=57)	All Cervical (Pool 2) (N=158)	All Tumor Types (Pool 3) (N=272)
Subjects with any treatment-emergent bleeding adverse events	57/101 (56.4%)	41/57 (71.9%)	98/158 (62.0%)	192/272 (70.6%)
Grade 1	46 (45.5)	36 (63.2)	82 (51.9)	166 (61.0)
Grade 2	5 (5.0)	3 (5.3)	8 (5.1)	13 (4.8)
Grade 3	6 (5.9)	2 (3.5)	8 (5.1)	13 (4.8)
Subjects with any treatment-related treatment-emergent bleeding adverse events	39 (38.6)	34 (59.6)	73 (46.2)	158 (58.1)
Grade 1	34 (33.7)	31 (54.4)	65 (41.1)	145 (53.3)
Grade 2	3 (3.0)	2 (3.5)	5 (3.2)	9 (3.3)
Grade 3	2 (2.0)	1 (1.8)	3 (1.9)	4 (1.5)
Time to onset of first event (months), n	57	41	98	192
Mean (STD)	0.91 (1.36)	0.47 (0.56)	0.73 (1.12)	0.59 (0.87)
Median	0.30	0.26	0.26	0.26
Min, Max	0.0, 6.5	0.0, 2.5	0.0, 6.5	0.0, 6.5
Subjects with all events resolved	45/57 (78.9%)	25/41 (61.0%)	70/98 (71.4%)	127/192 (66.1%)
Subjects with some events resolved or improved	6/57 (10.5%)	5/41 (12.2%)	11/98 (11.2%)	24/192 (12.5%)
Subjects with no events resolved or improved	6/57 (10.5%)	11/41 (26.8%)	17/98 (17.3%)	41/192 (21.4%)
Number of events	99	79	178	318
Number of events resolved	86/99 (86.9%)	58/79 (73.4%)	144/178 (80.9%)	246/318 (77.4%)
Time to resolution (months), n	86	58	144	246
Mean (STD)	1.05 (1.51)	0.88 (1.31)	0.98 (1.43)	0.94 (1.30)
Median	0.33	0.33	0.33	0.33
Min, Max	0.0, 6.1	0.0, 6.1	0.0, 6.1	0.0, 6.1
Number of events with improvement	1/99 (1.0%)	1/79 (1.3%)	2/178 (1.1%)	2/318 (0.6%)
Subjects with ongoing events at the last follow-up				
Maximum Grade 1	8/57 (14.0%)	14/41 (34.1%)	22/98 (22.4%)	58/192 (30.2%)
Maximum Grade 2	2/57 (3.5%)	2/41 (4.9%)	4/98 (4.1%)	5/192 (2.6%)
Maximum Grade 3	2/57 (3.5%)	0	2/98 (2.0%)	2/192 (1.0%)

Source: Adapted from ISS Table 10.2.70; Table 10.2.65; Table 10.2.64

Major bleeding events were typically associated with tumor location, were manageable with standard supportive care (eg, transfusions), and did not require more aggressive measures such as use of clotting factors. There were no AEs of bleeding associated with fatal outcomes. In GCT1015-04, 6 subjects (5.9%) experienced grade 3 bleeding events that were generally related to tumor progression, including the preferred terms of vaginal haemorrhage, rectal haemorrhage, cystitis haemorrhagic, and haematuria (ISS Table 10.2.62 and ISS Table 10.2.66).

The Applicant's Position:

The most commonly occurring bleeding event was epistaxis, more than 90% of all epistaxis events were grade 1 and did not require intervention. Major bleeding events were typically associated with tumor location, were manageable with standard supportive care (eg, transfusions), and did not require more aggressive measures such as use of clotting factors. There were no AEs of bleeding associated with fatal outcomes. No subject discontinued due to Bleeding AEs in GCT1015-04 or Pool 2.

The FDA's Assessment:

FDA conducted an independent analysis of hemorrhage which focused on patients with cervical cancer receiving tisotumab vedotin in GCT1015-04 and in Pool 2. Hemorrhage was common, with 62% of patients in the Pool 2 population experiencing hemorrhage. Although most hemorrhage TEAEs were grade 1, 5% of patients in Pool 2 experienced grade 3 events. In the 90-day safety update, there was one additional patient enrolled to GCT1015-04 who experienced grade 3 hematuria. The increased frequency of hemorrhage in the Pool 2 population compared to the GCT1015-04 population could be due to differences in patient characteristics, although FDA notes that eligibility criteria with respect to hemorrhage were similar for all trials with patients included in Pool 2.

In Pool 2, the most common types of hemorrhage were epistaxis (44%), hematuria (10%), and vaginal hemorrhage (10%). Hemorrhage occurred early after exposure to tisotumab vedotin, with median time to onset 0.3 months (range: 0, 6.5) in the Pool 2 population. Dose modifications due to hemorrhage were infrequent. In the Pool 2 population, 3% of patients experienced dose interruption and 0.6% of patients experienced dose reduction due to hemorrhage. There were no dose discontinuations due to hemorrhage.

FDA disagrees with portions of the Applicant's characterization of hemorrhage with tisotumab vedotin. Although grade 3 hemorrhage was infrequent, patients experiencing grade 3 hemorrhage required red blood cell transfusion, tranexamic acid, and more aggressive measures such as tumor resection or radiation treatment. While grade 3 hemorrhage occurred at sites of tumor, FDA believes that exposure to tisotumab vedotin may have increased the propensity of tumor to bleed at these locations based on its mechanism of action and the overall frequency of hemorrhage in patients receiving tisotumab vedotin. FDA acknowledges that there are limitations in making an assessment in a single arm trial without a control arm.

Given the frequency of hemorrhage and the potential for severity in patients receiving

tisotumab vedotin, FDA included hemorrhage in Section 5: Warnings and Precautions of the tisotumab vedotin USPI.

FDA reviewed narratives for Grade 3 hemorrhage occurring on GCT1015-04 which are summarized briefly below.

Narratives:

Patient ID: GCT1015-04- (b) (6) :

This 41 yo woman had metastatic SCC of the cervix involving the cervix, liver, and rectum. On study day -4, she had grade 1 rectal hemorrhage and grade 1 anemia. She received treatment with tranexamic acid. On study day 8, she developed grade 3 rectal hemorrhage and grade 3 anemia. She received a blood transfusion. On study day 20, the patient had rectal bleeding and a fever and was admitted to the hospital. She received another blood transfusion as well as antibiotic treatment and tisotumab vedotin administration was delayed. On study day 28, she received another blood transfusion and was discharged. On study day 30, she was readmitted with rectal hemorrhage grade 3 and she continued treatment with tranexamic acid and blood transfusions. On study day 36, rectal hemorrhage improved to grade 2 and she received cycle 2 of tisotumab vedotin. On study day 48, she was found to have radiographic progression of disease and tisotumab vedotin was discontinued. Her aPTT was within normal limits and platelets were 200 to 300 x10⁹/L throughout the trial. Her INR was increased (1.5-1.8) and PT was slightly prolonged throughout the trial for unclear reasons.

Patient ID: GCT1015-04- (b) (6)

This 75 yo woman had metastatic adenosquamous carcinoma of the cervix involving the uterus, extrapelvic lymph nodes, and lung. On day 1, after receiving tisotumab vedotin, she experienced grade 2 vaginal hemorrhage and was hospitalized. On day 4, hemorrhage improved to grade 1, and the patient underwent arterial transcatheter embolization. The procedure was unsuccessful. On day 13, the patient underwent another unsuccessful arterial transcatheter embolization. She received cycle 2 of tisotumab vedotin on study day 21. On study day 38, she underwent an epicystostomy. On study day 39, she had worsening vaginal hemorrhage to grade 3. She received red blood cell transfusion and tranexamic acid. On study days 53 to 65, the patient received palliative radiation for vaginal bleeding. Tisotumab vedotin had been discontinued due to clinical progression of disease. On study day 82, the patient died due to underlying disease. Her aPTT, PT, and INR were within normal limits throughout the trial and platelets were in the 200 to 400 x 10⁹/L range.

Patient ID: GCT1015-04- (b) (6)

This patient is a 53 yo woman with metastatic adenocarcinoma of the cervix involving the bladder, uterus, and vagina. On study day 23, the patient developed grade 3 hematuria. She was admitted and an indwelling catheter was placed for bladder irrigation. She received prophylactic enoxaparin on study day 23. On day 28, she developed grade 2 anemia. On study

day 29, the patient had transurethral resection of her bladder and received red blood cell transfusion for anemia. On study day 31, hematuria resolved. On study day 42, she received her third cycle of tisotumab vedotin. On study day 69, she discontinued tisotumab vedotin per her request. Her aPTT, PT, and INR were within normal limits throughout the trial. Her platelet count was $170\text{-}350 \times 10^9/\text{L}$.

Patient ID: GCT1015-04- (b) (6)

This patient is a 68 yo woman with metastatic SCC of the cervix involving the cervix, pelvic and extrapelvic lymph nodes, bone, right ventricle, and liver. She received three cycles of tisotumab vedotin. From study days 42 to 67, she was treated with dalteparin sodium for a cardiac thrombus (which was subsequently determined to be a cardiac metastasis). On study day 68, she developed grade 3 vaginal hemorrhage and was admitted. She received treatment with vaginal compression, tranexamic acid, and metholprednisolone. She had concurrent grade 3 anemia and thrombocytopenia and received transfusions of red blood cells and platelets. Her vaginal hemorrhage improved to grade 1 and she was discharged. On study day 70, she resumed dalteparin sodium. On study day 81, vaginal hemorrhage worsened to grade 3, she received transfusions with red blood cells and platelets and receive tranexamic acid. On study day 84, tisotumab vedotin was discontinued because of radiographic progression of disease. On study days 85-90, she received palliative radiation for hemorrhage. On study day 101, she died due to underlying disease.

Patient ID: GCT1015-04- (b) (6)

This patient is a 42 yo woman with SCC of the cervix involving extra-pelvic lymph nodes. Following five cycles of tisotumab vedotin, she developed grade 1 lower GI hemorrhage. Following eight cycles of tisotumab vedotin, on study day 153, she developed grade 3 rectal hemorrhage, received a transfusion, and hemorrhage resolved. She continued to receive 13 cycles of tisotumab vedotin until treatment was discontinued due to radiographic progression of disease. It appears the patient received enoxaparin sodium from study day -14 to 106 for a DVT and may have also briefly received warfarin. Her platelets were between 170 and $250 \times 10^9/\text{L}$ for the duration of the trial.

Patient ID: GCT1015-04- (b) (6)

This patient is a 51 yo woman with SCC involving the bone and extrapelvic LN. On study day 3 she experienced grade 1 epistaxis which resolved on study day 105. She received seven cycles of tisotumab vedotin. On study day 133, she developed grade 3 hemorrhagic cystitis. She was admitted and a urinary catheter was placed. She received TMP/SMX for treatment of cystitis and hematuria resolved. She developed grade 2 anemia. On study day 134, hematuria resolved and she was discharged. On study day 157, the patient underwent cystoscopy due to hematuria which was reported as normal. She received 12 cycles of tisotumab vedotin until treatment was discontinued due to radiographic progression of disease. She died on study day 496 due to underlying disease. Her aPTT, PT, and INR were within normal limits throughout the trial. Her platelet count was between 180 and $350 \times 10^9/\text{L}$ through the trial.

Patient ID: GEN701- (b) (6)

The patient is a 30 yo woman with cervical cancer. On study day 4, she experienced grade 1 epistaxis and this resolved on study day 6. Following eight cycles of tisotumab vedotin, on study day 178, the patient experienced grade 2 vaginal hemorrhage. This resolved on the same day and she was discharged. On study day 184, she developed grade 3 vaginal hemorrhage and this resolved on study day 187. On study day 190, MRI showed disease progression with increase in cervical tumor size and tisotumab vedotin was discontinued. Her aPTT, PT, and INR were reported as within normal limits on study day 184, and platelets were $224 \times 10^9/L$

Patient ID: GEN701- (b) (6)

This patient is a 56 yo woman with cervical cancer. Following three cycles of tisotumab vedotin, on study day 69, she developed grade 3 hematuria. She received cycle four of treatment on study day 71. On study day 75, due to persistent symptoms of hematuria, the patient was admitted. A urinary catheter was placed, and the patient had a cystoscopy with transurethral resection of tumor in the bladder. There were no radiation changes visible. The patient received eight cycles of tisotumab vedotin, experience grade 2 hematuria on study day 157, and discontinued treatment on study day 177 due to progression of disease. Coagulation labs data and platelet count are not provided.

8.2.4.4 Infusion-related Reactions

Data:

Infusion-related reactions were first programmatically identified in case report forms via a check box for such reactions and must have occurred the day of, or after, an infusion of tisotumab vedotin, followed by individual case clinical review to assess whether the event represented a potential infusion-related reaction (IRR.) Clinical review of each event identified took into consideration the temporal relationship to dose infusion, reported signs and symptoms, action taken with dosing (eg, interruption of infusion, reduced rate of infusion on resuming or subsequent infusion and/or introducing pre-medications), treatments or management used for the event, concurrent conditions, medical history, and recurrence of similar events on rechallenge, if available. In addition, exploratory analyses using MedDRA SMQs of Anaphylaxis and Hypersensitivity were performed.

Infusion-related reactions (IRRs) meeting the programmatic search strategy were identified in 1 subject (1.0%) in GCT1015-04 (ISS Table 10.3.57). This subject developed grade 2 fatigue and grade 2 pyrexia. The subject received subsequent doses of tisotumab vedotin with premedication without recurrence of IRR.

A total of 7 subjects were assessed as having events representing possible IRR (Table 10.3.57).

Only 1 subject from the pivotal GCT1015-04 trial experienced an episode of potential IRR reported as pyrexia and fatigue (both grade 2). The remaining 6 subjects were all from the GEN701 trial and included 2 subjects with events of hypersensitivity, 2 subjects with events of pyrexia, and 1 subject each of lethargy and hypotension. None of these events were life-threatening, and only 3 subjects received treatment with antihistamines, steroids, and/or acetaminophen. Three subjects received additional subsequent doses of tisotumab vedotin without recurrence of IRR; only 1 of which received premedication on subsequent doses.

The incidence and severity of IRRs was similar across safety analysis groups.

No events consistent with anaphylaxis/anaphylactoid reactions or severe, life threatening hypersensitivity were identified. There is no safety signal for anaphylaxis or systemic hypersensitivity with tisotumab vedotin to date.

The Applicant's Position:

Few subjects experienced infusion-related reactions and these were of low clinical impact and manageable by standard of care.

The FDA's Assessment:

FDA conducted an independent analysis of IRRs associated with tisotumab vedotin which were infrequent. Given the low frequency of IRRs, FDA relied on the Pool 3 population for the assessment and agrees with the Applicant's assessment. The overall frequency of IRRs was low with 1 patient enrolled to GCT1015-04 who experienced a grade 2 IRR, and 6 additional patients in the Pool 3 population who experienced IRRs. Only one patient experienced a grade 3 IRR. Four of the 7 patients experiencing IRRs were able to get subsequent treatment with tisotumab vedotin, including the patient who experienced the grade 3 IRR.

8.2.4.5 Pneumonitis

The FDA's Assessment

The Applicant did not include an assessment of pneumonitis in their submission. However, FDA conducted an independent analysis of pneumonitis as pneumonitis has been observed with other antibody-drug conjugates containing vedotin.

In the Pool 2 population, there were 2 patients who experienced pneumonitis, including 1 patient who died. Both patients were enrolled to GCT1015-04 and narratives are summarized below.

As antibody-drug conjugates containing vedotin are associated with pneumonitis, and there was one patient who received tisotumab vedotin, experienced pneumonitis and died, FDA included this toxicity in Section 5: Warnings and Precautions of the USPI.

Narratives:

GCT1015-04- (b) (6) (copied from Section 8.2.3 "Deaths")

This 70 yo woman with history of type 2 diabetes mellitus had metastatic SCC of the cervix

involving lungs, bone, rectum, and pelvis. She received two cycles of tisotumab vedotin. On study day 27, she was admitted to the hospital with fever and shortness of breath and was diagnosed with pneumonitis based on chest CT. CT also showed lung metastases and a L-sided pleural effusion, size unspecified. She received treatments with antibiotics, prednisone, and furosemide. The narrative states that the patient was believed to be at the end-of-life and was discharged from the hospital. It is not clear if she was discharged to hospice, but on day 42 she received palliative sedation with morphine and on day 45 she died. FDA disagrees with the investigator and Sponsor and thinks that pneumonitis and death are possibly related to tisotubmab vedotin.

GCT1015-04- (b) (6)

This patient is a 68 yo woman with metastatic SCC of the cervix involving the cervix, pelvic lymph nodes, extra-pelvic lymph nodes, bone, right ventricle, and liver. She received two cycles of tisotumab vedotin. On study day 41, she was diagnosed with grade 2 pneumonitis based on symptoms of dyspnea and fatigue, and a high-resolution CT scan showing bilateral diffuse ground glass infiltrates consistent with pneumonitis. She received treatment with prednisone, and on study day 78, pneumonitis was reported as resolved.

8.2.5 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Data:

See Section 8.1.2 for the secondary endpoints relating to COA.

The Applicant's Position:

HRQOL was in general maintained or showed small but not clinically meaningful decreases on most domains between baseline and Cycle 4. The larger decreases in some domains/items at time of treatment discontinuation are expected as most subjects at the timepoint experienced progressive disease or discontinuation of trial drug due to ongoing AEs. Given the single-arm trial design, limited data collected, lack of published data on HRQOL in cervical cancer, the clinical meaningfulness of these declines is hard to interpret.

The FDA's Assessment:

FDA did not consider HRQOL PRO data in our assessment of safety or tolerability. FDA agrees with the Applicant that interpretation of HRQOL is limited due to the lack of a control arm. Refer to Section 8.1.2 for more details on HRQOL data.

8.2.6 Safety Analyses by Demographic Subgroups

Data:

The safety populations were assessed with subgroup analyses for intrinsic and extrinsic factors.

Age

In GCT1015-04, the median age was 50 years old (m2.7.4 Table 6). Analyses were conducted for subjects <65 years versus ≥65 years. In GCT1015-04, the incidence of SAEs and grade 3 and higher TEAEs was higher in the older subgroup. However, the number of subjects in the ≥65 years group was small (n=13) and therefore limits interpretation of the data. No differences by age subgroup were apparent for the most common TEAEs (ISS Table 10.2.20). The results of the pivotal trial were generally consistent with the pooled analysis groups (m2.7.4 Table 28).

Sex

In the safety analysis groups focused on subjects with cervical cancer, all subjects were female. In Pool 3, 46 subjects (16.9%) were male (ISS Table 10.1.2). Subgroup analyses by sex were not performed as the intended indication is cervical cancer.

Race and Ethnicity

Across all safety analysis groups, 89.5% to 95.0% of subjects were white, and 94.1% to 96.5% of subjects were classified as not of Hispanic or Latino ethnicity (ISS Table 10.1.2). The limited subgroup sizes for race and ethnicity in this study population preclude subgroup analysis.

Hepatic Insufficiency

Mild hepatic impairment at baseline was observed in a low number of subjects; 8 subjects in the GCT1015-04 trial and 31 subjects across all trials in Pool 3.

In GCT1015-04, the incidence of TEAEs and SAEs were similar regardless of baseline hepatic function, although subjects who had mild hepatic impairment had a higher incidence of grade 3 and higher TEAEs. However, the small number of subjects in this group (n=8) limits interpretation of the data.

These results were consistent with the pooled safety analysis groups and there did not appear to be a notable increase in incidence of treatment emergent SAEs or grade 3 and higher TEAEs between the GCT1015-04 trial and the pooled analysis groups (m2.7.4 Table 29).

Based on population PK analysis, tisotumab vedotin exposures in subjects with mild hepatic impairment were similar to those with normal hepatic function. MMAE exposures in subjects with mild hepatic impairment were 37% higher than those with normal hepatic function. Subjects who had mild hepatic impairment did not appear to have a notably increased incidence of treatment emergent SAEs or grade 3 and higher TEAEs, indicating the increase of MMAE exposure in mild hepatic impairment subjects is not clinically meaningful.

No dose modifications are required for subjects with mild hepatic impairment. Tisotumab vedotin has not been studied in subjects with moderate or severe hepatic impairment.

Renal Insufficiency

In GCT1015-04, 40 subjects were enrolled who had mild renal impairment, and 15 subjects had moderate renal impairment. Subjects who had moderate renal impairment did not appear to have a notably increased incidence of treatment emergent SAEs (47% in subjects with moderate renal impairment and 46% in those with normal renal function). Similarly, moderate renal impairment did not appear to have notably increased incidence of grade 3 and higher

TEAEs (60% in subjects with moderate renal impairment and 61% of those with normal renal function).

Results from the pooled analysis groups were similar to GCT1015-04; no meaningful differences were observed between subjects with mild or moderate renal insufficiency at baseline compared to those with normal renal function.

Based on population PK analysis, tisotumab vedotin and MMAE exposures were similar in subjects with mild and moderate renal impairment compared to those with normal renal function.

No dose modifications are required for patients with mild or moderate renal impairment. Tisotumab vedotin has not been studied in subjects with severe renal impairment. Therefore, the effect of severe renal impairment on tisotumab vedotin and free MMAE PK is unknown.

Prior Lines of Therapy

Per the ISS SAP, prior lines of therapy were not analyzed for the safety pooled analysis data sets. In GCT1015-04, most subjects (71 subjects, 70.3%) had received 1 prior line of therapy (m2.7.4, Table 31). Generally, subjects with 2 lines of prior therapy appeared to have a similar safety profile as those subjects with 1 prior line, with similar rates of TEAEs and grade 3 and higher TEAEs. The incidence of some TEAEs varied between the 2 groups; alopecia and fatigue were more frequently reported in the subjects with 2 lines of therapy, perhaps reflecting more advanced disease in these patients, while constipation was more frequent in subjects with 1 prior line. The incidence of SAEs was higher in subjects with 2 prior lines of therapy (15 subjects, 50.0%) compared to 1 prior line (28 subjects, 39.4%).

Overall, tisotumab vedotin is well tolerated in subjects with 1 to 2 prior lines of therapy in the metastatic setting.

Prior Bevacizumab Therapy

In GCT1015-04, most subjects (70 subjects, 69.3%) had received prior bevacizumab therapy (m2.7.4 Table 32). The overall number of SAEs and grade 3 and higher TEAEs were similar in subjects who had prior bevacizumab therapy as compared to those without it. Subjects who had prior bevacizumab had higher incidences of some TEAEs than subjects without; in the GCT1015-04 trial, 24 subjects (34%) with prior bevacizumab reported TEAEs of conjunctivitis compared to 7 subjects (23%) without (ISS Table 10.2.26). In addition, some grade 3 and higher TEAEs were more frequent in subjects with prior bevacizumab therapy, including anemia in 8 subjects (11.4%), fatigue in 5 subjects (7.1%), pneumonia in 4 subjects (5.7%), and urinary tract infection in 3 subjects (4.3%), compared to 0 subjects in those without prior bevacizumab (ISS Table 10.2.28).

The safety pooled analysis groups showed similar results. Tisotumab vedotin can be safely administered after bevacizumab or bevacizumab + chemotherapy doublet therapy.

Prior Radiotherapy

Most subjects (82 subjects, 81.2%) in GCT1015-04 received prior radiotherapy (m2.7.4, Table 33). The number of SAEs or grade 3 and higher TEAEs was similar in subjects who had prior radiotherapy compared to those who did not receive it.

Subjects who had prior radiotherapy had higher incidences of some TEAEs than subjects without. In the GCT1015-04 trial, 40 subjects (48.8%) with prior radiotherapy reported TEAEs of nausea compared to 1 subject (5.3%) without (ISS Table 10.2.23), and 34 subjects (41.5%) with prior radiotherapy experienced epistaxis compared to 5 subjects (26.3%) without (ISS Table 10.2.23). The results were generally similar across the safety pooled analysis groups.

Tisotumab vedotin was well tolerated in subjects with prior radiotherapy.

The Applicant's Position:

Overall, there were no safety-related differences observed between subgroups based on intrinsic factors including age, mild hepatic impairment or renal impairment that were considered to be clinically meaningful. Tisotumab vedotin has not been studied in subjects with moderate or severe hepatic impairment or severe renal impairment. Meaningful analysis of tisotumab vedotin safety by sex, race, and ethnicity could not be performed due to small subgroup sample sizes.

Overall, tisotumab vedotin is well tolerated in subjects with 1 to 2 prior lines of therapy in the metastatic setting and in subjects who had previously received bevacizumab or bevacizumab + chemotherapy doublet therapy. Tisotumab vedotin was well tolerated in subjects with prior radiotherapy.

The FDA's Assessment:

FDA conducted an independent analysis of safety in patients ≥ 65 years compared to patients < 65 years. As no tumor responses were observed in patients ≥ 65 years receiving tisotumab vedotin, FDA was particularly concerned about risk-benefit in this patient population.

Patients ≥ 65 years compared to patients < 65 years experienced a higher frequency of grade 3-4 TEAEs and SAEs, 62% vs. 56% and 54% vs. 41%, respectively. Patients ≥ 65 years compared to patients < 65 years also experienced more frequent dose discontinuations: 23% vs. 11%, and dose interruptions: 62% vs. 44%. Dose reductions were the same in the two groups: 23% vs. 23%.

FDA also assessed exposure to tisotumab vedotin in patients ≥ 65 years compared to patients < 65 years to determine if decreased exposure could be driving lack of tumor responses. Patients ≥ 65 years had one fewer median number of cycles of treatment compared to patients < 65 years. Relative dose intensity was similar between the two age groups for cycles of treatment received. It is unclear if this difference in exposure could affect tumor response. FDA's summary of exposure to tisotumab vedotin in patients ≥ 65 years compared to patients < 65 years is shown in Table 38.

Table 38: Exposure to tisotumab vedotin by age in GCT1015-04

	Patients <65 years	Patients ≥65 years
Duration of exposure in months, median (range)	4.3 (0.7, 16.0)	3.7 (1.3, 7.9)
Number of cycles, median (range)	6 (1, 21)	5 (2, 11)
Actual cumulative dose in mg/kg, median (range)	12.0 (2.0, 33)	9.4 (4.0, 19.2)
Relative dose intensity in %, median (range)	96.1 (43.8, 114.0)	94.4 (71.2, 105.9)

Although patients ≥ 65 years experienced higher grade TEAEs and SAEs slightly more frequently than patients <65 years, this analysis is limited by the small number of patients ≥65 years enrolled to GCT1015-04. The details of the modest difference in AE incidence according to age are described in Section 8.5 of product labeling.

FDA did not analyze safety by sex as all patients with cervical cancer enrolled included in GCT1015-04 and Pool 2 were female. FDA did not analyze safety by race or ethnicity due to the small numbers of patients representing racial or ethnic minority groups enrolled to receive tisotumab vedotin.

FDA did not conduct independent analyses of safety by number of prior lines of therapy, prior bevacizumab therapy, or prior radiotherapy but did review the Applicant's analyses. In general, these subgroups are small, and the clinical relevance of differences in safety in these subgroups is uncertain. FDA does not consider the differences in safety to change the risk-benefit of tisotumab vedotin for any of these subgroups defined by prior therapy.

FDA agrees that no tisotumab vedotin dose modifications are needed in patients with mild hepatic impairment and in patients with mild or moderate renal impairment. Tisotumab vedotin should be avoided in patients with moderate or severe hepatic impairment. Please refer to Clinical Pharmacology section 6.3.2.3 for further information.

8.2.7 Specific Safety Studies/Clinical Trials

Data:

N/A

The Applicant's Position:

No specific study or clinical trial was conducted to evaluate specific safety concerns.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

8.2.8 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Data:

N/A

The Applicant's Position:

N/A

The FDA's Assessment:

There were no human carcinogenicity studies of tisotumab vedotin and data are limited regarding long-term use.

Human Reproduction and Pregnancy

Data:

N/A

The Applicant's Position:

There are no available human data on tisotumab vedotin use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. Tisotumab vedotin can cause fetal harm based upon findings from animal studies of MMAEs. Female subjects of childbearing potential treated with tisotumab vedotin should be advised of the potential risk to the fetus.

The FDA's Assessment:

FDA agrees that there were no pregnancies in the tisotumab vedotin development program. In the USPI, FDA advises that female patients of reproductive potential should have pregnancy status verified prior to initiating treatment with tisotumab vedotin. In addition, female patients of reproductive potential should use effective contraception during treatment and for 2 months after the last dose. Male patients with female partners of reproductive potential should use effective contraception during treatment and for 4 months after the last dose. Embryo-fetal toxicity is listed under Warnings and Precautions. Refer to Section 5.5.4 for additional information.

Pediatrics and Assessment of Effects on Growth

Data:

N/A

The Applicant's Position:

Tisotumab vedotin has not been assessed in children. Due to the effect of MMAE on microtubules, the treatment of children would be considered unethical. Tisotumab vedotin should not be given to children as it may affect their development. The FDA-agreed initial pediatric study plan (iPSP) received on 20 June 2019 includes a full waiver for the condition of cervical cancer in all pediatric age groups (birth to 16 years).

The FDA's Assessment:

Although tisotumab had previously been granted a waiver for pediatric studies, it was

determined during this review cycle that tissue factor is a relevant target in pediatric tumors, and therefore, a new pediatric study plan, including a larger plan to investigate tisotumab in pediatric tumors, was needed. After discussion with the pediatric groups at FDA (CDER PERC Committee), it was determined that 2 post-marketing requirements would be put forth, requiring conduct of preclinical and clinical studies of tisotumab in pediatric tumors. These are described in section... In addition, an amended iPSP including a full waiver for pediatric studies for the cervical cancer indication, but a deferral for additional pediatric studies with tisotumab, based upon information from additional studies assessing tissue factor as a relevant molecular target in pediatric malignancies.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data:

A single subject in pivotal trial GCT1015-04 received an overdose at 117% of the recommended 2.0 mg/kg dose of tisotumab vedotin (in cycle 1 and cycle 2). No TEAEs were experienced by this subject that were attributable to this accidental overdoses.

The Applicant's Position:

Neither the effects of overdose of tisotumab vedotin nor an antidote to overdose are known. Tisotumab vedotin is not likely a drug of abuse potential. The potential for tisotumab vedotin drug abuse and dependence is unknown.

The FDA's Assessment:

FDA agrees that the Applicant's assessment.

8.2.9 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Data:

N/A

The Applicant's Position:

Tisotumab vedotin is not currently approved or marketed in any country.

The FDA's Assessment:

FDA agrees that tisotumab vedotin is not currently approved or marketed in any country.

Expectations on Safety in the Postmarket Setting

Data:

In addition to the studies presented in this application, which includes ongoing pivotal trial GCT1015-04 and trial SGNTV-001 (ADA, ECG, and QTcF data), additional ongoing trials with tisotumab vedotin include the following:

- GCT1015-05, a Phase 1b/2 open-label trial of tisotumab vedotin (HuMax-TF-ADC) monotherapy and in combination with other agents in subjects with recurrent or stage 4b cervical cancer treated with 2.0 mg/kg 1Q3W or (b) (4). This includes 142 subjects as of 16 Aug 2020 data cutoff.

- GCT1015-06, an open-label phase 1/2 trial of tisotumab vedotin in Japanese subjects with previously treated recurrent or metastatic cervical cancer (Part 2) or advanced solid malignancies (alveolar sarcoma, squamous esophageal, squamous cervical, ovarian, colon adenocarcinoma; Part 1). As of the data cutoff of 16 Aug 2020, 23 subjects had been treated with [REDACTED] (b) (4) or 2.0 mg/kg 1Q3W, including 17 subjects in Part 2 and 6 subjects in Part 1).
- SGNTV-002, an open-label phase 2 study of tisotumab vedotin in patients with platinum-resistant ovarian cancer. As of the data cutoff of 16 Aug 2020, 55 subjects have been treated with a safety run-in of a dose-dense regimen: 2.0 mg/kg 1Q3W, [REDACTED] (b) (4)
- SGNTV-003, a randomized, open-label phase 3 trial of tisotumab vedotin (2.0 mg/kg 1Q3W) versus investigator's choice of chemotherapy in second- or third-line recurrent or metastatic cervical cancer.

The Applicant's Position:

All safety concerns that have been identified are adequately represented in the safety database for tisotumab vedotin. Ongoing clinical trials will contribute additional safety information to further elucidate the safety profile of tisotumab vedotin.

The FDA's Assessment:

FDA agrees that the safety of tisotumab vedotin has been characterized in GCT1015-04 and other trials reviewed as part of this application. FDA agrees that additional ongoing trials will contribute additional safety information. FDA will also continue to monitor post-marketing reports and safety reports submitted after approval.

8.2.10 Integrated Assessment of Safety

Data:

The integrated safety profile of tisotumab vedotin in this application is based upon a total of 272 subjects with malignant tumors, primarily cervical cancer. The pivotal trial GCT1015-04 consists of 101 subjects with previously treated, recurrent or metastatic cervical cancer. All subjects received the recommended dose of 2.0 mg/kg of tisotumab vedotin 1Q3W. Overall exposure is adequate to support the characterization of the safety profile of tisotumab vedotin.

At 2.0 mg/kg 1Q3W most AEs were manageable with either supportive or preventative care or dose modifications. The overall characteristics of the population studied in GCT1015-04 are representative of, and generalizable to, subjects with recurrent or metastatic cervical cancer who have received at least one prior systemic therapy. AESIs for tisotumab vedotin are ocular AEs, epistaxis, and peripheral neuropathy. Of those, ocular AEs and peripheral neuropathy have been classified as important AESIs. Most ocular events were grade 1 or 2, were transient, and achieved resolution. The protocol-defined OMP measures are effective. With these measures, most events are low grade and resolve or improve quickly. The measures also reduced frequency of ocular events and led to fewer treatment discontinuations. Peripheral neuropathy AESIs were mostly grade 1 and 2 and were manageable with dose modifications and standard supportive care. Major bleeding events were typically associated with tumor location, were

manageable with standard supportive care (eg, transfusions), and did not require more aggressive measures such as use of clotting factors. There were no AEs of bleeding associated with fatal outcomes.

No new safety signals were identified.

The Applicant's Position:

Based on the safety results observed, tisotumab vedotin, at the recommended dose of 2.0 mg/kg 1Q3W, has a manageable and tolerable safety profile in subjects with recurrent or metastatic cervical cancer who previously received chemotherapy doublet plus bevacizumab, if eligible.

The FDA's Assessment:

FDA agrees with the Applicant that the safety database is adequate to characterize the safety profile of tisotumab vedotin.

In GCT1015-04, the most common ($\geq 30\%$) adverse reactions were hemorrhage, fatigue, nausea, peripheral neuropathy, alopecia, and conjunctival adverse reactions.

Serious adverse reactions occurred in 43% of patients and included ileus, hemorrhage, pneumonia, peripheral neuropathy, acute kidney injury, sepsis, constipation, and pyrexia. Fatal adverse reactions occurred in 4% of patients and included septic shock, pneumonitis, sudden death, and multisystem organ failure, each in 1 patient.

Treatment discontinuations due to TEAEs occurred in 13% of patients, most commonly due to peripheral neuropathy and corneal adverse reactions. Dose reductions occurred in 23% of patients, most commonly due to conjunctival adverse reactions and corneal adverse reactions.

FDA disagrees with the Applicant's identification and characterization of important AESIs. Ocular toxicity is an important safety signal for tisotumab vedotin and to alert providers to the potential for severe ocular toxicity such as development of corneal ulcers, FDA elevated ocular toxicity to a Boxed Warning in the USPI.

While FDA agrees that the OMP measures reduced the frequency of ocular toxicity, FDA notes that the OMP measures, particularly ophthalmic steroids, also have risk. Ophthalmic corticosteroids should be used consistent with current labeling which includes a slit lamp exam prior to the initial prescription and prior to all renewals.

FDA agrees that peripheral neuropathy is an important AESI and labeled this under Warnings and Precautions. In addition, FDA classified hemorrhage as an important AESI due to its frequency and the potential for severity and labeled it under Warnings and Precautions. Pneumonitis is an important safety signal associated with antibody-drug conjugates containing vedotin, and two patients in GCT1015-04 experienced pneumonitis, including one patient who died. FDA also included pneumonitis under Warnings and Precautions.

Overall, the safety profile of tisotumab vedotin is manageable through labeling and supportive oncologic care and acceptable for the indicated population which has a serious and life-threatening disease and limited therapeutic options.

SUMMARY AND CONCLUSIONS

8.3 Statistical Issues

The FDA's Assessment:

There were no major statistical issues with the study design, statistical analysis plan, or efficacy results of Study GCT1015-04. The study showed a confirmed IRC-assessed ORR of 23.8% (95% CI: 15.9%, 33.3%) in 101 subjects with recurrent or metastatic cervical cancer, and the median DOR among the 24 confirmed responders was 8.3 months (95% CI: 4.2 month, NR).

No inferential procedures were 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 PFS and OS results were summarized, time-to-event endpoints are uninterpretable without a comparator arm.

8.4 Conclusions and Recommendations

The FDA's Assessment:

In GCT1015-04, treatment with tisotumab vedotin resulted in an ORR of 23.8% (95% CI: 15.9, 33.3) and a median DOR of 8.3 months (95% CI: 4.2, NR) in patients with recurrent or metastatic cervical cancer who had received ≤ 2 lines of systemic treatment in the recurrent or metastatic setting, including doublet chemotherapy, with bevacizumab if eligible. Available therapies in this treatment setting include single agent chemotherapies with ORRs ranging from 5%-21% and median DORs ranging from 2-4 months, but these data collected prior to establishment of a chemotherapy doublet with bevacizumab as standard-of-care first-line treatment for patients in the U.S. Given that all patients who received tisotumab vedotin on GCT1015-04 received first-line doublet chemotherapy and 69% of patients had prior bevacizumab as per U.S. standard of care, the review team considers that the efficacy of tisotumab vedotin demonstrates an improvement compared to available therapies and is reasonably likely to predict clinical benefit in the indicated population.

Tisotumab vedotin demonstrated acceptable safety and tolerability in the indicated patient population with a serious and life-threatening condition and limited therapeutic options. The safety of tisotumab vedotin is manageable through labeling, which includes a boxed warning for ocular toxicity, premedication, dose modification, and supportive care.

Based on a favorable benefit-risk assessment, FDA clinical and statistical reviewers recommend accelerated approval for the following indication:

Tivdax is a tissue factor-directed antibody and microtubule inhibitor conjugate indicated for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy.

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

X

X

Primary Statistical Reviewer
Zhou Feng, PhD

Statistical Team Leader
Erik Bloomquist, PhD

X

X

Primary Clinical Reviewer
Mirat Shah, M.D.

Clinical Team Leader
Gwynn Ison, M.D.

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

FDA did not refer this application to an advisory committee as there were no efficacy or safety issues identified during the review which required external input for the proposed indication.

10 Pediatrics

The Applicant's Position:

The Agreed iPSP, dated 20 June 2019, includes a full waiver for the condition of cervical cancer

in all pediatric age groups (birth to 16 years).

The FDA’s Assessment:

On 9/3/21, an amended pediatric study plan was agreed upon which includes a full waiver for the indication of tisotumab for the treatment of cervical cancer in all pediatric age groups (because studies are highly impracticable as cervical cancer rarely occurs in pediatrics. A deferral of reports on other molecularly targeted (tissue factor-related) pediatric cancer investigations was granted and two PMRs were issued for preclinical and clinical investigation of tisotumab vedotin for cancer(s) affecting pediatric patients.

11 Labeling Recommendations

Data:

This is an original application. Draft labeling is provided in Module 1.14.1.

The Applicant’s Position:

N/A

The FDA’s Assessment:

Summary of Labeling		
Section	Applicant’s Proposed Labeling	FDA’s Proposed Labeling (As of 9/7/21)
Highlights of Labeling		
Boxed Warning	None proposed	Boxed Warning for Ocular Toxicity was added based upon FDA safety review for this NME.
Indications and Usage	...	Added “adult” to the indications statement.
Warnings and Precautions	N/A	Added Warnings and Precautions for Hemorrhage and Pneumonitis. (b) (4) Warning and Precaution for Ocular Toxicity (b) (4) (redundant, moved to Boxed Warning)
Adverse Reactions	...	Revised the most common adverse reactions statement to include laboratory abnormalities, change the incidence rate (b) (4) to 25%, and add adverse reactions and laboratory abnormalities based on FDA safety review (see Section 6 below).
Drug Interactions	Concomitant use of strong inhibitors of CYP3A4 with [TRADENAME] may	FDA revised to: “Strong CYP3A4 Inhibitors: Closely monitor for [TRADENAME] adverse reactions. (7.1)”

	increase the exposure to monomethyl auristatin E (MMAE).	
Use in Specific Populations	...	FDA added: “Moderate or severe hepatic impairment: Exposure to MMAE and adverse reactions are increased. Avoid use. (8.6)”
Full Prescribing Information		
1. Indications and Usage	...	Added “adult” to the indications statement to specify indicated age range.
2. Dosage and Administration	2.2 [redacted] (b) (4) ...	Revised this section to 2.2 Premedication and Required Eye Care Revised existing recommendations to reduce ocular adverse reactions to make these actions requirements; and added the following: - Ophthalmic exams including visual acuity and a slit lamp at baseline, prior to each dose, and as clinically indicated - Monitoring for new or worsening ocular signs and symptoms before each infusion; and referral to eye care provider when these occur - Other proposed eye care actions with revisions to align with registrational study protocol.
2. Dosage and Administration	2.3 Dosage Modifications ...	Revised the Dosage Modifications for Adverse Reactions (Table 2) [redacted] (b) (4) [redacted] to optimize management of specific ocular adverse reactions (ARs). Additional revisions to Table 2 for each AR were: - Keratitis: - o Added monitoring for superficial punctate keratitis and revised to require permanent discontinuation for recurrent confluent superficial keratitis or any ulcerative keratitis or perforation. - Conjunctival ulceration:

		○ Revised to clarify resolution of this AR; and to require permanent discontinuation on the second occurrence. - Peripheral Neuropathy: ○ Revised to require permanently discontinue for Grade 3 peripheral neuropathy based on FDA safety review. - Hemorrhage: AR Added by FDA. - Pneumonitis: AR Added by FDA.
5. Warnings and Precautions	5.1 Ocular Adverse Reactions ...	Revised the rates of ocular ARs based on FDA safety review and grouped terms [i.e., conjunctival ARs (increased (b) (4) to 40%), dry eye (increased (b) (4) to 29%), replaced (b) (4) with corneal ARs (21%)]. Grade 3 ulcerative keratitis was revised (b) (4) to 3.2% and FDA added that one patient experienced perforation requiring corneal transplantation. Deleted and revised (b) (4) to specify rate (55%) and better clarify AR resolution and ongoing ocular ARs. Revised the premedication, required eye care, and monitoring consistent with requirements added in Section 2.2.
5. Warnings and Precautions	5.2 Peripheral Neuropathy ...	Revised to add “motor neuropathy (3%), muscular weakness (3%), and demyelinating peripheral polyneuropathy (1%)” and one patient who developed Guillan-Barre syndrome. Removed general statements (b) (4) and replaced with “led to discontinuation in 8% of patients with cervical cancer”.
5. Warnings and Precautions	5.3 Hemorrhage	Added this Warning and Precaution.

5. Warnings and Precautions	5.4 Pneumonitis	Added this Warning and Precaution.
5. Warnings and Precautions	5.5 Embryo-fetal Toxicity ...	Revised embryo-fetal “toxicity” to “mortality” and added advice for males for the use of effective contraception.
6. Adverse Reactions	6.1 Clinical Trials Experience ...	Revised the serious adverse reactions reported to add ileus (6%), hemorrhage (5%), peripheral neuropathy (3%), and sepsis (3%). Added fatal adverse reactions for septic shock (1%), pneumonitis (1%), sudden death (1%), and multisystem organ failure (1%). Added “hemorrhage (4%)” to the list of adverse reactions leading to dose interruption. Added the most common adverse reactions statement, including laboratory abnormalities, statement to Section 6. Made the following revisions to Table 4: Adverse Reactions (≥10%) in Patients Who Received [TRADE NAME] in innovaTV 204: - Added ARs for fatigue (fatigue and asthenia), pyrexia, hemorrhage (All Grades - 32%, Grade 3-4 – 6%), muscular disorders (myalgia, arthralgia, pain in extremity), decreased appetite, urinary tract infection (All Grades - 14%, Grade 3-4 – 2%), and weight decreased. - Revised AR rates for rash ((b) (4) to 25%) and for eye disorders, based on FDA safety review and grouped AR terms. Added Table 5: Select Laboratory Abnormalities (>10%) That Worsened from Baseline In Patients Who Received [TRADE NAME] in innovaTV 204.
6. Adverse Reactions	6.2 Immunogenicity ...	Removed (b) (4) and revised to a statement that no conclusions can be drawn for PK based on the

		low number of patients who developed these antibodies.
7. Drug Interactions	7.1 (b) (4)	Added “MMAE is a CYP3A4 substrate” and revised to clarify that strong CYP3A inhibitors may increase the risk of adverse reactions.
8. Use in Specific Populations	8.1 Pregnancy	Revised the <u>Data, Animal Data</u> section to align with other MMAE ADC labeling relying on the same data.
8. Use in Specific Populations	8.3 Females and Males of Reproductive Potential	Added advice for males with female partners of reproductive potential to the use of effective contraception during treatment.
8. Use in Specific Populations	8.5 Geriatric Use	Added “No patients aged ≥65 years treated with [TRADENAME] in innovaTV 204 experienced a tumor response.”
8. Use in Specific Populations	8.6 Hepatic Impairment	Revised (b) (4) to closely monitor patients with mild hepatic impairment; and avoid use in patients with moderate or severe hepatic impairment.
11. Description		Revised to add the dosage form as required by regulation and to include the pH and pH adjusters utilized in the final drug product.
12. Clinical Pharmacology	12.1 Mechanism of Action	Revised to describe the antibody target (TF) function by adding “that is the primary initiator of the blood coagulation cascade” and removing general information to be concise and consistent with the tisotumab vedotin-xxxx primary mechanisms of action.
12. Clinical Pharmacology	12.2 Pharmacodynamics	Removed proposed (b) (4) and revised to state that the exposure-response relationships and the time course of pharmacodynamics response have not been fully characterized.

		In the <i>Cardiac Electrophysiology</i> subsection, FDA revise (b) (4) to “no large mean effect on QTc prolongation (>20 msec)” based on FDA QT IRT review.
12. Clinical Pharmacology	12.3 Pharmacokinetics ...	FDA reorganized this section to align with best labeling practices for pharmacokinetic labeling information with the following revisions: - Revised the central volume of distribution (Vd) to provide steady state Vd. - Revised to include the half-life of both the ADC and unconjugated MMAE. - Revised Specific Populations information to provide race, ethnicity, and organ impairment information where no clinically significant differences were observed. - Revised (b) (4) for mild hepatic impairment to provide the unconjugated MMAE increases of 37% compared to patients with normal hepatic function. - Removed statements (b) (4) - Added additional information for CYP inhibition and induction (MMAE) potential based on currently available in vitro data.
13. Nonclinical Toxicology	13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	Revised this subsection to provide a concise summary of relevant toxicity data and exposure margins.
14. Clinical Studies	14.1 Recurrent or Metastatic Cervical Cancer	Added “(patients) received no more than two prior systemic regimens in the recurrent or metastatic setting, including and at least one prior platinum-based chemotherapy regimen.” Added “2% were Asian, and 1% were Black. Six percent of patients were Hispanic or Latino.” To

		be consistent with FDA Guidance for Race and Ethnicity Data in Clinical Trials. Deleted (b) (4) information. Deleted (b) (4) information.
16. How Supplied/ Storage and Handling	...	Added “to protect from light” in the <u>Storage</u> subsection.
17. Patient Counseling Information	...	Added patient counseling topics for hemorrhage and pneumonitis to reflect new Warnings and Precautions for these adverse reactions. Revised Embryo-Fetal Toxicity information to add statements for males with female partners of reproductive potential to use effective contraception during treatment and for 4 months after the last dose.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA’s Assessment:

Based on the benefit-risk assessment for tisotumab vedotin, safety issues can be managed through appropriate labeling and routine post-marketing surveillance. FDA does not require REMS for this application.

13 Postmarketing Requirements and Commitment

The FDA’s Assessment:

The following PMRs and PMCs were agreed upon in association with this accelerated approval:

Clinical PMRs:

PMR-1 (Accelerated Approval):

Conduct the clinical trial innovaTV 301 titled, “Tisotumab Vedotin versus Chemotherapy in Recurrent or Metastatic Cervical Cancer” and provide the final overall survival (OS) and

progression-free survival (PFS) analyses to describe and verify the clinical benefit of tisotumab vedotin in patients with recurrent or metastatic cervical cancer.

Trial Completion: 05/2024
Final Report Submission: 11/2024

PMR-2:

Conduct a pre-clinical study in pediatric-specific pre-clinical models with input from recognized key opinion leaders in pediatric oncology to support the conduct of clinical investigations of tisotumab in pediatric tumors.

Draft Protocol Submission: 03/2022
Final Protocol Submission: 06/2022
Study Completion: 03/2023
Final Report Submission: 06/2023

PMR-3:

Conduct a clinical investigation of the dose, tolerability, and preliminary evidence of activity of tisotumab vedotin in pediatric patients with cancer(s) in which tissue factor is a relevant therapeutic target.

Draft Protocol Submission: 6/2024
Final Protocol Submission: 1/2025
Study Completion: 6/2029
Final Report Submission: 12/2029

CMC PMCs:

OBP-1: To perform a real-time leachable study for tisotumab vedotin drug product in its commercial container closure system to detect, identify, and quantify potential organic, non-volatile, volatile, and semi-volatile species, and metals through the end of shelf life. The final study reports and risk evaluation will be submitted to the BLA.

Final report submission date: 12/2024.

OBP-2: To develop, characterize, validate, and implement functional activity assay(s) with appropriately justified acceptance criteria to control for Fc effector functions of tisotumab vedotin drug substance at release. The final study results, analytical procedures, method validation reports, and updates to the drug substance release specification will be submitted to the BLA per 21 CFR 601.12.

Final report submission date: 11/2022.

OBP-3: Implement (b) (4) monitoring (b) (4) of tisotumab vedotin drug

product and update module 3.2.P.3.4 of the BLA with (b) (4) as a Critical Process Parameter.

Final report submission date: 12/2020.

OBP-4: Implement a validated dye ingress method for container closure integrity testing with the sensitivity to detect breaches $\leq$ (b) (4) μm that could allow microbial ingress.

Final report submission date: 10/2021.

14 Division Director (DHOT) (NME ONLY)

X

15 Division Director (OCP)

X

16 Division Director (OB)

X

17 Division Director (Clinical)

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

Julia Beaver, MD
Deputy Director (Acting), Office of Oncologic Diseases
Chief of Medical Oncology, Oncology Center of Excellence

19 Appendices

19.1 References

The Applicant's References:

References available upon request. FDA sent IR to the Applicant on March 31, 2021 asking for the reference list and received the following list on April 4, 2021.

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19.2 Financial Disclosure

The Applicant's Position:

Financial disclosures information is described in Section 8.1.2.

The FDA's Assessment:

FDA reviewed financial disclosure information provided by Applicant. Out of 257 investigators, there were 7 sub-investigators who signed financial disclosure forms with Genmab listed as the Applicant, but did not sign forms with Genmad-Seagen listed as sponsor. The Applicant could not obtain the updated signed forms from these investigators because they no longer worked at the respective sites. Also refer to Section 8.1.2.

Covered Clinical Study (Name and/or Number):* GCT1015-04

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 257 unique investigators		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
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: <u>0</u> Significant payments of other sorts: <u>0</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in study: <u>0</u> Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements: <u>N/A</u>	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided: <u>N/A</u>	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>N/A</u>		
Is an attachment provided with the reason: <u>N/A</u>	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:

N/A

The Applicant's Position:

All nonclinical pharmacology and toxicology data are included in Section 5.

The FDA's Assessment:

FDA agrees.

19.4 OCP Appendices (Technical documents supporting OCP recommendations)

The FDA's Assessment:

19.4.1 Summary of Bioanalytical Method Validation and Performance

ADC (tisotumab vedotin), total antibody and unconjugated MMAE concentrations were measured throughout the tisotumab vedotin development program. A list of the clinical trials and associated bioanalytical reports is provided in Table 39.

Table 39: Bioanalytical Methods by Clinical Trial

	ADC	Total Antibody	MMAE
GEN701	PRA-NL-LML-1507	PRA-NL-LML-1535	HB-13-059
GEN702	PRA-NL-LML-1776	PRA-NL-LML-1535	HB-13-059
GCT1015-04	PRA-NL-LML-1776	PRA-NL-LML-1535	HB-13-059
TV-001	PRA-US-LML-0356	PRA-US-LML-0357	PRA-US-SML-0378

ADC (tisotumab vedotin)

The bioanalytical methods for measuring tisotumab vedotin plasma concentrations are shown in Table 40. ELISA assays were used to measure tisotumab vedotin concentrations, which utilized TFECDHis as a capture reagent and an anti-MMAE antibody for detection. Briefly, TFECDHis was coated on an ELISA plate. Diluted calibrators, QCs, and study samples were transferred to the plate and the tisotumab vedotin present was allowed to bind to the coated TFECDHis. A mouse IgG2amm-Aur1F10 (anti-MMAE) detection antibody directed against the MMAE part of HuMax-TF-ADC, was added to bind to the conjugated tisotumab vedotin present. A horseradish peroxidase (HRP)-conjugated goat-anti-mouse IgG was added to bind the formed complexes, followed by ABTS substrate for color development.

Table 40: Methods for the Measurement of Plasma ADC Concentration

Bioanalytical Method Validation Report	PRA-NL-LML-1507 GNM200EL-132003		PRA-NL-LML-1776 GNM695EL-156953-B		PRA-US-LML-0356 SGB012UL-170127-D	
Validation Parameters	Method Validation Summary	Source Location	Method Validation Summary	Source Location	Method Validation Summary	Source Location
Materials used for standard calibration curve and concentration	Blank Matrix K2EDTA, HuMax-TF-ADC reference standard					
Material used for quality controls (QCs) and concentration	Blank Matrix K2EDTA, HuMax-TF-ADC reference standard					
Validated assay range	60-1000 ng/mL					
LLOQ	60 ng/mL					
Minimum required dilutions (MRDs)	20					
Standard calibration curve performance	8 calibrators	Table 2	8 calibrators	Table 2	8 calibrators	Table 2
	Bias: -0.9% to 5.0%		Bias: -4.2% to 3.9%		Bias: 6.0% to 4.8%	
	CV: 2.1% to 5.2%		CV: 1.3% to 7.9%		CV: 3.8% to 9.3%	

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Performance of QCs during accuracy and precision runs	Intra-run accuracy (%Bias): LLOQ: -11.2 to 0.6% All other (LQC, MQC, HQC): -17.5 to 13.2% ULOQ: -4.3 to 26.9% Inter-run accuracy (%Bias): LLOQ: -4.2 % All other: -11.9 to 4.1 % ULOQ: 5.6% Intra-run precision (%CV): LLOQ: <7.5% All other: < 13.5% ULOQ: < 13.9% Inter-run precision (%CV): LLOQ: 4.4% All other: < 5.4% ULOQ: 7.1%	Response to IR	Intra-run accuracy (%Bias): LLOQ: -13.0 to 16.1 % All other: -14.9 to 4.9 % ULOQ: -26.8 to 11.4% Inter-run accuracy (%Bias): LLOQ: 1.0 % All other: -6.0 to 2.0 % ULOQ: -6.4% Intra-run precision (%CV): LLOQ: <5.8% All other: < 5.5% ULOQ: <6.8% Inter-run precision (%CV): LLOQ: 9.9% All other: <6.6 % ULOQ: 16.1	Response to IR	Intra-run accuracy (%Bias): LLOQ: -21.4 to -0.2% All other: -13.9 to 6.9% ULOQ: -15.9 to 6.7% Inter-run accuracy (%Bias): LLOQ: -11.9% All other: -9.3 to -4.6 % ULOQ: -5.5% Intra-run precision (%CV): LLOQ: <14.9% All other: < 20.4% ULOQ: <15.2% Inter-run precision (%CV): LLOQ: 6.3% All other: < 5.5% ULOQ: 6.5%	Response to IR
Selectivity and matrix effect	Unspiked (< LLOQ) and spiked @100 ng/mL (bias -9.3% to 15.9%) and @800 ng/mL (bias -9.8% to 15.4%) bias in 10 blank matrices; in 5 subject matrices @100 ng/mL (bias from -9.1% to 1.4%) and @800 ng/mL (bias from -17.9% to -10.6%)	Table 8 and 9	Unspiked (< LLOQ) and spiked @90 ng/mL (bias -7.1% to 16.6%) and @800 ng/mL (bias 2.9% to 19.4%; 20.9 failed) bias in 10 blank matrices; in 10 subject matrices unspiked (< LLOQ) and spiked @90 ng/mL (bias from -4.5% to 12.1%, 1 at 25.4% failed) and 20 subjects matrices at @800 ng/mL (bias from -14.9% to 16.2%; 3 failed at 27.3%, 20.6% and 27.1%)	Table 8 and 9	Unspiked and spiked @100 ng/mL (bias 0.8% to 18.2%) and @800 ng/mL (bias -0.4% to -14.2%) in 10 blank matrices	Table 8
Hemolysis effect	1 for unspiked (< LLOQ), 3 @100 ng/mL (Bias 8.8% to 11.5%)	Table 10	1 for unspiked (< LLOQ), 3 @90 ng/mL (Bias 2.0% to 22.6%)	Table 10	1 for unspiked, 2 (3rd failed CV) @100 ng/mL (Bias -0.4% to -3.1%)	Table 9
Lipemic effect	1 for unspiked (< LLOQ), 3 @100 ng/mL (Bias	Table 11	1 for unspiked (< LLOQ),	Table 11	N/A	

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	11.5% to 18.7%) 1 failure at 26%		3 @90 ng/mL (Bias 12.2% to 16.5%)			
Dilution linearity and hook effect	High 200,000 ng/mL low 48.9 ng/mL in 2 fold dilutions with no hook effect (Bias -10.1% to 11.6%)	Table 7	High 200,000 ng/mL low 37.9 ng/mL in 2.2 fold dilutions with no hook effect (Bias -8.2% to 9.7%)	Table 7	High 200,000 ng/mL low 48.9 ng/mL in 2 fold dilutions with no hook effect (Bias -5.8% to -10.2%)	Table 7
Bench top/process stability	24 hrs at RT	Table 13	24 hrs at RT	Table 13	24 hrs at RT	Table 11
Freeze thaw stability	5 cycles at both -20°C and -70°C	Table 12	5 cycles at both -20°C and -70°C	Table 12	3 cycles at both -20°C and -70°C	Table 10
Long-term storage	Storage for 64 days at -20°C and -70°C. Amend 1 adds 198 days	Table 14	13 days at -20°C and -70°C. Amend 1 adds 189 days	Table 14	Amend 1 405 days at both -20°C and -70°C	Amend 1 Table 5

Source: Adapted from Applicant's Summary of Biopharmaceutical Studies

Total antibody

The bioanalytical methods for measuring total antibody plasma concentrations are shown in Table 41. ELISA assays were used to measure total antibody concentrations, which utilized TFECdHis as a capture reagent and an anti-hIgG1 antibody for detection. Briefly, TFECdHis was coated on an ELISA plate. Diluted calibrators, QCs, and study samples were transferred to the plate and allowed to bind to the coated TFECdHis. A mouse anti-human IgG1-HRP detection antibody was added to the wells to detect the tisotumab and/or tisotumab vedotin present. ABTS substrate was subsequently added for color development.

Table 41: Methods for the Measurement of Plasma Total Antibody Concentration

Bioanalytical Method Validation Report	PRA-NL-LML-1535 GNM200EL-132003-I		PRA-US-LML-0357 SGB012UL-170127-F	
Validation Parameters	Method Validation Summary	Source Location	Method Validation Summary	Source Location
Standard calibration curve performance	8 calibrators	Table 2	8 calibrators	Table 2
	Bias: -1.5% to 3.2%		Bias: -3.0% to 0.9%	
	CV: 2.21% to 3.6%		CV: 2.9% to 6.8%	
Materials used for standard calibration curve and concentration	Blank Matrix K2EDTA, HuMax-TF-ADC reference standard			
Material used for quality controls (QCs) and concentration	Blank Matrix K2EDTA, HuMax-TF-ADC reference standard			
Validated assay range	300-8000 ng/mL			
LLOQ	300 ng/mL			
Minimum required dilutions (MRDs)	20			

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Performance of QCs during accuracy and precision runs	Intra-run accuracy (%Bias): LLOQ: -7.3 to 7.8% All other (LQC, MQC, HQC): -11.8 to 6.6 % ULOQ: -8.7 to 3.7% Inter-run accuracy (%Bias): LLOQ: -3.8% All other:-8.3 to -1.5% ULOQ: -3.5 Intra-run precision (%CV): LLOQ: <8.5% All other: < 6.7 ULOQ: <7.3% Inter-run precision (%CV): LLOQ: 5.3% All other: < 5.1% ULOQ: 4.1%	Response to FDA IR	Intra-run accuracy (%Bias): LLOQ: -15.5 to 29.2% All other: -11.1 to 13.7 % ULOQ: -12.5 to 5% Inter-run accuracy (%Bias): LLOQ: 4.9% All other: -1.5 to -0.1% ULOQ: -2.1% Intra-run precision (%CV): LLOQ: < 15.0% All other: < 15.9% ULOQ: < 15.7% Inter-run precision (%CV): LLOQ: 13.2% All other: < 5.5% ULOQ: 4.3%	Table 5 Response to FDA IR
Selectivity and matrix effect	Unspiked (<LLOQ) and spiked at @500 ng/mL (Bias -23.3% to -4.4%) and @6000 ng/mL (Bias -9% to 12.0%) in 10 blank matrices; in 5 subject matrices unspiked (<LLOQ) and spiked @500 ng/mL (Bias -3.9% to -12.6%) and @6000 ng/mL (Bias from -9.2% to 5.9%)	Table 10	Unspiked (<LLOQ) and spiked @500 ng/mL (Bias -0.9% to 16.6%) and @6000 ng/mL (Bias 1.4% to 8.2%) (1 failure for each) in 10 blank matrices	Table 8
Hemolysis effect	1 for unspiked, 3 @500 ng/mL (Bias -3.3% to -9.5%)	Table 11	1 for unspiked, 3 @500 ng/mL (Bias -8.7% to -11.9%)	Table 9
Lipemic effect	1 for unspiked, 3 @500 ng/mL (Bias -7.0% to -3.8%)	Table 12	N/A	
Dilution linearity and hook effect	High 180,000 ng/mL in 5 fold dilutions up to 30 fold with no hook effect (Bias -16.2% to -3.3%)	Table 8	High 180,000 ng/mL in 5 fold dilutions up to 30 fold with no hook effect (Bias -4% to 5.8%)	Table 7
Bench top/process stability	24 hrs at RT	Table 14	24 hrs at RT	Table 11
Freeze thaw stability	3 cycles at both -20°C and -70°C	Table 13	3 cycles at both -20°C and -70°C	Table 10
Long-term storage	33 days (Amendment 1, 181 days at -20°C and -70°C)	Table 15	19 days @-20°C and -70°C (Amendment 1 for 352 days at -20°C and -70°C)	Table 11

Source: Adapted from Applicant's Summary of Biopharmaceutical Studies

Unconjugated MMAE:

The bioanalytical methods for measuring unconjugated MMAE plasma concentrations are shown in Table 42. Plasma unconjugated MMAE concentrations were measured using liquid chromatography with tandem mass spectrometry (LC-MS/MS) after extraction of MMAE and the internal standard, deuterated MMAE (D8-MMAE), from matrix the by solid phase extraction.

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Table 42: Methods for the Measurement of Plasma MMAE Concentration

Bioanalytical Method Validation Report	HB-13-059 8291518		PRA-US-SML-0378 SGB012UL-170127-B	
Validation Parameters	Method Validation Summary	Source Location	Method Validation Summary	Source Location
Validated assay range	25 to 1000 pg/mL			
LLOQ	25 pg/mL			
Standard calibration curve performance	8 calibrators Bias: 1.0% to -2.1% CV 1.7% to 5.3%	Table 8.4	8 calibrators Bias: -1.6% to 2.4% CV 1.3% to 2.4%	Table 2
Performance of QCs during accuracy and precision runs	Intra-run accuracy (%Bias)*: LLOQ: - 8.0% All other (LQC, MQC, HQC): -4.0 to 2.7% Intra-run precision (%CV)*: LLOQ: 10.0% All other: < 3.3%	Response to FDA IR	Intra-run accuracy (%Bias): LLOQ: -4.9 to -2.7% All other (LQC, MQC, HQC): -5.7 to 1.0 % Inter-run accuracy (%Bias): LLOQ: -3.7% All other: -2.1 to -0.3% Intra-run precision (%CV): LLOQ: <5.0% All other: < 5.5% Inter-run precision (%CV): LLOQ: 0.0% All other: < 2.8%	Response to FDA IR
Selectivity and matrix effect	6 lots, 2.5% CV Matrix effect is -8.7% on free MMAE and -9.9% on internal standard	Table 8.3	Unspiked in 6 blank matrices. Bias -9.0%	Table 9
Interference and specificity	Specificity tested in presence of HuMax-TF-ADC	Table 8.2 and 8.10	Specificity tested in presence of HuMax-TF-ADC	Table 12
Hemolysis effect	5 lots tested, @800 ng/mL, Bias -3.1%, CV 1.7%	Table 8.17	3 @25 ng/mL (Bias -11.3% to -13.8%)	Table 10
Lipemic effect	6 lots tested, @75 ng/mL, Bias 0.9%, CV 2.1% @800 ng/mL Bias 1.0%, CV 2.0%	Table 8.18	3 @25 ng/mL (Bias -13.4% to -16.2%)	Table 11
Dilution linearity and hook effect	N/A		@8000 pg/mL with 10 fold dilution. Bias -6.1%	Table 7
Bench top/process stability	Spike @75 ng/mL, Bias -1.1, CV 4.1% @300 pg/mL, Bias 0.0%, CV 3.1% @800 pg/mL, Bias 0.0%, CV 0.8% at 5°C for 108 hrs. Samples spiked with ADC in whole blood stable for 2 hrs at RT and wet ice	Table 8.8, 8.9, 8.10, and 8.13	22 hrs on ice or at RT with (18 hrs) or without (24 hrs) the presence of ADC, stable at 10°C in autosampler	Table 22, 23, and 21

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Freeze thaw stability	Samples were stable for 5 freeze/thaws at both -20°C and -80°C	Table 8.11 and 8.12	5 cycles at both -20°C and -70°C for MMAE 5 cycles at -20°C and -70°C in the presence of ADC	Table 24 and 25
Long-term storage	When samples spiked with ADC, stable for 24 hrs at RT, and wet ice. Long-term frozen samples spiked with ADC were stable for 121 days at -80°C but did not pass stability for 64 days at -20°C. In addendum 8326090, ADC spiked samples were shown to be stable for 374 days at -80°C	Table 8.13-8.16. In Table 6.6 of 8326090	LTS 11 days at -20 or -70°C. 10 days in the presence of ADC. Amend 2: 337 day at -20°C and -70°C. For MMAE; in the presence of ADC, 163 days at -20°C and 274 days at -70°C	Table 26 and 27
Carry over	N/A		No observed carry over	Table 17 and 18
* Only a single precision and accuracy run was performed for this method transfer. Assay was previously validated and used across ADC programs where there is a need to assay unconjugated MMAE				

Source: Adapted from Applicant's Summary of Biopharmaceutical Studies

Cross validation: Since mirror assays were performed in across bioanalytical sites for total antibody, ADC and MMAE, a cross-validation was performed to ensure the assays were providing similar results. Spiked QC samples and incurred sample pools were generated as detailed below:

- QC samples at the appropriate concentrations for each assay
- 30 pooled incurred samples

Six replicates of QC samples at each level and 1 replicate per pooled incurred 30 samples were tested at each site. Two-thirds of the samples were to be within $\pm 30\%$ of each other for total antibody and ADC and within $\pm 20\%$ of each other for the MMAE assay in order to meet acceptance criteria. Summary of the data is provided in Table 43.

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extrinsic factors		(b) (4) (b) (4)	increase in moderate and severe HI and Tisotumab vedotin-xxxx is currently dosed very close to the its MTD. Race has no meaningful effect on PK of tisotumab vedotin-xxxx.
	Extrinsic factor	NA	NA
Derive exposure metrics for Exposure-response analyses		Exposure measures in Cycle 1: • For ADC: AUC (AUC1,ADC) and Cmax (Cmax1,ADC); • For MMAE: AUC1,MMAE, Cmax1,MMAE , and Ctrough (Ctrough1,MMAE).	Tisotumab vedotin-xxxx exposure-response relationships and the time course of pharmacodynamics response have not been fully characterized.
Predict exposures at alternative dosing regimen		NA	NA

Population PK Analyses

Objectives: 1) Develop population models that describe the pharmacokinetics (PK) of antibody-drug conjugate (ADC) and Monomethyl auristatin E (MMAE) following intravenous administration in patients with metastatic solid tumors; 2) Estimate population PK parameters of the models and estimate and summarize individual PK parameters; 3) Estimate the inter-individual variability of model parameters in

the patient population; 4) Estimate the residual (intra-individual) variability of ADC and MMAE concentrations in the patient population; 5) Identify intrinsic and extrinsic covariate factors that influence distribution and elimination of ADC and MMAE, and to estimate the effects of these covariates on patient's PK parameters and exposure estimates; 6) Determine whether presence of anti-drug antibodies (ADAs) affects PK of tisotumab vedotin following IV administration in patients with metastatic solid tumors; and 7) Estimate individual values of ADC and MMAE exposure for characterization of covariate effects and for exposure-response analyses.

Data: The data include a total of 4847 ADC and 5145 MMAE concentration values from 399 patients enrolled in studies GEN701, GEN702, GCT1015-04 and SGNTV-001. The data cut for the ongoing studies (GCT1015-04 and SGNTV-001) was 22 Aug 2019. Some of the concentrations below the limit of quantification were included in the analysis using M3 method. Patients covariates are summarized overall and by study in Table 45 and Table 46. Note that there are 68.2% baseline HSC scores missing and the missing values were imputed with median of 120 per the data define file. This may reduce the power of investigating the relationship between baseline HSC and confirmed best overall response. In addition, only 6 black patients (1.5% of the overall study population) were enrolled in the studies. The studied population may not represent the real disease population.

Table 45. Summary of continuous covariates.

Mean(SD)	Median[range]

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Covariate	Description	Total	Study			
			SGNTV-001	GCT1015-04	GEN701	GEN702
Number of Patients		399	70	101	195	33
AGE	Age (years)	56.1 (11.6)	60.7 (10.9)	50.7 (10.7)	57.3 (11.7)	55.9 (9.76)
WT	Weight (kg)	72.0 (17.9)	77.3 (23.3)	68.2 (15.8)	72.9 (16.7)	67.1 (13.8)
BSA	Body Surface Area (m ²)	1.79 (0.224)	1.89 (0.287)	1.73 (0.187)	1.81 (0.208)	1.72 (0.19)
BMI	Body Mass Index(kg/m ²)	25.9 (5.84)	25.9 (6.46)	25.6 (5.77)	26.2 (5.9)	25.2 (4.32)
ALB	Albumin (g/L)	39.4 (4.66)	37.2 (4.81)	41.8 (4.19)	39 (4.33)	38.4 (4.46)
ALP	Alkaline Phosphatase (u/L)	128 (130)	143 (139)	91.3 (54.9)	142 (152)	127 (106)
ALT	Alanine Aminotransferase (u/L)	23.7 (22.3)	29.6 (29)	16.9 (13.3)	25.4 (23.8)	22.3 (11.8)
AST	Aspartate Aminotransferase (u/L)	26.7 (19.9)	28.9 (15.9)	19 (9.51)	29.4 (24.5)	29.5 (15.3)
BILI	Bilirubin (umol/L)	6.46 (3.82)	8.84 (4.68)	4.27 (2.24)	6.71 (3.59)	6.65 (3.51)
LDH ^a	Lactate Dehydrogenase (u/L)	254 (246)	279 (411)	186 (63.8)	275 (231)	291 (230)
CREAT	Serum Creatinine (umol/L)	0.81 (0.231)	0.816 (0.215)	0.839 (0.251)	0.793 (0.227)	0.813 (0.227)
SUMDIAM ^b	Tumor size (mm)	73.1 (56.6)	69.5 (54)	60.8 (43.5)	78.4 (58.8)	88.3 (76.9)
CRCL	Creatinine Clearance (ml/min)	97.3 (35.3)	103 (35.8)	91.3 (34.2)	100 (36.4)	88.1 (26.2)
CKDEPI	eGFR computed by CKDEPI (ml/min/1.73m ²)	87.5 (19.7)	90.7 (17.4)	84.2 (21.4)	88.6 (19.5)	84.7 (19.6)
BLHSC ^c	Baseline TFE H-score	144 (82.2)	-	110 (78.3)	122 (88.9)	-

Covariate	Description	Total	Study			
			SGNTV-001	GCT1015-04	GEN701	GEN702
Number of Patients		399	70	101	195	33
AGE	Age (years)	57 [21-81]	62 [35-81]	50 [31-78]	58 [21-79]	57 [30-71]
WT	Weight (kg)	70.1 [33-148]	75.1 [37.5-148]	65 [33-110]	72 [37-142]	65.5 [40-96.8]
BSA	Body Surface Area (m ²)	1.77 [1.2-2.68]	1.9 [1.38-2.68]	1.73 [1.2-2.25]	1.79 [1.26-2.37]	1.7 [1.33-2.08]
BMI	Body Mass Index(kg/m ²)	25.3 [13.1-53.9]	24.8 [13.1-44.2]	24.4 [14.7-44.3]	25.7 [15.6-53.9]	25.7 [16.1-33.3]
ALB	Albumin (g/L)	40 [27-52]	38 [27-45]	42 [31-52]	40 [27-48]	39 [31-48]
ALP	Alkaline Phosphatase (u/L)	90 [24-1060]	105 [36-920]	79 [24-394]	94 [36-1060]	89 [48-507]
ALT	Alanine Aminotransferase (u/L)	18 [4-228]	22 [6-228]	13 [4-88]	19 [6-222]	20 [9-57]
AST	Aspartate Aminotransferase (u/L)	21 [5-168]	25 [12-91]	17 [5-62]	22 [11-168]	27 [10-90]
BILI	Bilirubin (umol/L)	5.5 [1.3-29.1]	8.55 [3.42-29.1]	4 [2-14]	5.8 [2.1-27.7]	6.3 [1.3-15.3]
LDH ^a	Lactate Dehydrogenase (u/L)	186 [83-3230]	183 [111-3230]	173 [83-479]	200 [93-1990]	182 [110-1090]
CREAT	Serum Creatinine (umol/L)	0.78 [0.418-2.19]	0.799 [0.42-1.3]	0.802 [0.452-2.19]	0.768 [0.418-2]	0.749 [0.473-1.4]
SUMDIAM ^b	Tumor size (mm)	57 [0-299]	52 [15-299]	52 [10-221]	63 [0-281]	61 [0-273]
CRCL	Creatinine Clearance (ml/min)	92.5 [33.7-285]	94.4 [40.7-202]	86.1 [35.8-285]	94.7 [33.7-235]	86.1 [43.1-158]
CKDEPI	eGFR computed by CKDEPI (ml/min/1.73m ²)	91 [24.1-145]	94.2 [58.6-128]	86.4 [24.1-129]	91.2 [28.8-145]	87.4 [45.8-123]
BLHSC ^c	Baseline TFE H-score	120 (0-298)	-	120 (0-265)	120 (3-298)	-

a: A total of 3 (0.8%) LDH values were missing; b: A total of 8 (2.0%) SUMDIAM values were missing; c: A total of 272 (68.2%) BLHSC values were missing.

Source: Tables 9 and 10 in the population PK report.

Table 46. Summary of categorical covariates.

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Covariate	Level	Total	SGNTV-001	GCT1015-04	GEN701	GEN702
N (%)		399 (100%)	70 (17.5%)	101 (25.3%)	195 (48.9%)	33 (8.3%)
Sex (SEX)	Male	103 (25.8%)	44 (62.9%)	-	55 (28.2%)	4 (12.1%)
	Female	296 (74.2%)	26 (37.1%)	101 (100%)	140 (71.8%)	29 (87.9%)
Race (RACE)	White	368 (92.2%)	59 (84.3%)	96 (95%)	182 (93.3%)	31 (93.9%)
	Black	6 (1.5%)	3 (4.3%)	1 (1%)	2 (1%)	-
	Asian	10 (2.5%)	1 (1.4%)	2 (2%)	5 (2.6%)	2 (6.1%)
	Other	15 (3.8%)	7 (10%)	2 (2%)	6 (3.1%)	-
Ethnicity	Non-Hispanic	383 (96%)	63 (90%)	95 (94.1%)	193 (99%)	32 (97%)
	Hispanic	16 (4%)	7 (10%)	6 (5.9%)	2 (1%)	1 (3%)
ECOG Status	0	155 (38.8%)	21 (30%)	59 (58.4%)	63 (32.3%)	12 (36.4%)
	1	244 (61.2%)	49 (70%)	42 (41.6%)	132 (67.7%)	21 (63.6%)
Renal Impairment (RENAL)	Normal	215 (53.9%)	42 (60%)	46 (45.5%)	112 (57.4%)	15 (45.5%)
	Mild	142 (35.6%)	23 (32.9%)	40 (39.6%)	66 (33.8%)	13 (39.4%)
	Moderate	42 (10.5%)	5 (7.1%)	15 (14.9%)	17 (8.7%)	5 (15.2%)
Hepatic Impairment (HEP)	Normal	341 (85.5%)	56 (80%)	93 (92.1%)	167 (85.6%)	25 (75.8%)
	Mild	58 (14.5%)	14 (20%)	8 (7.9%)	28 (14.4%)	8 (24.2%)
Tumor Type	Cervical	172 (43.1%)	-	101 (100%)	57 (29.2%)	14 (42.4%)
	Other	227 (56.9%)	70 (100%)	-	138 (70.8%)	19 (57.6%)
Region	Europe	282 (70.7%)	5 (7.1%)	86 (85.1%)	162 (83.1%)	29 (87.9%)
	USA	117 (29.3%)	65 (92.9%)	15 (14.9%)	33 (16.9%)	4 (12.1%)
ADA status	Negative	386(96.7%)	68(97.1%)	96 (95%)	189(96.9%)	33 (100%)
	Positive	13 (3.3%)	2 (2.9%)	5 (5%)	6 (3.1%)	-

Note that only 6 black patients (1.5% of the overall study population) were enrolled in the studies.

Source: Table 11 in the Population PK report.

ADC Model: The ADC plasma concentration-time data is fitted with a two-compartment model with parallel linear and Michalis-Menten (MM) elimination (V_{max} , K_m). Baseline covariate effects of special interest: body weight on CL, V_1 , V_2 , and Q; albumin and sex on CL, V_1 and V_2 ; age, ECOG, hepatic impairment, eGFR, tumor size, and tumor type on CL; ECOG, hepatic impairment, and eGFR on V_1 were studied in the development of the ADC covariate model. All other covariates including race were tested by diagnostic plots of random effects versus covariates. No dependencies on race were noticeable to be clinically meaningful. The effects of body weight on CL, V_1 , V_2 , and Q, and the effects of albumin and sex on CL and V_1 were included in the final ADC model. None of the other covariates, including ADA status, drug material, and TFE H-score, have a clinically meaningful impact on ADC exposures. The final ADC model parameter estimates are summarized in Table 47. The covariate effects are summarized in Table

48. The final ADC model was incorporated into the combined ADC-MMAE model. The final ADC model was further assessed in the combined model.

ADC-MMAE Model: The structure of base ADC-MMAE Model is shown in Figure 14. 100% of the linear ADC output was directed to the delay MMAE compartment while the remaining fractions were estimated. The effects of weight, sex, age, albumin, tumor size and type, ECOG score, hepatic impairment, and eGFR on MMAE clearance and weight, sex, age, albumin, ECOG score, hepatic impairment, and eGFR on MMAE volume were investigated in addition to the covariate effects on ADC PK parameters that were included in the final ADC model. All other covariates including race were evaluated by diagnostic plots of random effects versus covariates. No dependencies of clearance on race were noticeable to be clinically meaningful. Dependence of the delay rate constant on age and weight were also studied. The effects of age and sex on MMAE clearance and sex, eGFR, and hepatic impairment on MMAE volume were removed from the final ADC-MMAE model. The estimates of fixed-effect parameters of the final ADC-MMAE model, covariate fixed-effect parameters and variance parameters are shown in Table 48, Table 49 and Table 50. The covariate effects are summarized in Table 51. The final ADC-MMAE model was assessed via goodness-of-fit indicators and prediction performance (e.g., plots, see Figure 16 and Figure 17).

Table 47. Summary of Final ADC Model Parameters Estimates.

Parameter		Description	Value	RSE%	95% CI
CL (L/day)	θ_1	non-specific clearance	1.61	4.78	1.46 ; 1.76
Q (L/day)	θ_2	inter-compartment clearance	3.73	2.69	3.53 ; 3.93
V ₁ (L)	θ_3	central volume	3.12	1.15	3.05 ; 3.19
V ₂ (L)	θ_4	peripheral volume	4.27	2.75	4.04 ; 4.5
V _{max} (ug/mL/day)	θ_5	maximum MM elimination	2.48	13.3	1.83 ; 3.13
K _M (ug/mL)	θ_6	MM constant	2.81	12.2	2.14 ; 3.49
σ_{prop}	θ_7	SD of residual error: proportional part	0.127	2	0.122 ; 0.132
σ_{add} (ug/mL)	θ_8	SD of residual error: additive part	0.0171	7.5	0.0146 ; 0.0196
σ_{702}	θ_9	Study 702 effect on ADC residual error	1.43	5.31	1.28 ; 1.58
CL _{WT} =Q _{WT}	θ_{10}	Weight effect on CL and Q	0.45	6.46	0.393 ; 0.507
V _{1,WT}	θ_{11}	Weight effect on V ₁	0.387	9.19	0.318 ; 0.457
V _{2,WT}	θ_{12}	Weight effect on V ₂	0.619	7.27	0.53 ; 0.707
CL _{ALB}	θ_{13}	Albumin effect on CL	-0.364	21.1	-0.514 ; -0.213
V _{1,ALB}	θ_{14}	Albumin effect on V ₁	-0.202	32.7	-0.332 ; -0.0728
CL _{SEXM}	θ_{15}	SEX=Male effect on CL	1.11	3.06	1.05 ; 1.18
V _{1,SEXM}	θ_{16}	SEX=Male effect on V ₁	1.12	1.99	1.08 ; 1.17

Parameter	Value	RSE%	95% CI	CV	Shrinkage	
ω^2_{CL}	Ω_{11}	0.0491	9.46	0.04 ; 0.0581	CV=22.1%	4.0%
R $\omega_{CL}\omega_{V1}$	Ω_{12}	0.0175	12.4	0.0133 ; 0.0218	R=0.467	
ω^2_{V1}	Ω_{22}	0.0286	8.32	0.024 ; 0.0333	CV=16.9%	2.8%
R $\omega_{V1}\omega_{V2}$	Ω_{23}	0.0136	14.7	0.00965 ; 0.0175	R=0.562	
ω^2_{V2}	Ω_{33}	0.0203	14	0.0148 ; 0.0259	CV=14.3%	19.8%
ω^2_{σ}	Ω_{44}	0.0571	11.2	0.0446 ; 0.0696	CV=23.9%	23.6%
σ^2	Σ_{11}	1	fixed			7.8%

ω^2 and σ^2 : variances of inter-individual and residual variability, respectively, SE: Standard Error; PE: Parameter Estimate; RSE%: Relative Standard Error = 100·abs(SE/PE); 95% CI: 95% confidence interval; CV: coefficient of variation

Source: Table 17 in the population PK report.

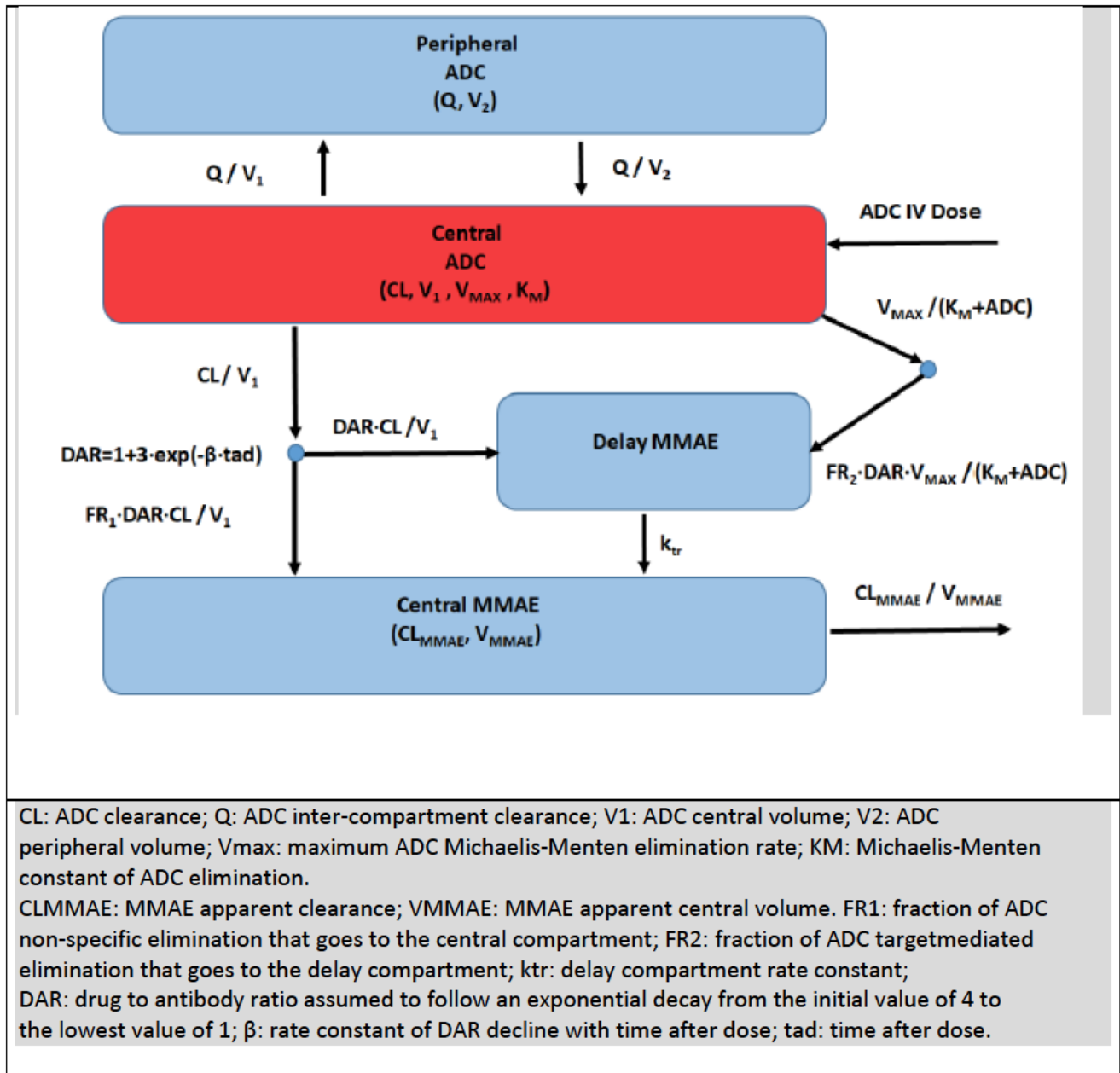
Table 48. Covariate Effects in Final ADC Model.

Parameter	Covariate	Reference Value	Covariate Value ^a	Covariate Effect Value [95%CI](%)
CL	Weight	70	43	-19.7 [-21.9;-17.4]
			112	23.6 [20.3;26.9]
	Albumin	40	29	12.4 [7.1;18]
			47	-5.7 [-8;-3.4]
Sex	Female	Male	11.3 [4.7;18]	
V ₁	Weight	70	43	-17.2 [-20;-14.3]
			112	20 [16.1;24]
	Albumin	40	29	6.7 [2.4;11.3]
			47	-3.2 [-5.2;-1.2]
Sex	Female	Male	12.1 [7.8;16.5]	
Q	Weight	70	43	-19.7 [-21.9;-17.4]
			112	23.6 [20.3;26.9]
V ₂	Weight	70	43	-26 [-29.1;-22.8]
			112	33.7 [28.3;39.4]

^a The values of the continuous covariates represent 2.5th and 97.5th percentiles of the values in the analysis dataset.

Source: Table 18 in the population PK report.

Figure 14. Schematic Representation of Structural ADC-MMAE Model.



Source: In-Text Figure 1 in the Population PK report.

Figure 15. Estimates of Structural Fixed-Effect Parameters, Final ADC-MMAE Model.

Parameter		Description	Value	RSE%	95% CI
ADC parameters					
CL (L/day)	θ_1	non-specific clearance	1.42	5.19	1.28 ; 1.57
Q (L/day)	θ_2	inter-compartment clearance	4.01	2.93	3.78 ; 4.24
V_1 (L)	θ_3	central volume	3.10	1.23	3.03 ; 3.18
V_2 (L)	θ_4	peripheral volume	4.47	2.3	4.27 ; 4.68
V_{max} ($\mu\text{g/mL/day}$)	θ_5	maximum MM elimination	3.35	11.7	2.58 ; 4.12
K_M ($\mu\text{g/mL}$)	θ_6	MM constant	3.44	12.3	2.61 ; 4.27
σ_{prop}	θ_7	SD of ADC residual error: proportional part	0.129	2.07	0.124 ; 0.134
σ_{add} ($\mu\text{g/mL}$)	θ_8	SD of ADC residual error: additive part	0.0173	7.66	0.0147 ; 0.0199
$t_{1/2,\alpha}$ (day)		ADC distribution half-life	0.28	Derived from CL, V_1 , V_2 , and Q	
$t_{1/2,term}$ (day)		ADC terminal half-life	4.19		
MMAE parameters					
k_{tr} (1/day)	θ_9	Rate constant of delay	0.271	1.35	0.264 ; 0.278
CL_{MMAE} (L/day)	θ_{10}	MMAE Clearance	42.8	7.4	36.6 ; 49.0
V_{MMAE} (L)	θ_{11}	MMAE central volume	2.09	9.82	1.69 ; 2.50
β_{DAR} (1/day)	θ_{12}	Rate constant of DAR decay	0.0189	26.5	0.0091 ; 0.0288
σ_{prop}	θ_{13}	SD of MMAE residual error: proportional part	0.282	2.13	0.27 ; 0.294
σ_{add} ($\mu\text{g/mL}$)	θ_{14}	SD of MMAE residual error: additive part	0.0113	4.42	0.0103 ; 0.0123
FR_1	θ_{15}	Fraction of MMAE non-specific elimination to central compartment	0.0205	7.94	0.0173 ; 0.0237
FR_2	θ_{16}	Fraction of MMAE target-mediated elimination to delay compartment	0.0508	27.7	0.0232 ; 0.0784
$t_{1/2,KTR}$ (day)		MMAE delay half-life	2.56	$t_{1/2,KTR} = \log(2)/k_{tr}$	
$t_{1/2,MMAE}$ (day)		MMAE terminal half-life	0.0339	$t_{1/2,KTR} = \log(2)/K_{MMAE}$; $K_{MMAE} = CL_{MMAE}/V_{MMAE}$	
SE: Standard Error; PE: Parameter Estimate; RSE%: Relative Standard Error = 100-abs(SE/PE); 95% CI: 95% confidence interval					

Source: In-Text Table 1 in the Population PK report.

Table 49. Estimates of Covariate Fixed-Effect Parameters, Final ADC-MMAE Model.

Parameter		Description	Value	RSE%	95% CI
$CL_{WT} = Q_{WT}$	θ_{17}	Weight effect on CL, Q	0.495	9.86	0.399 ; 0.591
$V_{1,WT}$	θ_{18}	Weight effect on V_1	0.380	12.1	0.29 ; 0.47
$V_{2,WT}$	θ_{19}	Weight effect on V_2	0.622	7.9	0.526 ; 0.718
CL_{ALB}	θ_{20}	Albumin effect on CL	-0.396	18.9	-0.543 ; -0.25
$V_{1,ALB}$	θ_{21}	Albumin effect on V_1	-0.197	32.1	-0.32 ; -0.0729
CL_{SEXM}	θ_{22}	Male effect on CL	1.09	3.55	1.02 ; 1.17
$V_{1,SEXM}$	θ_{23}	Male effect on V_1	1.13	2.11	1.09 ; 1.18
$CL_{MMAE,WT}$	θ_{24}	Weight effect on CL_{MMAE}	0.457	24.6	0.237 ; 0.677
$V_{MMAE,WT}$	θ_{25}	Weight effect on V_{MMAE}	0.895	13.2	0.663 ; 1.13
$CL_{MMAE,ALB}$	θ_{26}	Albumin effect on CL_{MMAE}	0.935	26.5	0.449 ; 1.42
$CL_{MMAE,Non-Cervical}$	θ_{27}	Non-cervical effect on CL_{MMAE}	1.22	5.99	1.07 ; 1.36
$CL_{MMAE,SUMDIAM}$	θ_{28}	Tumor size effect on CL_{MMAE}	-0.147	20	-0.205 ; -0.0895
$CL_{MMAE,GFR}$	θ_{29}	eGFR effect on CL_{MMAE}	0.271	38.6	0.0659 ; 0.475
$CL_{MMAE,ECOG}$	θ_{30}	ECOG > 0 effect on CL_{MMAE}	0.803	6.59	0.699 ; 0.907
$CL_{MMAE,HEP}$	θ_{31}	Hepatic impairment effect on CL_{MMAE}	0.853	7.98	0.719 ; 0.986
$V_{MMAE,ECOG}$	θ_{32}	ECOG > 0 effect on V_{MMAE}	0.827	6.13	0.727 ; 0.926
$V_{MMAE,ALB}$	θ_{33}	Albumin effect on V_{MMAE}	0.575	41.6	0.106 ; 1.04
$k_{tr,AGE}$	θ_{34}	Age effect on k_{tr}	-0.252	15.3	-0.327 ; -0.176
$k_{tr,WT}$	θ_{35}	Weight effect on k_{tr}	-0.175	24.3	-0.258 ; -0.0916
σ_{702}	θ_{36}	Study 702 effect on ADC residual error	1.42	5.79	1.26 ; 1.58

SE: Standard Error; PE: Parameter Estimate; RSE%: Relative Standard Error = $100 \cdot \text{abs}(\text{SE}/\text{PE})$; 95% CI: 95% confidence interval.

Source: In-Text Table 2 in the Population PK Report.

Table 50. Estimates of Variance Parameters, Final ADC-MMAE Model.

Parameter	Value	RSE%	95% CI	CV	Shrinkage	
ADC parameters						
ω^2_{CL}	Ω_{11}	0.0538	11.0	0.0422 ; 0.0654	CV=23.2%	3.6%
$R \omega_{CL}\omega_{V1}$	Ω_{12}	0.0166	14.0	0.012 ; 0.0211	R=0.415	
ω^2_{V1}	Ω_{22}	0.0296	8.59	0.0246 ; 0.0346	CV=17.2%	4.3%
$R \omega_{V1}\omega_{V2}$	Ω_{23}	0.0145	14.8	0.0103 ; 0.0187	R=0.586	
ω^2_{V2}	Ω_{33}	0.0208	13.9	0.0151 ; 0.0264	CV=14.4%	19.2%
ω^2_{σ}	Ω_{44}	0.0561	12.7	0.0422 ; 0.0701	CV=23.7%	24.6%
σ^2	Σ_{11}	1	fixed			7.9%
MMAE parameters						
ω^2_{ktr}	Ω_{55}	0.0212	10.6	0.0168 ; 0.0256	CV=14.5%	15.8%
ω^2_{CLmmae}	Ω_{66}	0.299	7.85	0.253 ; 0.345	CV=54.7%	3.6%
R_{MMAE} $\omega_{CLMMAE}\omega_{VMMAE}$	Ω_{67}	0.125	14.4	0.0901 ; 0.161	R=0.495	
ω^2_{VMMAE}	Ω_{77}	0.215	9.77	0.174 ; 0.256	CV=46.3%	8.0%
ω^2_{σ}	Ω_{88}	0.0712	10.6	0.0564 ; 0.0861	CV=26.7%	16.1%
σ^2	Σ_{22}	1	fixed			5.2%

ω^2 and σ^2 : variances of inter-individual and residual variability, respectively, R: correlation coefficient, SE: Standard Error; PE: Parameter Estimate; RSE (%): Relative Standard Error = $100 \cdot \text{abs}(\text{SE}/\text{PE})$; 95% CI: 95% confidence interval, CV: coefficient of variation

Source: In-Text Table 3 in the population PK report.

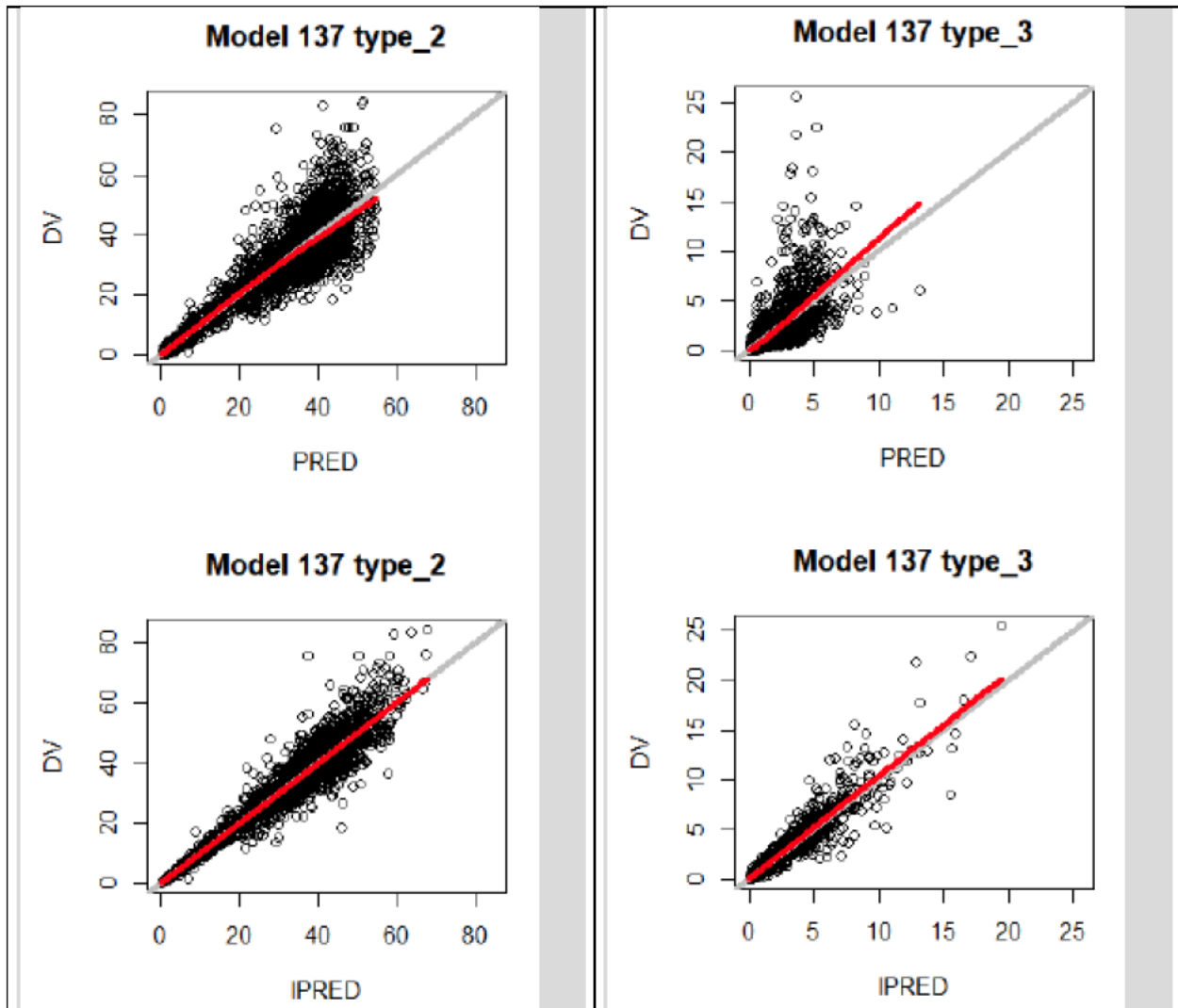
Table 51. Covariate Effects, Final ADC-MMAE Model.

Parameter	Covariate	Reference Value	Covariate Value ^a	Effect Value [95%CI](%)
CL	Weight	70	43	-21.4 [-25;-17.7]
			112	26.2 [20.6;32]
V1	Albumin	40	29	13.6 [8.4;19.1]
			47	-6.2 [-8.4;-3.9]
	Sex	Female	Male	9.4 [1.8;17]
			43	-16.9 [-20.5;-13.2]
V1	Weight	70	112	19.6 [14.6;24.7]
			29	6.5 [2.4;10.9]
	Albumin	40	47	-3.1 [-5;-1.2]
			Male	13.3 [8.6;18]
Q	Weight	70	43	-21.4 [-25;-17.7]
			112	26.2 [20.6;32]
V2	Weight	70	43	-26.2 [-29.5;-22.6]
			112	34.0 [28;40.2]
CL _{MMAE}	Weight	70	43	-20 [-28.1;-10.9]
			112	24 [11.8;37.5]
	Albumin	40	29	-26 [-36.7;-13.5]
			47	16.3 [7.5;25.7]
	eGFR	90	52.2	-14.9 [-24.7;-3.9]
			129	8.6 [2;15.6]
	Cancer	Cervical	Other	21.7 [7.5;36]
	ECOG	0	1	-19.7 [-30.1;-9.3]
	Hepatic Impairment	Normal	Impaired	-14.7 [-28.1;-1.4]
	Tumor Burden	60	12	12.5 [7.4;17.8]
254			-37.9 [-48.5;-25.1]	
V _{MMAE}	Weight	70	43	-35.4 [-42.3;-27.6]
			112	52.3 [36.6;69.9]
	Albumin	40	29	-16.9 [-28.5;-3.3]
			47	9.7 [1.7;18.3]
k _{tr}	Weight	70	43	8.9 [4.6;13.4]
			112	-7.9 [-11.4;-4.2]
	Age	60	32	13.1 [9;17.3]
			76	-11.2 [-14.3;-7.9]

^a The values of the continuous covariates represent 2.5th and 97.5th percentiles of the values in the analysis dataset.

Source: In-Text Table 4 in the Population PK Report.

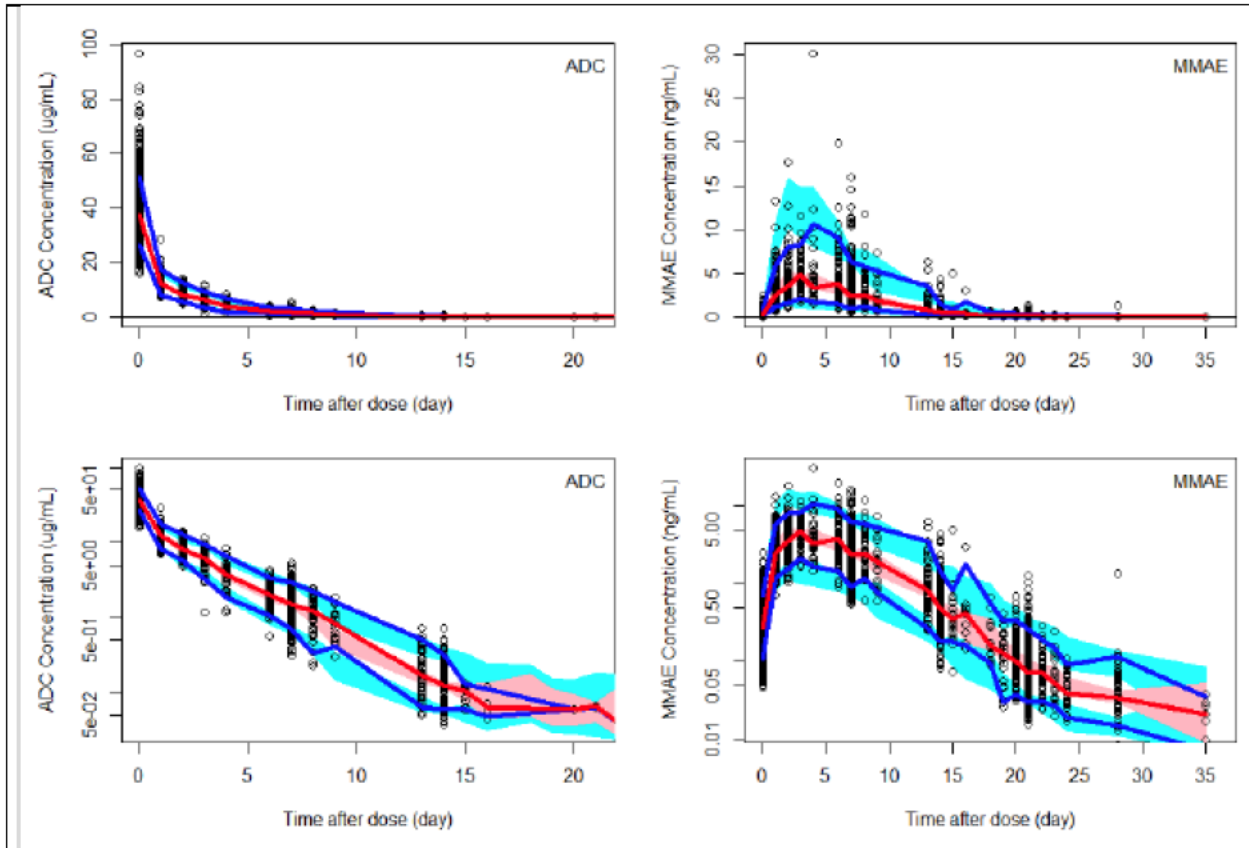
Figure 16. Goodness-of-Fit of Final ADC-MMAE Model 137.



DV: Observed concentrations, **PRED:** population predictions of the model, **IPRED:** individual predictions of the model, Type_2: ADC, Type_3: MMAE.
The gray solid $y=x$ or $y=0$ lines are included for reference. The bold red lines are the lowest (local regression smoother) trend lines.

Source: Figure 64 and Figure 65 in the Population PK Report.

Figure 17. Prediction-Corrected Visual Predictive Check of Final ADC-MMAE Model.

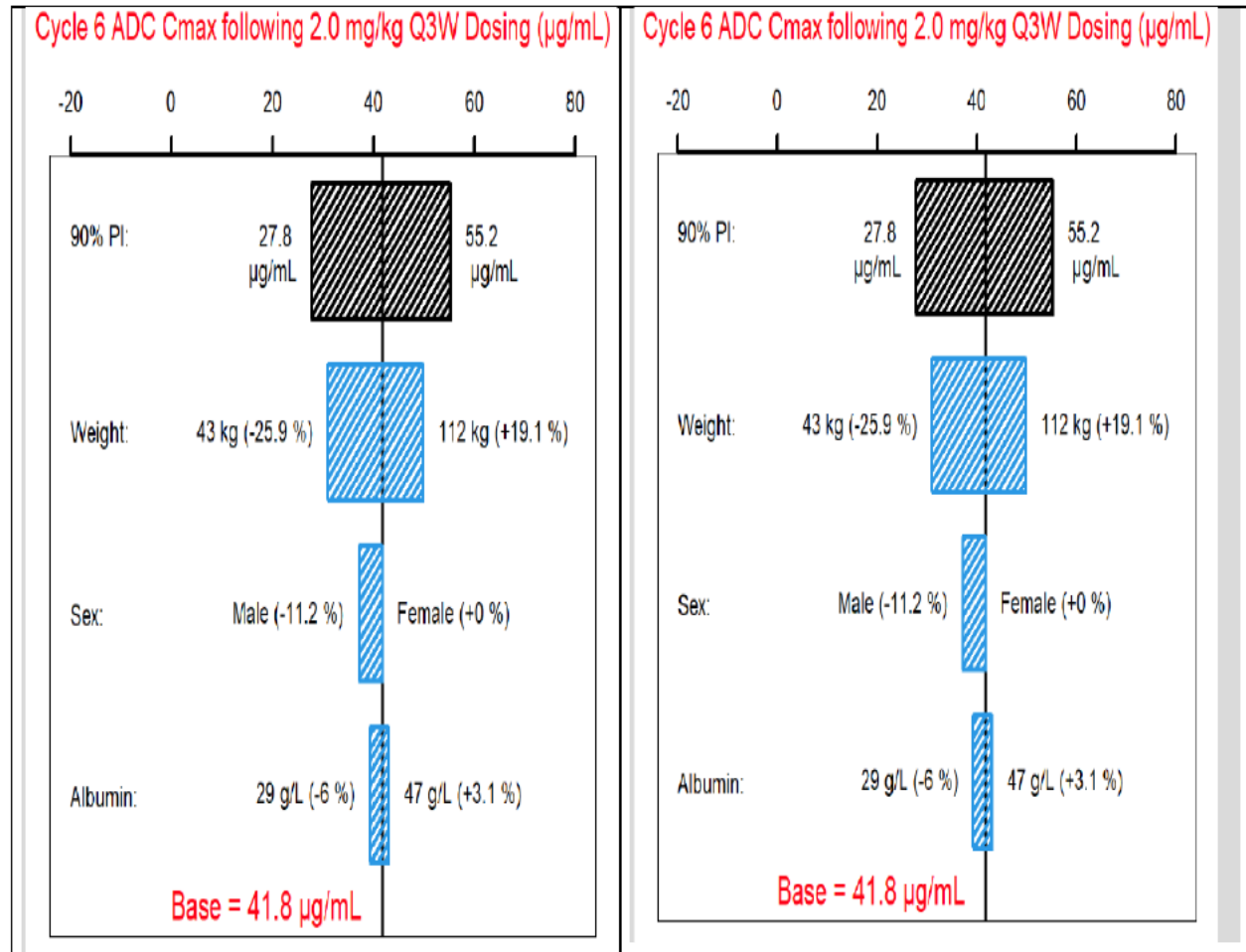


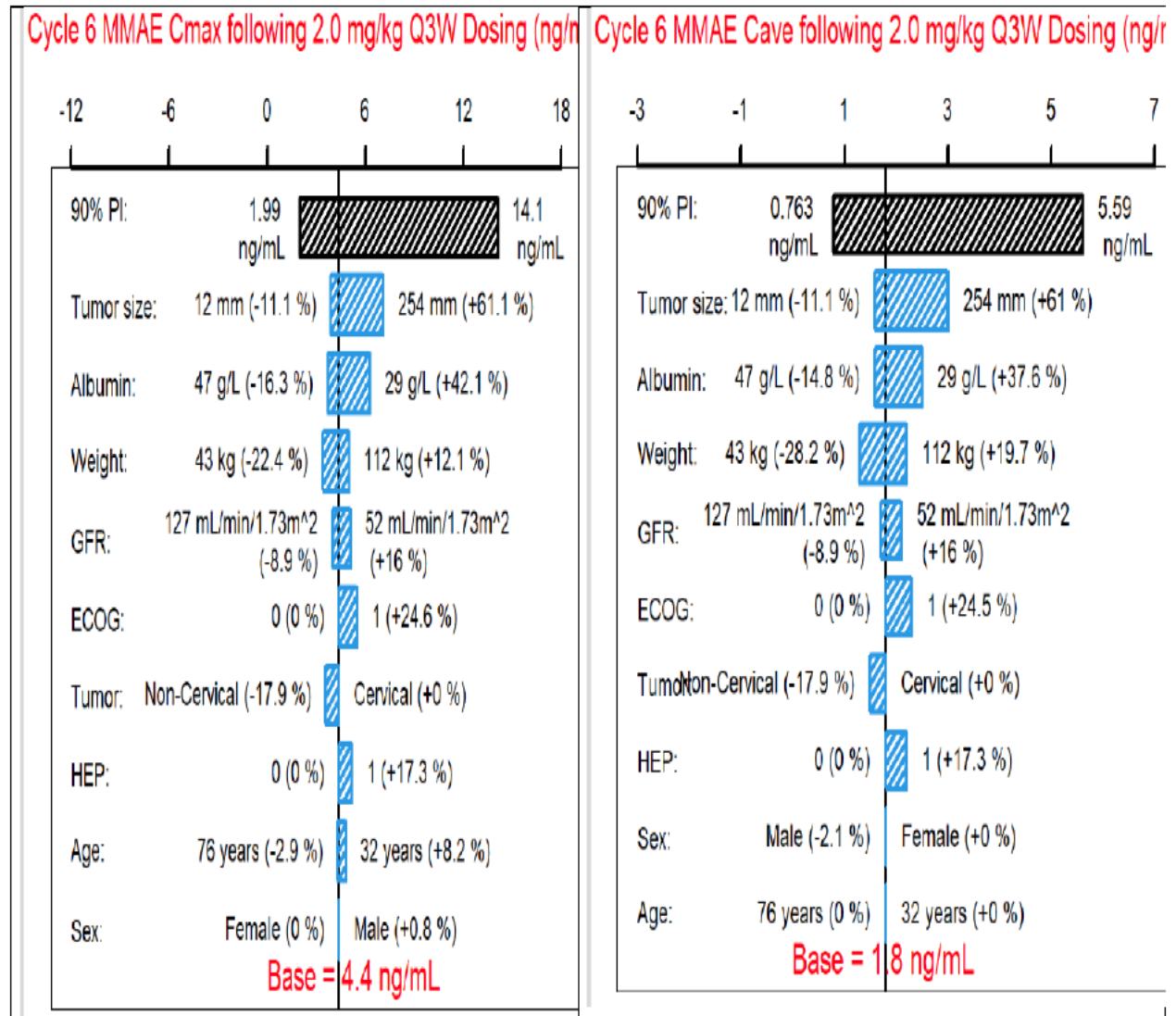
The solid lines are median (red), and 5th and 95th percentiles (blue) of observed prediction-corrected ADC (left) or MMAE (right) concentrations (top and middle) or fraction of BQL concentrations (bottom). The shaded regions show the 90% confidence intervals on these quantities obtained by simulations. The simulated values were computed from 500 trials with dosing, sampling, and the covariate values of the analysis dataset.

Source: Figure 99 in the Population PK Report.

Covariate Effects: The effects of covariates on steady-state exposure (in Cycle 6) is illustrated in Figure 18. ADC exposure was most influenced by weight, with higher exposure in heavier patients. MMAE exposure depended on 9 covariates. Tumor size had the strongest effect, with higher exposure in patients with higher tumor size. Several other covariates that are generally correlated with overall patients' condition (albumin, ECOG, decrease of eGFR and hepatic impairment) also increased MMAE exposure. The combined effect of these covariates may more than double the exposure in patients with poor overall health status compared to exposure of the reference (healthier) subject. This is consistent with the high value of the upper bound of 90% prediction interval of MMAE exposure in the study population.

Figure 18. Effects of Covariates on Steady-state Exposure (in Cycle 6).





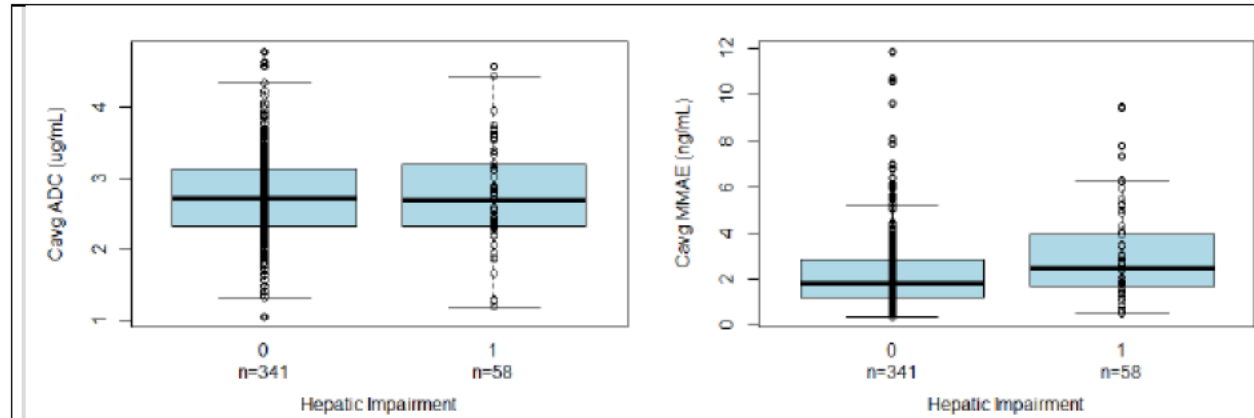
Base (black vertical line and red text): predicted Cycle 6 exposure in a typical patient following 2.0 mg/kg Q3W doses (with 200 mg cap). Black shaded bar: exposure range correspond to 5th and 95th percentiles of exposure distribution. Blue shaded bars: influence of each single covariate on the Cycle 6 exposure. For each continuous covariate, two subjects were generated with extreme covariate values (2.5th and 97.5th percentile). For each categorical covariate, one subject from each category was created; other covariates were fixed at the reference category. The length of each bar describes the potential impact of that particular covariate on MMAE exposure, with the percentage values representing the percent change of exposure from the base. The most influential covariate is at the top of the plot.

Source: Figures 8,9,10, and 11 in the population PK report.

Impact of Hepatic Impairment on ADC and MMAE Exposure: As shown in Figure 19, predicted ADC exposure for patients with mild hepatic impairment based on NCI organ dysfunction working group (NCI-ODWG) is similar to patients with normal hepatic function, while MMAE exposures are 37% higher. This

is in agreement with the population PK model that included the effect of hepatic impairment on MMAE clearance.

Figure 19. Impact of Hepatic Impairment on ADC and MMAE Exposure.



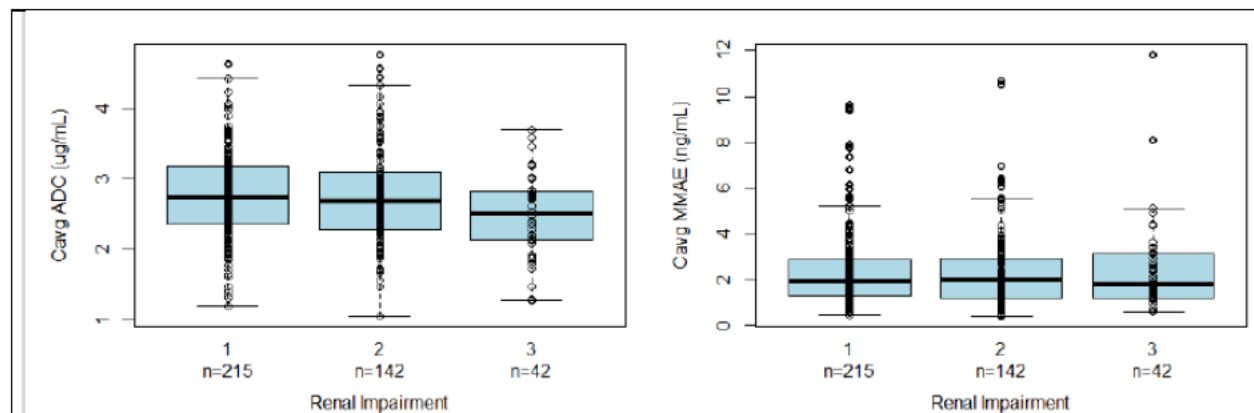
Hepatic impairment: 0: Normal hepatic function; 1: mild impairment;

Covariate	N	C _{ave,ADC} (µg/mL)		C _{ave,MMAE} (ng/mL)		
		Mean (SD)	Median (Range)	Mean (SD)	Median (Range)	
HEP	normal	N=341	2.74 (0.620)	2.71 [1.06-4.77]	2.26 (1.60)	1.79 [0.391-11.8]
	mild	N=58	2.76 (0.742)	2.67 [1.19-4.56]	3.07 (2.09)	2.46 [0.535-9.49]

Source: Adapted from Table 30 and Figure 113.

Impact of Renal Impairment on ADC and MMAE Exposure: Comparison of exposures between patients with normal renal function, mild renal impairment, and moderate renal impairment is shown in Figure 20. Predicted ADC exposure in patients with renal impairment is similar to patients with normal renal function.

Figure 20. Impact of Renal Impairment on ADC and MMAE Exposure.



Renal impairment: 1 = normal; 2 = mild; 3 = moderate

Covariate	N	C _{ave,ADC} (µg/mL)		C _{ave,MMAE} (ng/mL)		
		Mean (SD)	Median (Range)	Mean (SD)	Median (Range)	
RENAL	normal	N=215	2.78 (0.601)	2.74 [1.19-4.63]	2.37 (1.63)	1.91 [0.459-9.65]
	mild	N=142	2.76 (0.694)	2.68 [1.06-4.77]	2.37 (1.70)	2.00 [0.391-10.7]
	moderate	N=42	2.49 (0.583)	2.51 [1.28-3.70]	2.48 (2.10)	1.78 [0.585-11.8]

Source: Adapted from Table 30 and Figure 113.

Exposure Response Analyses:

Exposure Metrics: The population PK analysis showed that there was no appreciable accumulation of ADC and MMAE with repeated dosing. Therefore, Cycle 1 exposure measures were used for all exposure-response analyses. Cycle 1 was defined as the interval between the first and the second doses. Moreover, trough concentrations of ADC were either below quantification limit (BQL) or close to it. Therefore, ADC trough (minimum) concentration was not a useful measure of exposure. Thus, the individual estimates of the following exposure measures in Cycle 1 were used for the exposure-response analyses in addition to average ADC concentration from time zero to the end of the cycle in which event occurred (C_{av}gLast):

- For ADC: AUC (AUC_{1, ADC}) and C_{max} (C_{max1, ADC});
- For MMAE: AUC_{1, MMAE}, C_{max1, MMAE}, and C_{trough1, MMAE}.

Data: The database for the exposure-safety analysis included the data from 272 subjects administered TV 2.0 mg/kg 1Q3W doses in studies GEN701 (expansion cohort), GEN702 (expansion cohort), and GCT1015-04 (cutoff date February 6, 2020). The database for the exposure-efficacy analysis included the data from 101 subjects from Study GCT1015-04 (cutoff date February 6, 2020).

Exposure Safety Analyses: Treatment-emergent adverse events (AEs) investigated include treatment related AEs, All SAEs, treatment-related Grade 3+ TEAEs, treatment-related TEAEs leading to dose interruption, treatment-related TEAEs leading to dose reduction, treatment-related TEAEs leading to dose discontinuation, Grade 2+ bleeding TEAEs, Grade 2+ ocular TEAEs, and Grade 2+ peripheral neuropathy. For each TEAE type, linear logistic regression base models were implemented to assess the relationship between the probability of TEAE occurrence and exposure. To define the confidence interval for the logistic regression function, 1000 bootstrap samples were drawn with replacement from the analysis population, and the logistic regression base model was fitted to each of these samples. For each exposure value, 95% confidence interval of the logistic regression curve was defined as the 5th and 95th percentiles of the model predictions among 1000 bootstrap data sets. A significance level of $\alpha = 0.05$ was used for evaluation of the exposure coefficient of the base model (slope parameter). For each TEAE type, a covariate analysis was conducted using the full model approach. The full model had the following structure: $\text{logit}(\text{EVENT}) \sim \text{Intercept} + \text{Exposure} + \text{AGE} + \text{WT} + \text{SUMDIAM} + \text{ALB} + \text{LDH} + \text{TFE} + \text{factor}(\text{SEXF}) + \text{factor}(\text{USA}) + \text{factor}(\text{CERVICAL}) + \text{factor}(\text{RENAL2}) + \text{factor}(\text{RENAL3}) + \text{factor}(\text{HEP}) + \text{factor}(\text{ECOG})$, where *Exposure* was represented by one of the investigated ADC or MMAE exposure

measures, *AGE* is individual age at baseline (years), *WT* is individual body weight at baseline (kg), *TFE* is individual membrane tissue factor expression (H-score) at baseline, *SUMDIAM* is individual sum of tumor diameters at baseline (mm), *ALB* is individual albumin concentration at baseline (g/L), *LDH* is individual LDH concentration at baseline (U/L), *SEXF* is equal to 1 for females and 0 for males, *USA* is equal to 1 for patients from USA and 0 otherwise, *CERVICAL* is 1 for patients with cervical cancer, *RENAL2* is 1 for patients with mild or moderate renal impairment, *RENAL3* is 1 for patients with moderate renal impairment; *HEP* is 1 for patients with mild hepatic impairment, and *ECOG* is the ECOG score (0 or 1). The main goal of the covariate analysis was to confirm association of exposure with response after adjustment for covariates. Therefore, specific covariate results are not discussed. A significance level of $\alpha = 0.05$ was used for evaluation of the exposure coefficient of the covariate model (slope parameter). The main safety results are summarized in Table 52.

Table 52. Summary of Main Exposure Safety Analyses Results.

Probability of treatment-related TEAEs leading to dose interruptions (TEAE4), reductions (TEAE5) or Discontinuations (TEAE6) significantly increased with increase of ADC Cycle 1 AUC (E1) based on pooled data.							
E1	AE	Coefficient	SE	RSE	95%CI	p-value	Model
TEAE 4		0.0475	0.01396	29.4	0.02013;0.07488	0.001*	Base
		0.03845	0.01728	44.95	0.004571;0.07232	0.026*	Full
TEAE 5		0.05	0.01356	27.11	0.02343;0.07657	<0.0005*	Base
		0.04648	0.01695	36.46	0.01327;0.0797	0.006*	Full
TEAE 6		0.03848	0.01195	31.06	0.01506;0.06191	0.001*	Base
		0.032	0.01534	47.92	0.001942;0.06207	0.037*	Full
Probability of Grade 2+ ocular TEAEs (TEAE8) significantly increased with increase of ADC Cycle 1 AUC (E1), ADC Cycle 1 Cmax (E2), and ADC CavgLast (E3) based on pooled data.							
E1	AE	Coefficient	SE	RSE	95%CI	p-value	Model
TEAE 8		0.05755	0.01169	20.32	0.03463;0.08047	<0.0005*	Base
		0.06375	0.01405	22.04	0.03621;0.09129	<0.0005*	Full
E2	TEAE 8	0.07057	0.01704	24.14	0.03718;0.104	<0.0005*	Base
		0.07864	0.02119	26.94	0.03712;0.1202	<0.0005*	Full
E3	TEAE 8	1.191	0.2447	20.55	0.7114;1.671	<0.0005*	Base
		1.263	0.2866	22.69	0.7016;1.825	<0.0005*	Full
Subset analysis of Study GCT1015-04 data was consistent with the pooled dataset. The probability of Grade 2+ ocular TEAEs significantly increased with increase of ADC Cycle 1 AUC (E1), ADC Cycle 1 Cmax (E2), and ADC CavgLast (E3);							

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{tisotumab vedotin}

Exposure	Coefficient	SE	RSE	95%CI	p-value	Model
ADC Cycle 1 AUC	0.07622	0.01963	25.75	0.03775;0.1147	<0.0005*	Base
	0.1063	0.02976	27.99	0.04799;0.1646	<0.0005*	Full
ADC Cycle 1 C _{max}	0.09031	0.02853	31.59	0.03439;0.1462	0.002*	Base
	0.1312	0.04432	33.78	0.04434;0.2181	0.003*	Full
ADC C _{avgLast}	1.689	0.4374	25.9	0.8315;2.546	<0.0005*	Base
	1.802	0.5362	29.76	0.751;2.853	0.001*	Full
MMAE Cycle 1 AUC	-0.03035	0.01159	38.18	-0.05307;-0.00764	0.009*	Base
	-0.0281	0.01501	53.42	-0.05753;0.001324	0.061	Full

Probability of treatment-related serious TEAEs (1) and all serious TEAEs (2) significantly increased with increase of MMAE Cycle 1 AUC (ME1)

AE	Coefficient	SE	RSE	95%CI	p-value	Model
TEAE 1	0.007851	0.003676	46.83	0.0006452;0.01506	0.033*	Base
	0.01228	0.004893	39.83	0.002693;0.02187	0.012*	Full
TEAE 2	0.01131	0.00372	32.88	0.004022;0.0186	0.002*	Base
	0.009767	0.004353	44.57	0.001235;0.0183	0.025*	Full

Probability of Grade 2+ bleeding TEAEs and Grade 2+ peripheral neuropathy TEAEs were not correlated with ADC exposure.

Probability of Grade 2+ bleeding TEAEs and Grade 2+ peripheral neuropathy TEAEs were not correlated with MMAE exposure.

Coefficient: exposure slope of the logistic regression model; SE: standard error; RSE: relative standard error (%); 95%CI: 95% confidence interval for exposure slope; p-value: significance of exposure slope as provided by glm() function. Analyses associated with p <0.05 are denoted in red and marked with “*”.

Source: Adapted from Tables 11-15 in the ER analyses report.

Agency asked the sponsor to update the ER for safety endpoints on ocular toxicity defined by the terms: Asthenopia, Chalazion, Chorioretinopathy, Conjunctival abrasion, Conjunctivitis allergic, Corneal epithelium defect, Corneal bleeding, Corneal erosion, Corneal irritation, Corneal toxicity, Diplopia, Erythema of eyelid, Eyelids pruritus, Eye discharge, Eye movement disorder, Eye pruritus, Foreign body sensation in eyes, Herpes ophthalmic, Keratopathy, Meibomian gland dysfunction, Ocular hypertension, Open angle glaucoma, Periorbital oedema, Retinal exudates. In case no incidence of any the following terms, no action is needed. In addition, covariates such as ‘history of dry eye’ if available should be considered. The sponsor responded on 5/10/2021 as follows:

- The Agency’s requested preferred terms of Asthenopia, Chalazion, Chorioretinopathy, Conjunctival abrasion, Conjunctivitis allergic, Corneal epithelium defect, Corneal bleeding, Corneal erosion, Corneal irritation, Corneal toxicity, Diplopia, Erythema of eyelid, Eyelids pruritus, Eye discharge, Eye movement disorder, Eye pruritus, Foreign body sensation in eyes, Herpes ophthalmic, Keratopathy, Meibomian gland dysfunction, Ocular hypertension, Open angle glaucoma, Periorbital oedema, and Retinal exudates were included in the ocular AE

specifications. However, there were no grade 2+ ocular AEs with these terms reported in the BLA dataset. Thus, the dataset for analysis remained the same.

- Two additional covariates were considered in the updated exposure response (ER) safety analysis for ocular toxicities: 1) history of dry eye and 2) any pre-existing ocular AE at baseline. Inclusion of these covariates (history of dry eye or any ocular AE at baseline) did not alter the relationships of ocular AEs for any grade or for grade 2+ with exposure.

The requested analysis yielded the same conclusion for the ocular ER safety analysis as previously submitted in the BLA. An additional ER safety analysis has been conducted for the all grade AEs of special interest (AESIs; ocular, bleeding, and peripheral neuropathy). The trends above are identical to the ER safety analysis for grade 2+ AESIs, and thus the overall conclusions remain the same.

Exposure Efficacy Analyses: The overall response rate (ORR) was investigated using logistic regression models. The linear logistic models were implemented to assess the relationships between the probability of ORR and exposure measures. A covariate analysis was conducted using the full model approach. Categorical covariates with less than 10% representation were not included in the full model. The full models had the following structure: $\text{logit(ORR)} \sim \text{Intercept} + \text{Exposure} + \text{AGE} + \text{WT} + \text{SUMDIAM} + \text{ALB} + \text{LDH} + \text{TFE} + \text{factor(RENAL2)} + \text{factor(RENAL3)} + \text{factor(ECOG)} + \text{factor(SQUAM)} + \text{factor(RADI2)} + \text{factor(BEVA)}$, where SQUAM is 1 for patients with squamous cancer, RADI2 is 1 for patients with prior radiation therapy, BEVA is 1 for patients with prior bevacizumab therapy.

The relationships between exposure and TTE were first characterized using base Cox proportional hazard (CPH) models that describe the marginal effect of exposure on survival without consideration of covariates. Linear dependence of $\log(\text{hazard})$ on exposure was tested. A significance level of $\alpha = 0.05$ was used for model selection and for evaluation of the exposure coefficients of the selected models. The covariates were added linearly in the log hazard scale as follows:

$\log(\text{hazard}) \sim \text{Exposure} + \text{AGE} + \text{WT} + \text{SUMDIAM} + \text{ALB} + \text{LDH} + \text{TFE} + \text{factor(RENAL2)} + \text{factor(RENAL3)} + \text{factor(ECOG)} + \text{factor(SQUAM)} + \text{factor(RADI2)} + \text{factor(BEVA)}$.

Covariate analysis was not conducted for DOR as DOR analysis data included only 24 patients, not sufficient for a meaningful covariate analysis. The main exposure efficacy analyses results are summarized in Table 53. For all significant exposure-efficacy relationships, the relationship with MMAE exposure was opposite to the relationship with ADC exposure even though there were no strong correlations between ADC exposure measures and MMAE exposure measures. Note that the ER relationships have not been fully characterized given the data included in ER analyses were from studies at one dose level.

Table 53. Summary of Main Efficacy Exposure Response Analyses Results.

For the base models, probability of response significantly increased with increase of ADC exposure (Cycle 1 AUC and Cycle 1 Cmax). After accounting for the covariate effects, only the relationship with ADC Cycle 1 Cmax remained statistically significant.

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OR	Exposure	Coefficient	SE	RSE	95%CI	p-value	Model
	ADC Cycle 1 C _{max}	0.06612	0.02858	43.23	0.0101;0.1221	0.021*	Base
		0.1464	0.05244	35.81	0.04366;0.2492	0.005*	Full

For both the base and full models, the risk of death significantly decreased with increase of ADC Cycle 1 AUC and Cycle 1 C_{max}, but was not correlated with CavgLast; while Risk of death significantly increased with increase of MMAE exposure (Cycle 1 AUC and C_{max}, and CavgLast). Similar to the other relationships of safety and efficacy versus MMAE exposure, this relationship may be due to some confounding factor(s) that cannot be explained by covariates evaluated in the exposure-efficacy analyses.

OS	Exposure	β	SE	RSE	HR	95%CI	p-value	Model
	ADC Cycle 1 AUC	-0.03818	0.01059	27.73	0.9625	0.9428-0.9827	<0.0005*	Base
		-0.03383	0.01314	38.83	0.9667	0.9422-0.992	0.010*	Full
	ADC Cycle 1 C _{max}	-0.05299	0.01786	33.71	0.9484	0.9158-0.9822	0.003*	Base
		-0.04365	0.02164	49.58	0.9573	0.9175-0.9988	0.044*	Full
	ADC C _{avgLast}	-0.3683	0.2311	62.76	0.6919	0.4399-1.088	0.111	Base
		-0.2597	0.2708	104.28	0.7713	0.4537-1.311	0.338	Full
	MMAE Cycle 1 AUC	0.02293	0.004933	21.51	1.023	1.013-1.033	<0.0005*	Base
		0.02254	0.006898	30.61	1.023	1.009-1.037	0.001*	Full
	MMAE Cycle 1 C _{max}	0.1903	0.03968	20.85	1.21	1.119-1.307	<0.0005*	Base
		0.2017	0.05944	29.47	1.223	1.089-1.375	0.001*	Full
	MMAE Cycle 1 C _{tr}	1.816	0.7527	41.45	6.146	1.406-26.87	0.016*	Base
		1.144	1.04	90.88	3.14	0.409-24.1	0.271	Full
	MMAE C _{avgLast}	0.5115	0.09719	19	1.668	1.379-2.018	<0.0005*	Base
		0.5085	0.149	29.3	1.663	1.242-2.227	0.001*	Full

Risk of progression significantly increased with increase of MMAE Cycle 1 AUC, Cycle 1 C_{max}, and CavgLast. After accounting for the covariate effects, only the relationship between PFS and MMAE CavgLast was significant.

PFS	Exposure	β	SE	RSE	HR	95%CI	p-value	Model
	MMAE C _{avgLast}	0.393	0.1005	25.57	1.481	1.217-1.804	<0.0005*	Base
		0.3094	0.1444	46.67	1.363	1.027-1.808	0.032*	Full

Duration of response was not correlated with either ADC exposure or MMAE exposure.

Coefficient: exposure slope of the logistic regression model; SE: standard error; RSE: relative standard error (%); 95%CI: 95% confidence interval for exposure slope; p-value: significance of exposure slope as provided by glm() function. Analyses associated with p < 0.05 are denoted in red and marked with “*”.

Source: Tables 16-19 in the ER Analyses Report.

We agree with sponsor’s conclusions and rationale on inclusion of each of the covariates in the respective full final model as following:

- Demographic factors (age and weight), laboratory assessments (baseline albumin, baseline LDH) and subject health status (baseline tumor size, renal impairment, hepatic impairment, and baseline ECOG performance) are important prognostic factors for cervical and other cancers.
- Race has been identified as an important prognostic factor in cervical cancer.
- Histology (squamous/not) has been identified as an important prognostic factor in cervical cancer.
- Prior bevacizumab treatment and radiation therapy have a high probability of being employed in earlier lines (1L+) of cervical cancer therapy and have been identified as important prognostic factors in cervical cancer.
- Region (US versus Europe) captures potential geographic differences in subject care or environment.
- Tumor type captures potential differences between cervical cancer and the other pooled tumor types.
- Sex captures potential gender-related differences across cancer types.
- Baseline tumor tissue factor H-score is directly relevant to the mechanism of action of tisotumab vedotin. Differences in tumor tissue factor expression between subjects might confound the exposure response assessment.

19.5 Additional Safety Analyses Conducted by FDA

The FDA's Assessment:

Not applicable.

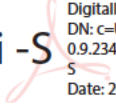
Signatures

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Clinical Pharmacology Reviewer	Krithika Arun Shetty	OCP/DCPI	Sections: 6, 19.4	Select one: ☒ Authored ☐ Approved
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Genomics Reviewer	Oluseyi Adeniyi	OCP/DTPM	Sections: 6	Select one: ☒ Authored ☐ Approved
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Pharmacometrics Team Leader	Jingyu Yu	OCP/DPM	Sections: 19.4.2	Select one: ☐ Authored ☒ Approved
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Clinical Pharmacology Team Leader	Salaheldin Hamed	OCP/DCPII	Sections: 6, 19.4	Select one: ☒ Authored ☒ Approved
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Clinical Pharmacology Division Director	Nam Atiqur Rahman	OCP/DCPII	Sections: 6, 19.4.2	Select one: ☐ Authored ☒ Approved
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Statistical Reviewer	Zhou Feng	OB/DBV	Sections: 1, 8	Select one: ☒ Authored ☐ Approved
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Division Director (OB)	Shenghui Tang	OB/DBV	Sections: 1, 8	Select one: ☐ Authored ☒ Approved
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Safety Analyst	Jonathan Herz	OND/OOD	Section: 8	Select one: ☐ Authored ☒ Approved
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Cross-Disciplinary Team Leader (CDTL)	Gwynn Ison	OOD/DO1	Sections: 1-17	Select one: ☐ Authored ☒ Approved
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Division Director (Clinical)	Laleh Amiri-Kordestani	OOD/DO1	Sections:1-17	Select one: ☐ Authored ☒ Approved
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JULIA A BEAVER
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