CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761208Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 09/07/21

To: Mirat Shah, Medical Officer, DO1

David Nartey, Regulatory Project Manager, DO1

From: Rachael Conklin, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Deputy Division Director, OPDP

Subject: OPDP Labeling Comments for tisotumab vedotin-tftv for injection, for intravenous use

BLA: 761208

In response to DO1's consult request dated February 25, 2021, OPDP has reviewed the proposed product labeling (PI) and Medication Guide (MG) for the original BLA submission for tisotumab vedotin-tftv for injection, for intravenous use.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling emailed to OPDP on August 25, 2021, and we do not have any comments at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed MG were sent under separate cover on September 7, 2021.

Thank you for your consult. If you have any questions, please contact Rachael Conklin at rachael.conklin@fda.hhs.gov.

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/s/

RACHAEL E CONKLIN
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	September 2, 2021
To:	David Nartey, PharmD, MPH Regulatory Project Manager **Division of Oncology 1 (DO1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Jessica Chung, PharmD, MS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Rachael Conklin, MS, RN Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	TIVDAK (tisotumab vedotin-tftv)
Dosage Form and Route:	for injection, for intravenous use
Application Type/Number:	BLA 761208
Applicant:	Seagen Inc.

1 INTRODUCTION

On February 10, 2021, Seagen Inc. submitted for the Agency's review an original Biologics License Application (BLA) 761208 for TIVDAK (tisotumab vedotin-tftv) injection. The proposed indication for TIVDAK (tisotumab vedotin-tftv) is (b) (4) We note that the proposed proprietary name TIVDAK was found to be conditionally acceptable on May 5, 2021 by the Division of Medication Error, Prevention, and Analysis (DMEPA).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology 1 (DO1) on February 25, 2021, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for TIVDAK (tisotumab vedotin-tftv) injection.

2 MATERIAL REVIEWED

- Draft TIVDAK (tisotumab vedotin-tftv) injection MG received on February 10, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 25, 2021.
- Draft TIVDAK (tisotumab vedotin-tftv) injection Prescribing Information (PI) received on February 10, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 25, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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RACHAEL E CONKLIN
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LASHAWN M GRIFFITHS
09/07/2021 08:49:29 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	July 20, 2021
Requesting Office or Division:	Division of Oncology 1 (DO1)
Application Type and Number:	BLA 761208
Product Name and Strength:	Tivdak (tisotumab vedotin-tftv) for Injection, 40 mg/vial
Applicant/Sponsor Name:	Seagen Inc.
OSE RCM #:	2021-357-1
DMEPA 2 Safety Evaluator:	Tingting Gao, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on July 16, 2021 for Tivdak. Division of Oncology 1 (DO1) requested that we review the revised container label and carton labeling for Tivdak (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Gao, T. Label and Labeling Review for Tivdak (BLA 761208). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 June 3. RCM No.: 2021-357.

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ASHLEIGH V LOWERY
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Clinical Inspection Summary

Date	July 13, 2021
From	Yang-min (Max) Ning, M.D., Ph.D. Min Lu, M.D., M.P.H. Kassa Ayalew, M.D., M.P.H. GCPAB/OSI/CDER/FDA
To	Mirat Shah, M.D. Gwynn Ison, M.D. Laleh Amiri-Kordestani, M.D. David Nartey, RPM DO1/OOD/CDER/FDA
BLA #	761208
Applicant	Seagen Inc.
Drug	Tisotumab vedotin
New Molecular Entity	Yes
Therapeutic Classification	Antibody-drug conjugate
Proposed Indication	(b) (4)
Consultation Request Date	February 26, 2021
Inspection Summary Date	July 30, 2021
Action Goal Date	September 17, 2021
PDUFA Date	October 10, 2021

I. OVERALL ASSESSMENT OF INSPECTIONAL FINDINGS AND RECOMMENDATIONS

Clinical data from an ongoing Phase 2 trial [Study GCT1015-04] were submitted to the Agency in support of this Biologics License Application (BLA) for tisotumab vedotin for use in (b) (4) Three participating investigators [Drs. Bradley Monk (Site US11), Michael Gold (Site US01), and Ignace Vergote (Site BE01)] and the study sponsor Genmab U.S., Inc., were selected for clinical inspection.

The inspections revealed no significant regulatory violations for the three investigators and the study sponsor. Based on the inspectional findings, Study GCT1015-04 appears to have been conducted adequately and the submitted clinical data from the three investigator sites to this BLA appear reliable.

II. BACKGROUND

Tisotumab vedotin is a new antibody-drug conjugate comprised of a human tissue factor-specific monoclonal antibody chemically linked to the microtubule-disrupting agent monomethyl auristatin E. The investigational name of this product is HuMax-TF-ADC, studied under IND 135476. For this BLA, the Applicants submitted clinical data from an ongoing Phase 2 trial [Study GCT1015-04] of tisotumab vedotin and proposed an initial indication for second line use of the product following chemotherapy.

Study GCT1015-04 [NCT03438396] is an open-label, single-arm trial of tisotumab vedotin in subjects with recurrent or metastatic cervical cancer who had received one or two prior systemic therapy regimens. Subjects were required to have had: 1) evidence of recurrent or metastatic cervical cancer of squamous cell, adenocarcinoma, or adeno-squamous histology; 2) disease progression during or after treatment with a doublet chemotherapeutic regimen of paclitaxel plus cisplatin/carboplatin or paclitaxel plus topotecan, in combination with bevacizumab if eligible; 3) measurable disease or lesion(s) at study entry. Subjects who had received more than two prior systemic treatment regimens or who had peripheral neuropathy of ≥ grade 2 at baseline were excluded.

The primary endpoint for this study was confirmed objective response rate (ORR) as assessed by an independent review committee (IRC) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Study subjects were scheduled to receive tisotumab vedotin at 2 mg/kg (up to a maximum of 200 mg for subjects ≥100 kg), administered as an intravenous infusion over a minimum of 30 minutes on Day 1 of a 21-day treatment cycle. Study treatment was to be continued until disease progression as verified by IRC, unacceptable toxicity, consent withdrawal, death, or investigator's decision to stop tisotumab vedotin in the best interest of study subjects.

For efficacy measures, tumor assessments were performed with computed tomography (CT)/contrast-enhanced magnetic resonance imaging (MRI) scans of the abdomen, pelvis, chest, and other areas [e.g., the neck or brain if clinically indicated] at baseline, every 6 weeks (±7 days) for the first 30 weeks from the first study treatment administration date, and then every 12 weeks (±7 days) thereafter until IRC-confirmed disease progression. All study scans, including baseline scans, were required to be submitted to the sponsor's designated IRC for central review per RECIST v1.1. Information on measurable disease at baseline and confirmed disease progression by the IRC was communicated directly to each study site for determination of study treatment initiation and discontinuation. In all instances, the IRC reviewers were to be blinded to the results of local assessments at each study site. Clinical safety assessments were performed according to the protocol's Visit Evaluation Schedule. All subjects were required to have an ophthalmological evaluation of their eyes by an ophthalmologist during screening and that additional ophthalmologist's evaluations were indicated for subjects experiencing ocular symptoms during study treatment or for subjects with abnormal ocular findings as assessed by the investigator. All adverse events (AE) were to be assessed for severity using the NCI Common Terminology

Criteria for Adverse Events (CTCAE) version 5.0.

From 06/06/2018 through 02/06/2020 [data cutoff date for analyses in the current submission], the study enrolled 102 subjects from 36 sites in Europe and the U.S., including Belgium (9 sites), Czech Republic (3 sites), Germany (3 sites), Denmark (2 sites), Spain (4 sites), Italy (5 sites), Sweden (1 site), and the U.S. (9 sites). Of the enrolled subjects, 15% were from the U.S. For the interim efficacy and safety analyses, 101 subjects who received at least one dose of tisotumab vedotin were included. Determination of tumor responses was performed by (b) (4) the sponsor's contacted IRC for the study. As of the data cutoff date of 02/06/2020, this study was ongoing.

The DO1 review team and OSI reviewed the investigator sites risk ranking for this application and selected the above-described three investigators for clinical inspection. Relative to other participating investigators in Study GCT1015-04, these three investigators enrolled large numbers of subjects and/or had a higher tumor response rate (43-50%) than the overall tumor response rate (24%) reported for this study. Dr. Vergote in Belgium was selected because of insufficient domestic data. Inspection of the study sponsor Genmab U.S., Inc., was also requested given this new molecular entity application and no prior inspection history for this sponsor.

III. RESULTS

1. **Bradley Monk, M.D. (Site US11)**
   2222 E. Highland Avenue
   Phoenix, AZ 85016

   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)], 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.

2. **Michael Gold, M.D. (Site US01)**
12697 E. 51st Street South
Tulsa, OK 74146

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.

3. **Ignace Vergote (Site BE01)**
Herestraat 49
Leuven, NA 3000
Belgium

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 of (b) (5)

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.

4. Genmab U.S., Inc. (Study Sponsor)
777 Scudders Mill Road Bldg. 2 Fl 4
Plainsboro, NJ 08536

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 on (b) (6) At the closeout meeting, no discussion items were presented to the sponsor.

{See appended electronic signature page}

Yang-min (Max) Ning, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

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Kassa Ayalew, M.D., M.P.H
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Review Division /Division Director
Review Division /Project Manager
Review Division /Clinical Team Lead
Review Division/Medical Officer
OSI/DCCE/GCPAB Reviewer
OSI/Office Director
OSI/DCCE/Division Director
OSI/DCCE/GCPAB Branch Chief
OSI/DCCE/GCPAB Team Lead
OSI/GCP Program Analyst
OSI/Database PM

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	June 3, 2021
Requesting Office or Division:	Division of Oncology 1 (DO1)
Application Type and Number:	BLA 761208
Product Name, Dosage Form, and Strength:	Tivdak (tisotumab vedotin-tftv) for Injection, 40 mg/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Seagen Inc.
FDA Received Date:	February 10, 2021
OSE RCM #:	2021-357
DMEPA Safety Evaluator:	Tingting Gao, PharmD
DMEPA Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 REASON FOR REVIEW

As part of the approval process for Tivdak (tisotumab vedotin-tftv) for Injection, the Division of Oncology 1 (DO1) requested that we review the proposed Tivdak prescribing information (PI), Medication Guide, container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed Tivdak PI, container label, and carton labeling and determined that they may be improved to ensure safe product use. The proposed Tivdak Medication Guide is acceptable from a medication error perspective.

4 CONCLUSION & RECOMMENDATIONS

The proposed Tivdak Medication Guide is acceptable from a medication error perspective. The proposed Tivdak PI, container label, and carton labeling may be improved to ensure safe product use. We provide specific recommendations in Sections 4.1 and 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 1 (DO1)

A. Prescribing Information

1. General
    a. Per our Nonproprietary Name Suffix Advice letter dated May 11, 2021, we find the nonproprietary name, tisotumab vedotin-tftv, conditionally acceptable for your proposed product. Revise the nonproprietary name to read "tisotumab vedotin-tftv".

2. Dosage and Administration Section, Section 2.4
    a. We recommend bolding the intended action and unbolding the actions to avoid. We recommend this because bolding the action to avoid may be misinterpreted as the affirmative action when the word "NOT" is overlooked.
    b. Revise the volume of Sterile Water for Injection (SWFI) to remove the trailing zero so that the statement states "4 mL of SWFI". We recommend this because trailing zeros can lead to tenfold dosing errors when the decimal point goes unnoticed (e.g., 4.0 mL is seen as 40 mL).
    c. In Step 5 and Step 10, clarify whether the reconstituted and diluted product should be (b) (4) rather than "Do not expose to direct sunlight". If the product needs to be protected from light, consider revising the statement to "Cover the [vial or infusion bag] to protect from light" instead of "Do not expose to direct sunlight".
    d. In Step 11, revise the statement (b) (4) to "Discard the infusion bag…" to use positive language (b) (4)
    e. In Table 3, revise the name of the diluents to USP monograph names if applicable.

3. How Supplied/Storage and Handling Section
    a. Clarify whether the product needs to be stored "in the original carton to protect from light (b) (4)" since reconstituted and diluted product need to be protected from direct sunlight.

4.2 RECOMMENDATIONS FOR SEAGEN INC.

We recommend the following be implemented prior to approval of this BLA:

A. General Comments (Container label & Carton Labeling)

1. Revise the strength statement to "40 mg/vial" to express the product strength in terms of total amount of drug per vial in accordance with USP General Chapter <7>.
2. Revise (b) (4) to "CAUTION: Hazardous Agent" to ensure consistency with Prescribing Information.

B. Carton Labeling

1. In addition to bolding the "10", also bold the unit of measure "mg/mL" so that the statement reads "After reconstitution with 4 mL of Sterile Water for Injection, USP, the concentration of TIVDAK (tisotumab vedotin-tftv) is 10 mg/mL".
2. Delete (b) (4) in the statement "(b) (4) Storage:" to ensure consistency with the information in the Prescribing Information.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Tivdak received on February 10, 2021 from Seagen Inc.

Table 2. Relevant Product Information for Tivdak	
Initial Approval Date	N/A
Nonproprietary Name	tisotumab vedotin-tftv
Indication	(b) (4)
Route of Administration	intravenous
Dosage Form	for Injection
Strength	40 mg/vial
Dose and Frequency	2 mg/kg (up to a maximum of 200 mg) given as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity
How Supplied	Carton of one 40 mg single-dose vial
Storage	(b) (4) Do not freeze. Do not shake.
Container Closure	10 mL tubular injection vial Clear (b) (4) glass with garnet plastic-disc flip-off seal

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Tivdak labels and labeling submitted by Seagen Inc.

- Container label received on February 10, 2021, available from \\CDSESUB1\evsprod\bla761208\0001\m1\us\114-labeling\draft\carton-and-container\draft-label.pdf
- Carton labeling received on February 10, 2021, available from \\CDSESUB1\evsprod\bla761208\0001\m1\us\114-labeling\draft\carton-and-container\draft-carton.pdf
- Prescribing Information (Image not shown) received on February 10, 2021, available from \\CDSESUB1\evsprod\bla761208\0001\m1\us\114-labeling\draft\labeling\draft-label-text.docx
- Medication Guide received on February 10, 2021, available from \\CDSESUB1\evsprod\bla761208\0001\m1\us\114-labeling\draft\labeling\draft-med-guide.docx

G.2 Label and Labeling Images

(b) (4)

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[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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Medical Officer's Review of BLA 761208
Ophthalmology Consultant

BLA 761208

Submission: 2/10/2021
Review completed: 4/26/2021

Name: Tisotumab vedotin

Sponsor: Seagen Inc.

Requested Indication: (b) (4)

Requested: On February 10, 2021, Seagen Inc. submitted a new NME BLA for BLA 761208 using tisotumab vedotin for the proposed indication: (b) (4) The Division of Oncology 1 Products is seeking an ophthalmology consult as the key adverse event category for this drug is eye toxicity. We have scheduled no meetings at the moment. DO1 will send meeting invitation to the assigned reviewer when we schedule the meetings. EDR Link to submission: \\CDSESUB1\evsprod\BLA761208\0001

Listing of Clinical Studies

Study	Study Objectives	Test Product(s); Dosage and Regimen	Number Treated	Population	Duration of Treatment
GCT1015-04 Ongoing Full CSR	Efficacy, safety and tolerability, PK, antitumor activity	Tisotumab vedotin; 2.0 mg/kg administered as an intravenous (IV) infusion once every 3 weeks (1Q3W)	101	Previously treated recurrent or metastatic cervical cancer	Subjects receive study treatment in 21-day cycles until unacceptable toxicity, disease progression, withdrawal of consent, investigator decision or death.
GEN701 Complete Full CSR	Safety and tolerability, MTD, RP2D, PK, and antitumor activity	Tisotumab vedotin; Dose escalation: 0.3,0.6, 0.9, 1.2, 1.5, 1.8, 2.0, 2 .2, or 2.6 mg/kg IV 1Q3W Cohort expansion: 2.0 mg/kg IV 1Q3W (RP2D)	Total:195 Dose escalation: 27 Dose expansion: 168	Locally advanced and/or metastatic solid tumors known to express TF, including cervical cancer	Subjects receive study treatment in 21-day cycles until unacceptable toxicity, disease progression, withdrawal of consent, investigator or sponsor decision. The maximum possible duration of treatment was 12 cycles (36 weeks).
GEN702 Complete Full CSR	Safety and tolerability, MTD, RP2D, PK, and antitumor activity	Tisotumab vedotin; Dose escalation: 0.9 or 1.2 mg/kg IV 3Q4W Cohort expansion: 1.2 mg/kg IV 3Q4W or 2.0 mg/kg IV 1Q3W. The RP2D for the expansion part initially identified as 1.2 mg/kg 3Q4W.	Total: 33 Dose escalation: 9 Dose expansion: 24	Locally advanced and/or metastatic solid tumors known to express TF, including cervical cancer	Subjects receive study treatment until unacceptable toxicity, more than 2 dose reductions, specific dose delay conditions, pregnancy, subject choice, or investigator or sponsor decision. In the dose escalation part, the maximum possible duration of treatment was 12 cycles (48 weeks). In the cohort expansion part, the maximum possible duration of treatment was 9 cycles (36 weeks, or less after changing to the 2.0 mg/kg 1Q3W dosing regimen).
GCT1015-03 Complete Full CSR	Safety and efficacy of continued treatment with tisotumab vedotin	Tisotumab vedotin; Dose and regimen followed by the subject in the base trial[a]	5	Locally advanced and/or metastatic solid tumors known to express TF, including cervical cancer	Subjects receive study treatment until disease progression, investigator decision, unacceptable toxicity, consent withdrawal or for other reasons as defined in the protocol.
SGNTV-001 Ongoing, Actively enrolling; Abbreviated CSR	Anti-tumor activity, safety and tolerability, and PK	Tisotumab vedotin; 2.0 mg/kg IV 1Q3W or 0.9 mg/kg IV 3Q4W[b]	Up to 250 (estimated)	Locally advanced or metastatic solid tumors known to express tissue factor	Subjects receive study treatment until disease progression, unacceptable toxicity, investigator decision, consent withdrawal, start of a subsequent anticancer therapy, study termination by the sponsor, or death, whichever comes first.

[a] Subjects were treated with the tisotumab vedotin dosing regimen followed by the subject in the base trial. Four subjects received the 2 mg/kg Q3W dose, and 1 subject received the 1.5 mg/kg Q3W dose.

[b] SGNTV-001 abbreviated CSR only includes patients who received the 2.0 mg/kg Q3W dosing regimen.

TF = tissue factor; RP2D = recommended phase 2 dose; MTD = maximum tolerated dose; 1Q3W = every 3 weeks; 3Q4W = weekly for 3 weeks and no dose on the fourth al study report; IV = intravenous; PK=pharmacokinetics

1.1.3.5 Ophthalmological Examinations

Baseline ophthalmology examinations were to be performed by ophthalmologists during screening. Such examinations were implemented from the start in pivotal trial GCT1015-04 and were incorporated later through amendments to other trials, e.g., 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).

Relevant physical findings from the ophthalmological examination were to be documented in the electronic case report form for each trial. Assessments performed included visual acuity, Schirmer's test, slit lamp, inspections of the conjunctivas and corneas including staining, intraocular pressure, and fundoscopy.

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

1Q3W=once every 3 weeks; TV=tisotumab vedotin

a GEN701 expansion n=54, GEN702 expansion n=3, and GCT1015-03 cervical subjects n=2 counted in GEN701 and GEN 702 totals.

b GCT1015-04 n=101, GEN701 expansion n=54, GEN702 expansion n=3, and GCT1015-03 cervical subjects n=2 counted in GEN701 and GEN 702 totals.

c GCT1015-04 n=101, GEN701 expansion n=167, GEN702 expansion n=4, and GCT1015-03 subjects n=4 counted in GEN701 and GEN702 totals.

Most Common Ocular Events

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[a]	101 (100)	57 (100)	158 (100)	271 (99.6)
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)
Keratitis	11 (10.9)	3 (5.3)	14 (8.9)	17 (6.3)

Multiple occurrences of events are counted only once within a subject.
10% cutoff applies to GCT1015-04. Table is sorted by descending frequency in the 1st column.
Data cutoff: GEN701 exp: 02May2019, GEN702 exp: 13Dec2017, GCT1015-03: 10Jan2019, GCT1015-04: 06Feb2020. Dictionary: MedDRA v22.1
a Note that the total number of subjects with any event include PTs that occurred in <10% of subjects in GCT1015-04 or only occurred in subjects in the pooled analysis groups.

Table 16: Treatment-Emergent Adverse Events Resulting in Dose Reduction Reported in ≥1% of Subjects in GCT1015-04 by Preferred Term (Integrated Safety Analysis Set)

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[a]	23 (22.8)	8 (14.0)	31 (19.6)	46 (16.9)
Conjunctivitis	7 (6.9)	3 (5.3)	10 (6.3)	13 (4.8)
Keratitis	6 (5.9)	0	6 (3.8)	6 (2.2)
Dry eye	3 (3.0)	0	3 (1.9)	3 (1.1)
Blepharitis	2 (2.0)	0	2 (1.3)	2 (0.7)
Punctate keratitis	2 (2.0)	0	2 (1.3)	2 (0.7)
Conjunctival erosion	1 (1.0)	0	1 (0.6)	1 (0.4)
Conjunctival haemorrhage	1 (1.0)	0	1 (0.6)	1 (0.4)
Peripheral sensorimotor neuropathy	1 (1.0)	0	1 (0.6)	1 (0.4)
Peripheral sensory neuropathy	1 (1.0)	0	1 (0.6)	1 (0.4)
Thrombocytopenia	1 (1.0)	0	1 (0.6)	1 (0.4)

a Note that the total number of subjects with any event includes PTs that were below the cutoff applied to this table.
Multiple occurrences of events within a subject are counted only once.
Data cutoff: GEN701 exp: 02May2019, GEN702 exp: 13Dec2017, GCT1015-03: 10Jan2019, GCT1015-04: 06Feb2020.
Dictionary: MedDRA v22.1

Table 18: Summary of Treatment Emergent Ocular Adverse Events (Integrated Safety Analysis Set)

	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%)
Subjects with any treatment-related treatment-emergent ocular adverse events	54 (53.5%)	38 (66.7%)	92 (58.2%)	165 (60.7%)
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[a]	40/55 (72.7%)	12/40 (30.0%)	52/95 (54.7%)	81/171 (47.4%)
Subjects with some events resolved[a] or improved	15/55 (27.3%)	13/40 (32.5%)	28/95 (29.5%)	55/171 (32.2%)
Subjects with no events resolved[a] 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[a]	135/161 (83.9%)	59/98 (60.2%)	194/259 (74.9%)	312/458 (68.1%)
Time to resolution[a] (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	15/55 (27%)	28/40 (70%)	43/95 (45%)	90/171 (53%)

n=number of events; STD=standard deviation
At each preferred term, multiple occurrences of events within a subject are counted only once at the highest severity grade.
a. Resolution is defined as events status outcome of 'Recovered/Resolved' or 'Recovered/Resolved with Sequelae'.
b. For events that are not resolved, improvement is defined as at least one grade decrease from the highest grade as of the last assessment.

Mandatory Ocular Medication
Ocular AEs were reported in the first in human clinical trial, GEN701, and preventive measures were implemented to prevent ocular AEs. Therefore, in this trial, all subjects were required to:

- Self-administer preservative-free lubricating eye drops during the whole treatment phase of the trial (i.e., from first dose of tisotumab vedotin until 30 days after the last dose of tisotumab vedotin).
- Apply steroid eye drops during the first 3 days of each treatment cycle (i.e., first drop to be given prior to start of infusion; continue treatment for 72 hours thereafter).
- Receive topical ocular vasoconstrictor prior to each infusion.
- Use eye cooling pads during the infusion.

In addition, subjects were recommended not to wear contact lenses during the whole treatment phase. Furthermore, all subjects had their eyes examined by the investigator at baseline and at each treatment visit, as specified on the visit assessment schedule (Appendix 16.1.1, Table 1-1). All subjects were evaluated by an ophthalmologist at baseline and referred for additional evaluation in case of any ocular symptoms or abnormal ocular findings anytime during the trial (refer to Section 12.1.7.1 for further information).

2.1.5.1.1 Impact of Protocol-Defined Ocular Mitigation Plan (OMP)
Protocol-defined OMP measures intended to limit the risk of ocular events 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) (4), 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 patients 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 (either as per the defined measures in the GCT1015-04 protocol or otherwise) are summarized in Table 19. Most subjects in Pool 2 (89.9%) had received the OMP as per GCT1015-04, while the remaining 16 subjects (10.1%) in this all cervical cancer analysis group had received the initial or an earlier version of the OMP. In Pool 3 including non-cervical cancer subjects, 188 subjects (69.1%) had received current OMP while a higher proportion of subjects (84 subjects, 30.9%) had not received this OMP compared to Pool 2.

Overall, results showed that when the current and most comprehensive OMP is 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 OMP (75.0% in Pool 2 and 72.6% in Pool 3) (Table 19). 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) (Table 20). Corneal disorders were consistent across all groups and irrespective of OMP received (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. PTs 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) (Table 20).

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 19). 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.

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). 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 (i.e., 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).

Table 19: Summary of Treatment-Emergent Ocular Adverse Events by Cycle 1 OMP Status (Yes, No[a]) (Integrated Safety Analysis Set)

	Pivotal Cervical (GCT1015-04) (N=101)	Pool 2 (All Cervical)		Pool 3 (All Tumor Types)	
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)
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)

Ocular AEs include preferred terms from 9 SMQs: Conjunctival Disorders, Corneal Disorders, Scleral Disorders, Retinal Disorders, Peri-orbital and Eyelid Disorders, Ocular Infections, Optic Nerve Disorders, Glaucoma, Lacrimal Disorders, and Eye Disorders SOC. a. Yes = received the full OMP measures as defined in GCT1015-04 (cooling pads, vasoconstrictor, steroid eye drops) at cycle 1, No=otherwise.
Data cutoff: GEN701 exp: 02May2019, GEN702 exp: 13Dec2017, GCT1015-03: 10Jan2019, GCT1015-04: 06Feb2020.

Table 20:Treatment-Emergent Ocular Adverse Events by Preferred Term and Cycle 1 OMP Status (Yes, No[a]) Reported in ≥2% Subjects in Pool 2 or Pool 3 (Integrated Safety Analysis Set)

	Pivotal Cervical	Pool 2 (All Cervical)		Pool 3 (All Tumor Types)	
Classification Preferred Term	**Yes (N=101)**	**Yes (N=142)**	**No (N=16)**	**Yes (N=188)**	**No (N=84)**
Subjects with any event	55 (54.5)	83 (58.5)	12 (75.0)	110 (58.5)	61 (72.6)
Conjunctival disorders	48 (47.5)	70 (49.3)	12 (75.0)	94 (50.0)	58 (69.0)
Conjunctivitis	31 (30.7)	43 (30.3)	12 (75.0)	57 (30.3)	45 (53.6)
Dry eye	25 (24.8)	38 (26.8)	2 (12.5)	46 (24.5)	18 (21.4)
Ocular hyperaemia	4 (4.0)	4 (2.8)	0	6 (3.2)	2 (2.4)
Conjunctival hyperaemia	2 (2.0)	3 (2.1)	0	6 (3.2)	0
Conjunctival ulcer	0	4 (2.8)	0	7 (3.7)	2 (2.4)
Conjunctival haemorrhage	2 (2.0)	2 (1.4)	0	2 (1.1)	3 (3.6)
Conjunctival scar	1 (1.0)	2 (1.4)	0	5 (2.7)	1 (1.2)
Noninfective conjunctivitis	1 (1.0)	1 (0.7)	0	4 (2.1)	1 (1.2)
Corneal disorders	21 (20.8)	30 (21.1)	3 (18.8)	37 (19.7)	3 (3.6)
Keratitis	11 (10.9)	13 (9.2)	1 (6.3)	16 (8.5)	1 (1.2)
Punctate keratitis	6 (5.9)	7 (4.9)	0	9 (4.8)	0
Ulcerative keratitis	3 (3.0)	4 (2.8)	2 (12.5)	4 (2.1)	2 (2.4)
Vital dye staining cornea present	0	4 (2.8)	0	5 (2.7)	0
Periorbital & eyelid disorders	16 (15.8)	21 (14.8)	3 (18.8)	30 (16.0)	10 (11.9)
Blepharitis	7 (6.9)	9 (6.3)	3 (18.8)	13 (6.9)	5 (6.0)
Meibomianitis	3 (3.0)	5 (3.5)	0	8 (4.3)	3 (3.6)
Entropion	3 (3.0)	3 (2.1)	0	4 (2.1)	0
Visual symptoms	9 (8.9)	14 (9.9)	1 (6.3)	25 (13.3)	8 (9.5)
Vision blurred	3 (3.0)	4 (2.8)	1 (6.3)	12 (6.4)	3 (3.6)
Eye pain	1 (1.0)	3 (2.1)	0	4 (2.1)	3 (3.6)
Eye irritation	1 (1.0)	2 (1.4)	0	3 (1.6)	3 (3.6)
Other eye disorders	5 (5.0)	6 (4.2)	0	8 (4.3)	3 (3.6)
Cataract	2 (2.0)	3 (2.1)	0	3 (1.6)	3 (3.6)
Lacrimal disorders	4 (4.0)	4 (2.8)	1 (6.3)	8 (4.3)	8 (9.5)
Lacrimation increased	4 (4.0)	4 (2.8)	1 (6.3)	8 (4.3)	8 (9.5)
Retinal disorders	1 (1.0)	2 (1.4)	0	2 (1.1)	3 (3.6)
Ocular infections	1 (1.0)	1 (0.7)	0	1 (0.5)	2 (2.4)

Multiple occurrences of events within a subject are counted only once. Ocular AEs include preferred terms from 9 SMQs: Conjunctival Disorders, Corneal Disorders, Scleral Disorders, Retinal Disorders, Peri-orbital and Eyelid Disorders, Ocular Infections, Optic Nerve Disorders, Glaucoma, Lacrimal Disorders, and Eye Disorders SOC.
a. Yes=received the full ocular mitigation plan (cooling pads, vasoconstrictor, steroid eye drops) at cycle 1, No=otherwise. Data cutoff: GEN701 exp: 02May2019, GEN702 exp: 13Dec2017, GCT1015-03: 10Jan2019, GCT1015-04: 06Feb2020. Dictionary: MedDRA v22.1

Reviewer's Comments: *The ocular mitigation plan did result in a decrease of ocular adverse events; however, the mitigation regimen carries risks. The use of ophthalmic corticosteroids, while effective in reducing ocular adverse events associated with tisotumab vedotin, increases the development of cataracts and increases the risk of sight threatening keratitis and corneal ulcers. It is recommended that prior to initiation of each dose of ophthalmic corticosteroids, a slit lamp examination be performed as described in the labeling of ophthalmic corticosteroids.*

Summary Comments:

1. The most common reported ocular events were consistent with the product causing dry eye symptoms. These were captured by the terms conjunctivitis, keratitis and dry eye. These events occurred in approximately 50% of patients and usually first occurred following the second or third treatment cycle.

2. Grading of ocular adverse events is potentially misleading and is not recommended.

3. While the use of ophthalmic corticosteroids at the beginning of each treatment cycle is recommended to reduce ocular adverse events, a slit lamp examination should be conducted prior to initiation of each cycle of dosing. These ocular events have the potential to be sight threatening.

Wiley A. Chambers, M.D.
Supervisory Physician, Ophthalmology

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/s/

WILEY A CHAMBERS
04/26/2021 08:23:11 AM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: April 21, 2021

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Clinical Analyst, DCN

To: David Nartey, RPM
DO1

Subject: QT Consult to BLA 761208 (SDN 001)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 3/4/2021 regarding the sponsor's QT analysis report. We reviewed the following materials:

- Sponsor's concentration-QTc analysis report (Submission 0001);
- Previous IRT review under IND 135476 dated 09/06/2019 in DARRTS;
- Proposed label (Submission 0001);
- Summary of clinical safety (Submission 0001); and
- Summary of clinical pharmacology (Submission 0001).

1 Responses for the Division

Tisotumab vedotin treatment at 2 mg/kg Q3W does not cause large mean increases in the QTc interval (20 msec). There are several limitations in the study design (including lack of placebo and positive controls, evaluation at therapeutic dose and sparsely collected ECG recordings); therefore, we are reluctant to conclude a lack of a QTc prolongation effect.

We propose the followings changes (addition; ~~deletion~~) to the sponsor's proposed product label. Our proposals are for suggestions only and we defer the final labeling decisions to the Division.

12.2 Pharmacodynamics
Cardiac Electrophysiology
At the recommended dose, tisotumab vedotin-xxxx had no large mean (b) (4) effect on QTc prolongation (>20 (b) (4) msec).

2 BACKGROUND

2.1 Product Information

Tisotumab vedotin is an antibody-drug conjugate (ADC) that contains a tissue factor-directed IgG1 antibody (tisotumab) conjugating via a protease-cleavable valine-citrulline linker to the microtubule-disrupting agent monomethyl auristatin E (MMAE). The sponsor is developing tisotumab vedotin injection (b) (4) The recommended therapeutic dose is 2 mg/kg (up to a maximum of 200 mg) given as an intravenous infusion over 30 min every 3 weeks until disease progression or unacceptable toxicity.

Tisotumab vedotin releases MMAE via proteolytic cleavage, and MMAE is primarily metabolized by CYP3A4 in vitro. In the proposed product label, the terminal half-life of MMAE and the ADC is approximately 2.6 and 4.0 days, respectively. Mean (s.d.) Cmax is predicted to be 5.9 (4.2) ng/mL for MMAE (unconjugated) and 40.8 (8.1) ug/mL for the ADC at the proposed therapeutic dosing regimen.

Reviewer's comment: *The reported maximum systemic exposure of the payload is not significantly higher than that with an approved ADC product containing MMAE.*

2.2 Sponsor's position related to the question

Previously the IRT reviewed the sponsor request to waive a thorough QT study based on concentration-QTc analysis in studies GCT1015-04 and SGNTV-001 (IRT review under IND 135476 dated 09/06/2019 in DARRTS). The sponsor did not provide sufficient information to support the proposed concentration-QTc analysis. However, it was concluded that a dedicated QT assessment may not be needed if the maximum systemic exposure of MMAE is not significantly higher than the exposures from approved ADC products containing MMAE and if mechanistic considerations or data from clinical or nonclinical studies do not suggest the potential for proarrhythmic risk.

2.3 Nonclinical Cardiac Safety

Refer to previous IRT review under IND 135476 dated 09/06/2019 in DARRTS.

According to the sponsor, the IC50 value from the in vitro hERG study is >100 uM and no effect were observed in ECG intervals in the general toxicology studies in cynomolgus monkeys at ADC doses up to 5 mg/kg or MMAE doses up to 0.058 mg/kg.

2.4 Clinical Cardiac Safety

The sponsor's Summary of Clinical Safety does not identify events of clinical importance per the ICH E14 guidelines (i.e., seizure, significant ventricular arrhythmias or sudden cardiac death).

2.5 Summary results of prior QTc assessments

The relationship between tisotumab vedotin and MMAE concentrations and change in the corrected QT interval by Fridericia (QTcF) from baseline was explored using linear mixed The analysis population consisted of 153 subjects (55 subjects from the SGNTV-001 trial and 98 subjects from the GCT1015-04 trial). In trial GCT1015-04, the largest mean ΔQTcF was predicted for the ADC steady-state Cmax (mean of 40.8 µg/mL from the population PK model) and was 6.70 msec (upper one-sided 95% CI: 7.94 msec), well below the safety threshold of 10

msec for a clinically meaningful effect on QTc prolongation. An analysis of the combined data from both studies resulted in a slightly lower predicted ΔQTcF value of 5.40 msec (upper one-sided 95% CI: 7.02 msec) at the ADC steady-state Cmax. MMAE appeared to have an opposite effect on ΔQTcF, resulting in a decrease of QTcF with an increase in MMAE concentrations.

The concentration-ΔQTcF analysis did not show a clinically relevant ΔQTcF risk at steady state Cmax for either ADC or MMAE following administration of tisotumab vedotin at a dose of 2.0 mg/kg 1Q3W, as the upper bounds of the one-sided 95% CI were below 10 msec.

Overall, the analysis suggests that tisotumab vedotin administered at the recommended dose of 2.0 mg/kg 1Q3W does not appear to have an adverse effect on ventricular repolarization and does not result in a clinically meaningful prolongation of the QTc interval in subjects with solid cancers.

Reviewer's comment:

1) *Based on the Summary of Clinical Pharmacology, Tmax of MMAE ranges between Day 2-8 after single doses up to 2.2 mg/kg. The sponsor's QT/PK dataset included PK/ECG pairs on Cycle 1 Day 3 in Study SGNTV-001 (1 data point per subject), before and at the end of infusion or on Cycle 1 Day 4 or 8 in Study GCT1015-04. The geometric mean Cmax of PK samples on Days 3, 4, or 8 were 3.6 or 4.6 ng/mL and the mean Cmax were 4.5 or 5.2 ng/mL in studies SGNTV-001 or GCT1015-04, respectively. Overall, while PK/ECG sampling schedule is sparse, the PK/ECG dataset appears to provide reasonable coverage for the therapeutic exposure.*
2) *Descriptive statistics on the sponsor's PK/ECG data suggested an upper bound of 95% CI in the change-from-baseline QTc (ΔQTcF) <10 msec in cycle 1 of both studies. In Study GCT1015-04, there appears to be a trend of higher ΔQTcF at the end-of-infusion as compared to predose data. The upper bound of 90% CI in ΔQTcF at the end-of-infusion were above 10 msec (mean values <10 msec). Because the study does not include placebo treatment, it is not clear if this change is caused by drug exposure or the infusion procedure.*
3) *The dataset does not suggest positive exposure-response relationship between ΔQTcF vs. MMAE concentration. The dataset suggests positive exposure-response relationship between ΔQTcF vs. ADC or total antibody concentration, but the observation cannot be explained by direct interaction with cardiac ion channels.*
4) *In the first cycle, no patients reported ΔQTcF >60 msec. 2 patients reported ΔQTcF >60 msec after at least 3 cycles. No patients reported QTcF > 500 msec in this dataset.*
5) *Overall, we agree that tisotumab vedotin treatment at 2 mg/kg Q3W does not cause large mean increases in the QTc interval. Due to limitations in the study design (no placebo control, no positive control or large exposure margin, sub-optimal ECG quality), we are reluctant to conclude a lack of clinically relevant effect on the QTc interval.*

2.6 Relevant details of planned Phase 3 study

Not applicable.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

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