CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761208Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 135476

MEETING MINUTES

Seattle Genetics, Inc.
Pierre Kiami, MPH
21823 30th Drive SE
Bothell, WA 98021

Dear Mr. Kiami:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tisotumab vedotin.

We also refer to the teleconference between representatives of your firm and the FDA on August 31, 2020. The purpose of the meeting was to discuss the topline clinical results from the pivotal phase 2 trial GCT1015-04 for the planned BLA.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact Clara Lee, Regulatory Project Manager, at Clara.Lee@fda.hhs.gov or (240) 402-4809.

Sincerely,

{See appended electronic signature page}

Clara Lee, PharmD
Regulatory Project Manager
Oncology 1 Group
Division of Regulatory Operations for Oncologic Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

{See appended electronic signature page}

Gwynn Ison, MD
Clinical Team Leader (Acting)
Division of Oncology 1
Office of Oncologic Diseases
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-BLA

Meeting Date and Time: August 31, 2020 / 2:00 – 3:00 (EDT)
Meeting Location: Teleconference

Application Number: IND 135476
Product Name: Tisotumab vedotin
Indication: (b) (4)

Sponsor Name: Seattle Genetics, Inc.
Regulatory Pathway: 351(a) of the Public Health Service Act

Meeting Chair: Gwynn Ison, MD
Meeting Recorder: Clara Lee, PharmD

FDA ATTENDEES

Laleh Amiri-Kordestani, MD, Division Director (Acting), OOD/DO1
Gwynn Ison, MD, Clinical Team Leader (Acting), OOD/DO1
Christy Osgood, MD, Clinical Team Leader (Acting), OOD/DO1
Preeti Narayan, MD, Clinical Reviewer, OOD/DO1
Erik Bloomquist, PhD, Biostatistics Team Leader, OB/DBV
Hui Zhang, PhD, Biostatistics Reviewer, OB/DBV
Pengfei Song, PhD, Clinical Pharmacology Team Leader, OCP/DCPV
Huiming Xia, PhD, Clinical Pharmacology Reviewer, OCP/DCPV
Clara Lee, PharmD, Regulatory Project Manager, ORO/DRO-OD

SPONSOR ATTENDEES

Seattle Genetics, Inc.
Nancy Whiting, PharmD, Executive Vice President, Late Stage Development
Leonardo Nicacio, MD, Vice President, Clinical Development
Joy Jiang, PharmD, Senior Manager
Samir Vattompadam, MSc, Executive Director, Portfolio and Strategy Management
Helen Winter, PhD, Senior Director, Quantitative Pharmacology and Disposition
Melinda Teng, PhD, Director, Biostatistics
Marissa Braff, PhD, RAC, Executive Director, Regulatory Affairs
Pierre Kiami, MPH, RAC, Associate Director, Regulatory Affairs

Genmab A/S
Richard Jansson, PhD Vice President, Compound Development Team Leader
Yali Fu, MD, PhD Senior Medical Director, Medical

Signe Diness Vindelov, MD, PhD, Director, Medical
Reginald Gay, MD, Senior Director, Global Drug Safety & Pharmacovigilance Physician
Chaitali Passey, PhD Director, Clinical Pharmacology
Kristian Windfeld, PhD, Senior Director, Biostatistics
Rima Nassar, PhD, Vice President, Head of Global Regulatory Affairs
Jessica Wang, PharmD, Director, Regulatory Affairs

1.0 BACKGROUND

Seattle Genetics, Inc. has requested a Type B, Pre-BLA meeting with the FDA to obtain feedback on the topline clinical results from the pivotal phase 2 trial GCT1015-04 and the data package for the proposed initial BLA submission for accelerated approval of tisotumab vedotin for the following indication:

(b) (4)

Tisotumab vedotin is an antibody-drug conjugate (ADC) composed of a tissue factor (TF)-directed human monoclonal IgG1κ antibody that is covalently attached to the microtubule disrupting agent, monomethyl auristatin E (MMAE), via a protease-cleavable valine citrulline linker. As of July 2020, there are 8 completed or ongoing clinical trials with tisotumab vedotin for the treatment of cervical cancer and other solid tumors.

The Sponsor plans to seek accelerated approval of tisotumab vedotin for the proposed indication at the recommended dose of 2.0 mg/kg intravenous Q3W and plans to submit a BLA in November 2020. The proposed BLA will be based primarily on phase 2 trial GCT1015-04, a single-arm study of 101 treated subjects with recurrent or metastatic cervical cancer, as well as supportive safety and/or efficacy data from all completed and ongoing clinical trials of tisotumab vedotin (Table 1). In addition, the analysis on anti-drug antibodies will include data from the SGNTV-001 study.

The Sponsor has met with DO1 on two previous occasions in April and September 2019 to discuss the potential for Study GCT1015-04 to support an accelerated approval for tisotumab vedotin (b) (4) At the September 2019 meeting, the Sponsor had enrolled 101 patients to the GCT1015-04, but topline results on ORR were not provided. FDA provided input on the need for topline results, as well as feedback on efficacy and safety dataset content and on the need for a literature review to support an assertion that a reported ORR for tisotumab vedotin could be considered better than available therapies in the therapeutic setting.

Table 1: Ongoing and completed trials of tisotumab vedotin to be included in proposed BLA

Trial Identifier	Phase	Description	Population	Dosage and Frequency	N[a]	Current Status	Inclusion in BLA				
							CSR	SCP m2.7.2	SCE m2.7.3	SCS m2.7.4	ISS m5.3.5.3
GEN701	1/2	Open-label TV FIH dose escalation and cohort expansion	Locally advanced or metastatic solid tumor types known to express TF	Multiple; RP2D chosen as 2.0 mg/kg Q3W	195	Completed	Full	Yes	Yes[b]	Yes[b]	Yes[b]
GEN702	1/2	Open-label TV dose escalation and expansion with different dose regimens	Locally advanced and/or metastatic solid tumors known to express TF	2.0 mg/kg Q3W, 0.9 mg/kg 3Q4W, and 1.2 mg/kg 3Q4W	33	Completed	Full	Yes	No	Yes[b]	Yes[b]
GCT1015-03	2	Open-label continued treatment with TV	Locally-advanced or metastatic solid tumor types known to express TF	2.0 mg/kg Q3W	4	Completed	Full	No	Yes	Yes	Yes
GCT1015-04	2	Single arm, open-label TV	Previously treated r/mCC	2.0 mg/kg Q3W	102	Primary analysis completed	Full	Yes	Yes	Yes	Yes
GCT1015-05	1b/2	Open-label TV in combination with other anticancer agents	Recurrent or stage IVB cervical cancer	2.0 mg/kg Q3W	140 (est.)	Enrollment ongoing	None	No	No	No	Yes[c]
GCT1015-06	1	Dose escalation and expansion in Japanese subjects	Previously treated r/mCC	1.5 mg/kg Q3W or 2.0 mg/kg Q3W	25 (est.)	Enrollment completed	None	No	No	No	Yes[c]
SGNTV-001	2	Open-label TV	Locally advanced or metastatic solid tumor types known to express TF	2.0 mg/kg Q3W	Up to 200 (est.)	Enrollment ongoing	Abbr.	Yes	No	No	Yes[c]
SGNTV-002	2	Open-label TV with a safety run-in of a dose-dense regimen	Platinum-resistant ovarian cancer	2.0 mg/kg Q3W or 0.9 mg/kg 3Q4W	Up to 142 (est.)	Enrollment ongoing	None	No	No	No	Yes[c]

TV = tisotumab vedotin; FIH = first in human; TF = tissue factor; RP2D = recommended phase 2 dose; Q3W = every 3 weeks; 3Q4W = weekly for 3 weeks and no dose on the fourth week; est. = estimated; Abbr = abbreviated

a Reflects total enrolled in the trial.

b 2.0 mg/kg Q3W, non-dose escalation (expansion cohort) subjects only.

c Data to be provided as listings for all SAEs; narrative text to be provided in SCS.

Source: Sponsor pre-BLA meeting background package

GCT1015-04 is a phase 2, single-arm, global trial of tisotumab vedotin in subjects with previously treated recurrent or metastatic cervical cancer. Eligible subjects had second- or third-line recurrent or metastatic cervical cancer and had experienced disease progression on or after receiving a chemotherapy doublet (paclitaxel + cisplatin/carboplatin OR paclitaxel + topotecan) in combination with bevacizumab, if eligible to receive bevacizumab according to local standards. Prior chemoradiation with curative intent was not considered a line of therapy for the purposes of the trial. Patients were treated until disease progression or unacceptable toxicity. The primary endpoint was confirmed ORR per independent review committee (IRC). Secondary endpoints included DOR, time to response (TTR) and PFS assessed by IRC and confirmed ORR, DOR, TTR, and PFS assessed by investigator, OS, and safety and tolerability.

Topline results: Tisotumab vedotin monotherapy demonstrated a confirmed ORR of 24% [95% CI 15.9%–33.3%], including 7 CRs (7%) and 17 PRs (17%), and median DOR of 8.3 months [95% CI 4.3 months – NR]. Median PFS per IRC was 4.2 months [95% CI 3.2–4.6 months] and median OS (57% fraction) was 12.1 months [95% CI 9.6 – 13.9 months]. All responders in the GCT1015-04 trial were followed for a minimum of 6 months following the first documented response (per investigator). Responses were confirmed at least 4 weeks (28 days) after the first assessment of response.

The most common TEAEs included nausea (41%), alopecia (39%), epistaxis (39%), fatigue (35%), anemia (34%), and conjunctivitis (31%). Grade 3 and higher TEAEs were reported for 61 subjects (60%). Treatment-emergent SAEs were reported in 43 subjects (43%). The most common SAEs (reported in 3 or more subjects) were pneumonia (4%), constipation (3%), and pyrexia (3%). Four subjects (4%) had TEAEs with fatal outcomes. These included TEAEs of death not otherwise specified (2%), ileus (1%), and septic shock (1%).

Adverse events of special interest (AESIs) for tisotumab vedotin include ocular AEs, peripheral neuropathy, and bleeding AEs. Ocular AEs were reported in 55 subjects (55%). Most ocular AEs were grade 1 or grade 2 in severity. Three subjects had grade 3 ocular events, all ulcerative keratitis. No grade 4 ocular events were reported. Thirty-eight subjects (38%) experienced AEs of peripheral neuropathy. Nineteen percent had grade 1 events, 12% had grade 2 events, and 7% had grade 3 events. No subjects experienced grade 4 events of peripheral neuropathy. Fifty-seven subjects (56%) experienced AEs of bleeding. The majority of bleeding events were grade 1 (46%). Five percent had grade 2 bleeding events and 6% had grade 3 bleeding events (vaginal hemorrhage, rectage hemorrhage and hematuria). No subjects experienced grade 4 or grade 5 bleeding events. The most commonly occurring bleeding event was epistaxis (39%), other bleeding events included vaginal hemorrhage (11%) and hematuria (9%).

The Sponsor plans to submit a safety update within 90 days of the original BLA submission. This update will include more than 7 months of additional safety data from GCT1015-04 (cut-off date of February 6, 2020, for the primary analysis and projected cut-off date of approximately September 25, 2020, for the 90-day safety update). Final data from the 3 completed supportive studies, GEN701, GEN702, and GCT1015-03, which contribute to the Summary of Clinical Safety (SCS), will be provided in the original BLA submission. At the time of the data cutoff for the primary analysis of GCT1015-04, 37 subjects remained on study (4 subjects on treatment and 33 subjects in survival/safety follow-up). Therefore, the 90-day safety update report will be based on the updated data from GCT1015-04, as there will be no additional clinical data from the supportive studies.

As noted above, the Sponsor proposes (b) (4)

FDA sent Preliminary Comments to Seattle Genetics, Inc. on August 21, 2020

2.0 DISCUSSION

Question 1: Does the FDA agree that the proposed efficacy and safety package for tisotumab vedotin in recurrent or metastatic cervical cancer, comprising primarily the data from pivotal phase 2 trial GCT1015-04, is adequate to support submission of a BLA for accelerated approval for the proposed indication?

FDA Response to Question 1: Yes, in general your proposed package is acceptable. We remind you (b) (4)

We have the following comments about content of your BLA submission:

- **You should include all CRFs and narratives for patients with SAEs, discontinuations due to AE, deaths on or within 30 days of treatment discontinuation. You will also need to make additional CRFs and narratives available for our review upon request.**

- **In your analysis datasets, you should include information on all prior lines of therapy, including all systemic therapies given in neoadjuvant, adjuvant and metastatic settings, and these should be clearly indicated as such.**

- **You also should provide all information on prior surgeries and radiation therapy in the datasets.**

- **There should be a specific flag indicating receipt of prior bevacizumab (yes vs. no).**

- **Finally, you should provide a dataset that includes tumor lesion measurements by both INV and IRC and overall response assessment (RECIST 1.1) by INV and IRC at each tumor assessment. You should provide the radiology charter for FDA review in your BLA submission.**

Sponsor's Response Dated August 28, 2020: Refer to the Sponsor's presentation slides.

Meeting Discussion: The Sponsor provided a summary of the study results outlined in the meeting package. They then provided a few slides to show their proposed confirmatory trial, innovaTV 301. The FDA expressed concerns that the confirmatory trial protocol has not yet been finalized, and the study is not underway. The FDA clarified that lack of an ongoing confirmatory trial will be an approvability issue. The FDA also expressed concerns that the proposed phase 3 trial would be difficult to enroll, given that it will enroll patients in the same treatment line as the study that would support the accelerated approval. The Sponsor stated that they are committed to initiating their confirmatory trial as soon as possible.

Question 2: Does the FDA agree with the proposed content and format for the 90-day safety update, including the proposed data cutoff date for the pivotal trial?

FDA Response to Question 2: Yes. You should also plan to submit an update for duration of response for trial GCT1015-04 using the same data cutoff date that is used for your 90-day safety update.

Sponsor's Response Dated August 28, 2020: None.

Meeting Discussion: None.

Question 3: Does the FDA agree that the proposed manufacturing timeframe for the Biologic Intermediate, Drug Substance, and Drug Product will support PLI timing based on the projected BLA review period?

FDA Response to Question 3: Yes, in general we agree. However, due to the ongoing travel restrictions, as well as changing entry requirements to enter foreign countries, you should provide additional future manufacturing plans in case the pre-license inspections cannot be completed at the times proposed in the meeting package. Additionally, you should take the following under consideration:

All facilities should be registered with the FDA at the time of the <351(a)> BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers. A preliminary manufacturing schedule for the drug substance and drug product should be provided in the BLA submission to facilitate the planning of pre-license inspections during the review cycle. Manufacturing facilities should be in operation and manufacturing the product under review during the inspection.

Given current circumstances and restrictions on travel, we are utilizing alternative approaches to inspections, where possible to mitigate the need or duration of inspections during the COVID-19 pandemic. However, if a pre-license inspection is required at any of the proposed manufacturing facility(ies) before the application can be approved, we may be unable to conduct the inspection within the proposed manufacturing timeframes due to restrictions on travel. We will continue to monitor the public health situation as well as travel restrictions. For more information, please see the FDA guidances related to COVID 19.[1] These guidances can be found at:

https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders.

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Sponsor's Response Dated August 28, 2020: None.

Meeting Discussion: None.

Question 4: Does the FDA agree that additional stability data can be submitted as simple stability updates both within the 30-day period following submission of the BLA and also during the BLA review period?

FDA Response to Question 4: Yes, we agree with your proposal to submit additional drug product stability data as stability updates both within the 30-day period and within 4 months after the initial submission of the proposed BLA. The adequacy of the data and the shelf-life of your drug product will be determined as review issues.

Additionally, we are providing additional product quality microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your <351(a)> BLA submission.

For facilities handling potent or toxic products, a risk assessment should be conducted to identify risks of cross-contamination between the products. Please refer to ICH Q9 and ISPE (2010), "Risk Based Manufacture of Pharmaceutical Products" (Risk-MaPP) for guidance. The quality risk management report and the segregations and controls implemented to mitigate the identified risks will be evaluated during the pre-license inspection. Cleaning validation limits of shared equipment should be science-based, e.g., based on Acceptable Daily Exposure (ADE) of products.

Information and data for CMC product quality microbiology should be submitted in the specified sections indicated below.

The CMC Drug Substance section of the <351(a)> BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control of the drug substance and drug substance intermediate. The information should include, but not be limited to the following:

- **Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. Bioburden sampling should occur prior to any 0.2 µm filtration step. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).**

- **Bioburden and endotoxin data obtained during manufacture of three process qualification (PPQ) lots (3.2.S.2.5).**

- **Microbial data from three successful product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels**

before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).

- **Chromatography resin and UF/DF membrane lifetime study protocols and acceptance criteria for bioburden and endotoxin samples. During the lifetime studies, bioburden and endotoxin samples should be taken at the end of storage prior to sanitization (3.2.S.2.5).**

- **Information and summary results from the shipping validation studies (3.2.S.2.5).**

- **Drug substance bioburden and endotoxin release specifications (3.2.S.4).**

- **Summary reports and results from bioburden and endotoxin test method qualification studies performed for in-process intermediates and the drug substance. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers (3.2.S.4).**

The CMC Drug Product section of the <351(a)> BLA (Section 3.2.P) should contain validation data summaries to support the aseptic processing operations. For guidance on the type of data and information that should be submitted, refer to the 1994 FDA Guidance for Industry *"Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products"* at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf.

The following information should be provided in Sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate.

- **Identification of the manufacturing areas and type of fill line (e.g., open, RABS, isolator), including area classifications.**

- **Description of the sterilizing filter (supplier, size, membrane material, membrane surface area, etc.); sterilizing filtration parameters (pressure and/or flow rate), as validated by the microbial retention study; wetting agent used for post-use integrity testing of the sterilizing filter and post-use integrity test acceptance criteria.**

- **Parameters for filling and capping for the vials.**

- **A list of all equipment and components that contact the sterile drug product (i.e., the sterile-fluid pathway) with the corresponding method(s) of sterilization and depyrogenation, including process parameters. The list should include single-use equipment.**

- **Processing and hold time limits, including the time limit for sterilizing filtration and aseptic filling.**

- **Sampling points and in-process limits for bioburden and endotoxin. Bioburden samples should be taken at the end of the hold time prior to the subsequent filtration step. Pre-sterile filtration bioburden limits should not exceed 10 CFU/100 mL.**

The following study protocols and validation data summaries should be included in Section 3.2.P.3.5, as appropriate:

- **Bacterial filter retention study for the sterilizing filter. Include a comparison of validation test parameters with routine sterile filtration parameters.**

- **Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three validation studies and describe the equipment and component revalidation program.**

- **In-process microbial controls and hold times. Three successful product intermediate hold time validation runs should be performed at manufacturing scale, unless an alternative approach can be scientifically justified. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.**

- **Isolator decontamination summary data and information, if applicable.**

- **Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Describe the environmental and personnel monitoring procedures followed during media fills and compare them to the procedures followed during routine production.**

- **Information and summary results from shipping validation studies.**

- **Validation of capping parameters, using a container closure integrity test.**

- **Lyophilizer sterilization validation summary data and information.**

The following product testing and method validation information should be provided in the appropriate sections of Module 3.2.P:

- **Container closure integrity testing. System integrity should be demonstrated initially and during stability. Container closure integrity method validation should demonstrate that the assay is sensitive enough**

to detect breaches that could allow microbial ingress (≤20 microns). Container closure integrity testing should be performed *in lieu* of sterility testing for stability samples every 12 months (annually) until expiry.

- **Summary report and results for qualification of the bioburden, sterility, and endotoxin test methods performed for in-process intermediates (if applicable) and the finished drug product, as appropriate. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers. Provide full descriptions and validation of non-compendial rapid microbial methods.**

- **Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR610.13(b).**

- **Low endotoxin recovery studies. Certain product formulations have been reported to mask the detectability of endotoxin in the USP <85> *Bacterial Endotoxin Test* (BET). The effect of hold time on endotoxin detection should be assessed by spiking a known amount of standard endotoxin (RSE or purified CSE) into undiluted drug product and then testing for recoverable endotoxin over time.**

Sponsor's Response Dated August 28, 2020: None.

Meeting Discussion: None.

Additional Comment:

- **In the submission, you should provide the SAS program used to derive the response status from raw data (target lesion measurements, non-target status, and new lesion status at each assessment) following RECIST v1.1 based on investigator and central radiology assessments. This program should be stand-alone (i.e., no macros) so that it can be run on FDA computers.**

Sponsor's Response Dated August 28, 2020: None.

Meeting Discussion: None.

3.0 ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. These items were addressed in the preliminary comments and captured meeting discussion. Also refer to the preliminary comments dated September 10, 2019.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated

pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to FDA.gov.[2]

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020, or Sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the Sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the FDA's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided.

Meetings requests should be sent to the appropriate review Division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The FDA strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing

[2] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

Information[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be

[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or Sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or Sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[6]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of

[6] http://www.fda.gov/ectd

regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[7]

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

[7] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[8] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[9]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and Sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[10]

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review

[8] https://www.fda.gov/media/84223/download
[9] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and
[10] https://www.fda.gov/media/85061/download

process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review Division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR[11]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.

- Assessment Aid[12]

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the FDA intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a Sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

To the extent that your proposed 351(a) BLA is within the scope of this guidance, FDA will assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

4.0 ATTACHMENTS AND HANDOUTS

Presentation slides provided by Seattle Genetics, Inc. on August 28, 2020.

[11] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[12] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CLARA J LEE
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09/10/2020 02:39:22 PM

IND 135476

MEETING PRELIMINARY COMMENTS

Seattle Genetics, Inc.
Attention: Pierre Kiami, MPH
21823 30th Drive SE
Bothell, WA 98021

Dear Mr. Kiami:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tisoutumab vedotin.

We also refer to your July 22, 2019, correspondence, received July 22, 2019, requesting a meeting to discuss the content and format of your planned BLA submission.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, contact Clara Lee, Regulatory Project Manager, at (240) 402-4809 or Clara.Lee@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Clara Lee, PharmD
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology & Oncology Products
Center for Drug Evaluation & Research

Sanjeeve Balasubramaniam, MD, MPH
Clinical Team Leader, DOP1
Division of Oncology Products 1
Office of Hematology & Oncology Products
Center for Drug Evaluation & Research

ENCLOSURE:

- Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: September 20, 2019 / 9:00 AM – 10:00 AM (EDT)
Meeting Location: FDA White Oak Campus, Building 22 – Room 1313

Application Number: IND 135476
Product Name: Tisotumab vedotin
Indication: (b) (4)

Sponsor Name: Seattle Genetics, Inc.

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for September 20, 2019 from 9:00 AM to 10:00 AM (EDT) between Seattle Genetics, Inc. and the Division of Oncology Products 1. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

The purpose of this Type B, Pre-BLA meeting is to obtain advice from the FDA regarding the content of the BLA submission packet primarily on data from pivotal trial GCT1015-04, an ongoing, open-label, phase 2, single-arm trial of tisotumab vedotin in subjects with previously treated, recurrent or metastatic cervical cancer (r/mCC).

Tisotumab vedotin is an antibody-drug conjugate (ADC) targeting tissue factor (TF)-expressing tumors through intracellular delivery of the microtubule-disrupting agent monomethyl auristatin E (MMAE). TF is a transmembrane receptor for Factor VII/VIIa. It

is constitutively expressed by cells surrounding blood vessels. Per the sponsor, TF is also expressed by tumor cells and contributes to a variety of pathologic processes, such as thrombosis, metastasis, tumor growth, and tumor angiogenesis. Some studies have reported that endothelial cells in the tumor vasculature express TF and this may enhance angiogenesis. MMAE-mediated tumor cell killing is the dominant mechanism of action of tisotumab vedotin in vivo. The sponsor states that upon binding to human TF-expressing cells, tisotumab vedotin is internalized, where it undergoes lysosomal degradation resulting in release of the cytotoxic payload. After intracellular release, MMAE disrupts tubulin polymerization and causes cell cycle arrest. Free MMAE may also diffuse out of the target cell and penetrate surrounding 'bystander' cells to cause cell death, potentially increasing antitumor efficacy but also contributing to off-target toxicity.

GCT1015-04: This is an open-label, single-arm, global, multicenter, Phase 2 trial of tisotumab vedotin dosed at 2.0 mg/kg Q3W in subjects with second-line (2L) or third-line (3L) r/mCC who experienced disease progression on or after receiving a platinum taxane- or topotecan-taxane-containing chemotherapy in combination with bevacizumab that completed enrollment (n=101) on April 11, 2019. Results from the GCT1015-04 trial will serve as the primary data to support the assessment of efficacy in the BLA for tisotumab vedotin. Supportive data from the 55 cervical cancer expansion subjects treated with tisotumab vedotin from trial GEN701 (including extension study data from 2 cervical cancer subjects who were subsequently enrolled in GCT1015-03) will be summarized side by side with the GCT1015-04 data as part of the Summary of Clinical Efficacy (SCE). The efficacy data to be presented in the SCE are based on all r/mCC subjects treated with tisotumab vedotin 2.0 mg/kg Q3W whose tumor assessments were evaluated by IRC.

The efficacy endpoints to be summarized in the SCE are confirmed ORR based on RECIST v1.1 as assessed by IRC, and secondary endpoints including investigator-assessed ORR, DOR assessed by IRC as well as investigator, time to response (TTR) by IRC and investigator, PFS by IRC and investigator, and overall survival (OS). OS will only be provided for the GCT1015-04 study as it is the only trial which includes follow up for OS.

Table 3: Subjects contributing efficacy data to summary of clinical efficacy

Study number	Study Title	Patients to be included in SCE	N	Study Statusa/ Study Report
GCT1015-04	A Single-Arm, Multicenter, International Trial of Tisotumab vedotin (HuMax-TF-ADC) in Previously Treated, Recurrent or Metastatic Cervical Cancer	r/mCC subjects who received 2mg/kg Q3W TV	101	Ongoing/Primary Analysis Study Report
GEN701	First-in Human, Dose-Escalating Safety Study of Tissue Factor Specific Antibody Drug Conjugate Tisotumab Vedotin (HuMax-TF-ADC) in Patients with Locally Advanced and/or Metastatic Solid Tumors Known to Express Tissue Factor	r/mCC subjects who received 2mg/kg Q3W TV; expansion cohort only (no dose escalation patients)	55	Completed/Final Study Report
GCT1015-03	A Multicenter, Open-Label Trial Investigating the Efficacy and Safety of Continued Treatment with Tisotumab Vedotin in Patients with Solid Tumors Known to Express Tissue Factor	r/mCC subjects from GEN701 who received 2 mg/kg Q3W TV and were enrolled in GCT1015-03 extension study	2[b]	Completed/Final Study Report

a Describes study status at the time of final data cutoff for the GCT1015-04 trial.
b Efficacy analyses includes two cervical cancer subjects from GEN701 who continued on Study GCT1015-03.

2.0 DISCUSSION

Preamble: An accelerated approval would be contingent on the totality of the evidence from your trial and data would be expected to show an improvement of objective response rate (ORR) over the best available therapy (the lower limit of the 95% confidence interval around the observed ORR should exclude the response rate of best available therapy), or a similar ORR with an improvement in durations of response (DOR).

Whether the ORR from study GCT1015-04 could support an accelerated approval will be a review issue based on comparison to the best available therapies for this patient population at that time of BLA review. In addition, you should follow all responders for a minimum of 6 months after their response, as duration of response along with the response rate will be an important part of any BLA review of a single-arm study.

You should request a meeting to discuss your study results and appropriateness for accelerated approval when your topline ORR results with adequate duration have been obtained. It is unlikely that your previously reported response rate of

approximately 20% coupled with approximately a 4-month DOR would be considered better than available therapy.

Question 1: Does the agency agree with the proposed efficacy data analyses and presentation within the electronic common technical document (eCTD) for the tisotumab vedotin BLA?

FDA Response to Question 1: See Preamble. This approach in general appears reasonable.

Question 2: Does the agency agree with the proposed safety data analyses and presentation within the eCTD?

FDA Response to Question 2: See Preamble. The proposed approach in general appears reasonable. In any submission, patients and the corresponding study must be clearly identifiable in all pooled safety data provided. The safety analyses should include prior therapies (number, type, duration, and dates) as parameters for each patient. In any anticipated filing, you should provide an analysis of safety data for all cervical cancer patients based on number and type of prior therapies for their underlying disease (for example, radiation or bevacizumab).

Question 3: Does the agency agree with the presentation of the systematic literature review and meta-analysis report in Module 5.3.5.4 with summaries in Modules 2.7.3 and 2.5 of the eCTD for the tisotumab vedotin BLA?

FDA Response to Question 3: See Preamble.

No, we remind you of our previous advice. While a systematic literature review can be useful to describe the treatment landscape and ORRs and DORs in the available therapy population, pooling of disparate ORRs is not appropriate.

Question 4: Does the agency agree with the proposed timing of the safety update report?

FDA Response to Question 4: See Preamble. In general, the proposed approach appears reasonable.

Question 5: Does the agency agree with the proposed CRF and subject narrative approach for the BLA?

FDA Response to Question 5: See Preamble. The proposed approach in general appears reasonable.

Question 6: Does the agency agree with the proposed datasets to be included in the tisotumab vedotin BLA?

FDA Response to Question 6: See Preamble. In general, we request that you provide a SAS program used to derive the response status from raw data (target lesion measurements, non-target status, and new lesion status at each assessment) following RECIST v1.1 based on investigator and central radiology assessments. This program should be stand-alone (i.e., no macros) so that it can be run on FDA computers. In addition, we generally require an output dataset (one record per patient per tumor assessment) including the following data:

- **Patient ID, Randomized arm, Visit number, Visit name, Visit date, Baseline target lesion SLD, Target lesion SLD at this visit, % change of SLD from baseline, Nadir SLD value, % change of SLD from nadir, Non-target lesion response status at this visit, New lesion (yes/no) at this visit, Response status at this visit, Best overall response, Confirmed response (yes/no), Evaluator (Investigator or Central radiology)**

Question 7: Does the agency agree with the proposal for providing bioresearch monitoring (BIMO) information and financial disclosure information only for GCT1015-04 in the tisotumab vedotin BLA?

FDA Response to Question 7: See Preamble. In general, your proposal is acceptable for a Phase 2 study.

Question 8: Does the agency agree with the proposed content for eCTD Modules 1, 2, 4 and 5 for the tisotumab vedotin BLA?

FDA Response to Question 8: See Preamble. As part of a BLA submission, you would be expected to provide the original protocol, protocol amendments and Statistical Analysis Plan(s) (if available) for each trial.

Question 9: In the absence of a clinical study evaluating drug-drug interactions, does the agency agree that the use of supplemental data from brentuximab vedotin (in vitro evaluation of free MMAE effects on CYPs and clinical data) will adequately predict the potential for clinically meaningful drug-drug interactions between tisotumab vedotin and CYP3A4/5 substrates or strong CYP3A4/5 inhibitors/inducers for the tisotumab vedotin BLA?

FDA Response to Question 9: See Preamble. In general, your proposal appears reasonable.

Question 10: Does the agency agree with the plan to evaluate renal and hepatic impairment by population pharmacokinetic analysis?

FDA Response to Question 10: See Preamble. In general, your proposal appears reasonable.

Question 11: Does the agency agree with the proposed clinical pharmacology plan (Population PK, exposure-response analysis, QT prolongation, and immunogenicity) for the tisotumab vedotin BLA?

FDA Response to Question 11: See Preamble. Your general clinical pharmacology evaluation strategy appears reasonable. In addition, we have the following specific recommendations for your consideration:

Population PK:

- **All PK data, including those from dose escalation patients, should be included in your population PK datasets for model development and covariate evaluation**

- **Sufficient patients with varying degree of renal and hepatic impairment should be included in the population PK dataset to evaluate the effect of renal or hepatic impairment on PK and free MMAE**

- **Submit datasets and control streams used for your important models, including the base and final model and those used for simulations**

- **Submit programming codes (R, SAS, etc.) used for modeling and simulations as well as those for producing important graphs**

Exposure-Response (E-R) Analysis:

- **Characterize the relationship of tisotumab vedotin and free MMAE exposures with efficacy endpoints;**

- **For exposure, the model-predicted individual exposures (C_{avg}, C_{max} and C_{trough}) of tisotumab vedotin and free MMAE during the first cycle and steady-state should be explored**

- **In addition to exploring the relationship between exposure and primary efficacy endpoint (ORR), you should also evaluate the exposure-response relationship for secondary efficacy endpoint (DCR, DOR, PFS OS, etc.)**

- **Characterize the relationship of tisotumab vedotin and free MMAE exposures with primary safety endpoints, including all drug-related Grade 3 or higher treatment-emergent adverse events (TEAEs), dose adjustment due to TEAEs and TEAEs of special interest (AESI)**

- **Submit dataset and programming codes (R, SAS, etc.) used for E-R analyses as well as those for producing important graphs**

- **Provide justification for the weight-based dosing regimen for tisotumab vedotin based on your results from population PK, Exposure-response analysis for efficacy and safety**

Effect of ADA on PK, Efficacy, and Safety:

- **Evaluate the effect of neutralizing antibodies on PK, efficacy and safety when data allowed**

QT Prolongation:

The data presented in the briefing material suggest that a dedicated QT assessment may not be needed because the maximum systemic exposure of the payload, MMAE, is not significantly higher than the exposures from approved ADC products containing MMAE. Unless the potential for proarrhythmic risk is suggested by mechanistic considerations or data from clinical or nonclinical studies (ICH E14 Q&A 6.3), the proposed analysis on QT prolongation potential can be submitted as supportive evidence for safety evaluation. We suggest that you submit your proposed QT assessment plan with sufficient information to IRT-QTc team to review.

3.0 ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our July 24, 2019, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[1]

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated

[1] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to FDA.gov.[2]

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult FDA's Guidance on Formal Meetings Between the FDA and Sponsors or Applicants[3] to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[4]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications

[2] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology
[3] See the guidance for industry *"Formal Meetings Between the FDA and Sponsors or Applicants."*
[4] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[5] and Pregnancy and Lactation Labeling Final Rule[6] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

[5] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[6] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[7]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[8]

SECURE EMAIL COMMUNICATIONS

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MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the

[7] http://www.fda.gov/ectd
[8] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

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ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR[10]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.

- Assessment Aid[11]

[9] https://www.fda.gov/media/85061/download
[10] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[11] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

Your proposed 351(a) BLA would be within the scope of this guidance. As such, FDA intends to assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CLARA J LEE
09/10/2019 12:45:40 PM

SANJEEVE BALASUBRAMANIAM
09/10/2019 06:51:23 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 135476

MEETING MINUTES

Seattle Genetics, Inc.
Attention: Pierre Kiami, MPH
21823 30th Drive, SE
Bothell, WA 98021

Dear Mr. Kiami:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tisotumab vedotin.

We also refer to the teleconference between representatives of your firm and the FDA on April 29, 2019. The purpose of the meeting was to discuss your proposed Phase 3 study.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact Clara Lee, Regulatory Project Manager, at (240) 402-4809 or Clara.Lee@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Clara Lee, PharmD
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

{See appended electronic signature page}

Sanjeeve Balasubramaniam, MD, MPH
Clinical Team Leader, DOP1
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End-of-Phase 2, Pre-Phase 3
Meeting Date and Time:	April 29, 2019 / 3:00 – 4:00 PM
Meeting Location:	Teleconference
Application Number:	IND 135476
Product Name:	Tisotumab vedotin
Indication:	(b) (4)
Sponsor/Applicant Name:	Seattle Genetics, Inc.
Meeting Chair:	Sanjeeve Balasubramaniam, MD
Meeting Recorder:	Clara Lee, PharmD

FDA ATTENDEES
Julia Beaver, MD, Director, DOP1
Sanjeeve Balasubramaniam, MD, Clinical Team Leader, DOP1
Shaily Arora, PharmD, Clinical Analysist, DOP1
Tara Berman, MD, Clinical Reviewer, DOP1
Tiffany Ricks, PhD, Supervisory Pharmacologist/Toxicologist Reviewer, DHOT
Shenghui Tang, PhD, Biometrics Associate Director (Acting), DBV
Erik Bloomquist, PhD, Biometrics Team Leader (Acting), DBV
Hui Zhang, PhD, Biostatistics Reviewer, DBV
Clara Lee, PharmD, Regulatory Project Manager, DOP1

SPONSOR ATTENDEES
Seattle Genetics, Inc.
Bob Lechleider, MD, Senior Vice President, Clinical Research and Development
Leonardo Nicacio, MD, Executive Medical Director, Clinical Research and Development
Melinda Teng, PhD, Director, Biostatistics
Norman Barlow, Executive Director, Nonclinical Science
David Wright, PhD, RAC Senior Director, Regulatory Affairs
Pierre Kiami, MPH, RAC Associate Director, Regulatory Affairs
Genmab US, Inc.
Richard Jansson, PhD, Vice President, Compound Development Team Leader
Reshma Rangwala, MD, PhD, Vice President, Medical
Kristian Windfeld, PhD, Senior Director, Biostatistics

Theodora Salcedo, PhD, Senior Director, Nonclinical Safety
Rima Nassar, PhD, Vice President, Head of Global Regulatory Affairs
Jessica Wang, PharmD, Director, Regulatory Affairs

1.0 BACKGROUND

The purpose of this Type B, Pre-Phase 3 meeting for the sponsor is to obtain advice from the FDA regarding nonclinical data package for the BLA and the proposed (b) (4)

Tisotumab vedotin is an antibody-drug conjugate (ADC) targeting tissue factor (TF)-expressing tumors through intracellular delivery of the microtubule-disrupting agent monomethyl auristatin E (MMAE). TF is a transmembrane receptor for factor VII/VIIa (FVII/VIIa). It is constitutively expressed by cells surrounding blood vessels. Per the sponsor, TF is also expressed by tumor cells and contributes to a variety of pathologic processes, such as thrombosis, metastasis, tumor growth, and tumor angiogenesis. Some studies have reported that endothelial cells in the tumor vasculature express TF and this may enhance angiogenesis. MMAE-mediated tumor cell killing is the dominant mechanism of action of tisotumab vedotin in vivo. The sponsor states that upon binding to human TF-expressing cells, tisotumab vedotin is internalized, where it undergoes lysosomal degradation resulting in release of the cytotoxic payload. After intracellular release, MMAE disrupts tubulin polymerization and causes cell cycle arrest. Free MMAE may also diffuse out of the target cell and penetrate surrounding 'bystander' cells to cause cell death, potentially increasing antitumor efficacy but also contributing to off-target toxicity.

The clinical program evaluating the safety and efficacy of tisotumab vedotin monotherapy in subjects with r/mCC is comprised of the following 2 ongoing trials:

- GEN701 (supportive trial) is a first-in-human (FIH), open-label, multicenter, Phase 1/2, dose-escalation and expansion trial evaluating tisotumab vedotin in subjects with previously treated locally advanced or metastatic solid tumors. In the dose-escalation phase, Tisotumab vedotin demonstrated a manageable safety profile, and 2.0 mg/kg every 3 weeks (Q3W) was established as the recommended Phase 2 dose (RP2D). The dose expansion phase included a cervical cancer cohort which enrolled 55 subjects. In January 2019, the Agency denied the Breakthrough Designation (BTD) Request for tisotumab vedotin as the preliminary clinical data from GEN701 demonstrating an ORR (24%) did not appear to represent a substantial improvement over available therapies (ORR of 8%-21%, with median durations of <2-16months), especially given the relatively short duration of response of 4.2 months.

- GCT1015-04 (main trial supporting potential BLA) is an open-label, single-arm, global, multicenter, Phase 2 trial of Tisotumab vedotin dosed at 2.0 mg/kg Q3W in approximately 100 subjects with previously treated r/mCC. As of 08-Mar-2019, a total of 88 subjects have been enrolled.

1 Page has been Withheld in Full as B4 (CCI/TS) immediately following this page

2.0 DISCUSSION

Question 1: Does the Agency agree that the proposed nonclinical toxicology studies provide adequate characterization of the toxicology profile of tisotumab vedotin to support a Biologics License Application for the proposed cervical cancer indication?

FDA Response to Question 1: Your proposed nonclinical package appears adequate to support a BLA of tisotumab vedotin for the proposed cervical cancer indication. The final determination will be made after we have reviewed your BLA.

Meeting Discussion: No discussion took place.

Question 2: Does the Agency agree (b) (4)

FDA Response to Question 2: (b) (4)

Meeting Discussion: No discussion took place.

Question 3: Does the Agency agree (b) (4)

FDA Response to Question 3: (b) (4)

Meeting Discussion: No discussion took place.

Question 4: Does the Agency agree (b) (4)

FDA Response to Question 4: (b) (4)

(b) (4)

Meeting Discussion: No discussion took place.

Question 5: Does the Agency agree (b) (4)

FDA Response to Question 5: (b) (4)

Meeting Discussion: No discussion took place.

Question 6: Does the Agency agree (b) (4)

FDA Response to Question 6: (b) (4)

(b) (4)

Meeting Discussion: No discussion took place.

Question 7: Does the Agency agree (b) (4) if accelerated approval is granted based on the Phase 2 trial (GCT1015-04)?

FDA Response to Question 7: (b) (4)

As discussed in our meeting dated August 15, 2017, accelerated approval will be contingent on the totality of the evidence from your single-arm phase 2 trial, GCT1015-04, which includes objective response rate and durability of response. The Agency has not received a statistical analysis plan for review but emphasizes again that the lower limit of the confidence interval for the expected ORR should exclude the response rates that are seen with available therapies in this treatment setting. Whether the ORR could support an accelerated approval will be a review issue based on comparison to available therapies for this patient population at that time of BLA review. Additionally, you should follow all responders for a minimum of 6 months after response. Your confirmatory study should be fully accrued, or at least well underway, at the time of an accelerated approval action.

Sponsor Response to Question 7: In Trial GCT1015-04, the main efficacy outcome measures are ORR and DOR, by an independent imaging review committee (IRC). According to the current protocol, the primary analysis is planned to be conducted after all subjects may have been

followed for at least 27 weeks from last patient first visit. The Sponsor acknowledges the FDA's comment to follow patients for a minimum of 6 months after response. Because the primary analysis of ORR and DOR is performed by a blinded IRC, the Sponsor proposes a fixed date for follow-up based upon time to and duration of response observed from the cervical cohort enrolled in GEN701, as well as simulation data (see attached slides) demonstrating the probability of responses with less than 6 months of follow-up.

In the GEN701 cervical cancer expansion cohort (n=55), radiological assessments were performed every 6 weeks; the median time to response (TTR) by IRC was 2.1 months (range, 1.1-4.6 months), with a median DOR of 6 months (range, 1.0^{+}–9.7 months). Based on simulations using these data, the Sponsor proposes that all subjects enrolled in Trial GCT1015-04 be followed for at least 32 weeks from the last patient first visit. This duration of follow-up is based on the median TTR of approximately 8 weeks followed by an additional 24 weeks.

The assumptions used and the results of the simulation are presented in Appendix 1 and the R codes used to run the simulation is contained in Appendix 2, both of which are attached.

Does the Agency agree with the proposed minimum duration of follow-up of (b) (4) weeks for subjects enrolled in Trial GCT1015-04?

Meeting Discussion: The sponsor agrees to follow all responders as assessed by the investigator for at least 6 months following that response. The primary endpoint will remain BICR ORR.

3.0 ADDITIONAL INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful

pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For the latest version of the molecular target list, please refer to https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm544641.htm.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

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- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
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LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review.

Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf.

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OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf.

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the Guidance for Industry, Collection of Race and Ethnicity Data in Clinical Trials (available at: https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126396.pdf) and for more information.

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR: https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm612927.htm. In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- AssessmentAid:https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm612923.htm.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

Not applicable.

5.0 ACTION ITEMS

Not applicable.

6.0 ATTACHMENTS AND HANDOUTS

The sponsor response document, simulation codes, and slide deck received on April 26, 2019.

Question 7: (b) (4)

Does the Agency agree (b) (4) ***in the proposed indication if accelerated approval is granted based on the Phase 2 trial (GCT1015-04)?***

FDA Response:

(b) (4)

As discussed in our meeting dated August 15, 2017, accelerated approval will be contingent on the totality of the evidence from your single-arm phase 2 trial, GCT1015-04, which includes objective response rate and durability of response. The Agency has not received a statistical analysis plan for review but emphasizes again that the lower limit of the confidence interval for the expected ORR should exclude the response rates that are seen with available therapies in this treatment setting. Whether the ORR could support an accelerated approval will be a review issue based on comparison to available therapies for this patient population at that time of BLA review. Additionally, you should follow all responders for a minimum of 6 months after response. Your confirmatory study should be fully accrued, or at least well underway, at the time of an accelerated approval action.

Sponsor Follow-up:

In Trial GCT1015-04, the main efficacy outcome measures are ORR and DOR, by an independent imaging review committee (IRC). According to the current protocol, the primary analysis is planned to be conducted after all subjects may have been followed for at least 27 weeks from last patient first visit. The Sponsor acknowledges the FDA's comment to follow patients for a minimum of 6 months after response. Because the primary analysis of ORR and DOR is performed by a blinded IRC, the Sponsor proposes a fixed date for follow-up based upon time to and duration of response observed from the cervical cohort enrolled in GEN701, as well as simulation data (see attached slides) demonstrating the probability of responses with less than 6 months of follow-up.

In the GEN701 cervical cancer expansion cohort (n=55), radiological assessments were performed every 6 weeks; the median time to response (TTR) by IRC was 2.1 months (range, 1.1-4.6 months), with a median DOR of 6 months (range, 1.0^{+}−9.7 months). Based on simulations using these data, the Sponsor proposes that all subjects enrolled in Trial GCT1015-04 be followed for at least 32 weeks from the last patient first visit. This duration of follow-up is based on the median TTR of approximately 8 weeks followed by an additional 24 weeks.

The assumptions used and the results of the simulation are presented in Appendix 1 and the R codes used to run the simulation is contained in Appendix 2, both of which are attached.

Does the Agency agree with the proposed minimum duration of follow-up of (b) (4) weeks for subjects enrolled in Trial GCT1015-04?

8 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CLARA J LEE
05/01/2019 01:55:10 PM

SANJEEVE BALASUBRAMANIAM
05/01/2019 02:25:19 PM

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	IND 135476
Request Receipt Date	11/20/2018
Product	Tisotumab vedotin (HuMax-TF-ADC)
Indication	(b) (4) .
Drug Class/Mechanism of Action	antibody-drug conjugate (ADC) comprised of a human IgG1K antibody targeting Tissue Factor (TF) that is conjugated to the microtubule-disrupting agent monomethyl auristatin E (MMAE) via a valine-citrulline linker.
Sponsor	Seattle Genetics, Inc.
ODE/Division	OHOP/DOP1
Breakthrough Therapy Request(BTDR) Goal Date (within 60 days of receipt)	January 19, 2019

Note: This document must be uploaded into CDER's electronic document archival system as a ***clinical review: REV-CLINICAL-24 (Breakthough Therapy Designation Determination) even if the review is attached to the MPC meeting minutes,*** *and will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

   Seattle Genetics is proposing that tisotumab vedotin be granted breakthrough therapy designation for the following indication: (b) (4)

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** No

3. **Was the BTDR submitted to a PIND?** No

a. **Consideration of Breakthrough Therapy Criteria:** Is the condition serious/life-threatening[1])? Yes

If 4a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequeate and sufficiently complete to permit a substantive review?

- ☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review
- ☐ Undetermined
- ☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

  i. Only animal/nonclinical data submitted as evidence ☐

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐

iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐

iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐

v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

4. **Provide below a brief description of the deficiencies for each box checked above in Section 4b:**

If 4b is checked "No", BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTD Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

5. **Clearance and Sign-Off (no MPC review)**

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

6. **A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history.**

- *Disease and intended population for the proposed indication:* Cervical cancer (carcinoma of the uterine cervix) is the fourth most common cancer in women worldwide, with 85% of cases occurring in developing countries. The National Cancer Institute estimates that more than 250,000 women are living with cervical cancer in the US, and approximately 13,240 new cases will be diagnosed in 2018. Persistent infection with human papilloma virus (HPV) is the most important factor in the development of cervical cancer and immunization to protect against the common types of HPV infection are expected to prevent specific HPV cancers in women [1,2,3] The most common histologic types of cervical cancer are squamous cell (69%) and adenocarcinoma (25%).[4] In the US, 46% of patients diagnosed with cervical cancer present with localized disease. Patients who have locally advanced disease at presentation (which includes Stage IB2-IVA) are typically managed with primary chemoradiation, and this often includes a regimen of either cisplatin alone during radiation therapy (RT) or a combination of cisplatin+ florouracil during RT. The 5-year survival rate for these patients is 91%.[5] In contrast, the prognosis of

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

patients with cervical cancer that has metastasized to, or recurred at, sites not amenable to treatment by surgery or radiation is poor, with a 5-year survival rate of only 17%.[6] Metastasis to distant sites occurs in 14% of cervical cancer patients.[7] In the setting of metastatic disease that is not amenable to surgery or radiation, chemotherapy is used. In the first-line metastatic setting, the treatment of choice in the US is platinum-based chemotherapy, usually cisplatin plus paclitaxel, with bevacizumab. Bevacizumab (in combination with chemotherapy) gained FDA approval for the treatment of recurrent, persistent, or metastatic carcinoma of the cervix in August 2014. This approval was based upon the GOG-240 trial which showed a 3.7 month improvement in median overall survival (HR 0.71) for chemotherapy + bevacizumab versus chemotherapy alone.[8] In June, 2018, based on the results of KEYNOTE-158 (Cohort E), pembrolizumab received accelerated approval for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) (ORR 14%, 95% CI 7.4, 24.1).[9]

- *Mechanism of action:* Tisotumab vedotin is an antibody-drug conjugate (ADC) targeting tissue factor (TF)-expressing tumors through intracellular delivery of the microtubule-disrupting agent monomethyl auristatin E (MMAE). TF is a transmembrane receptor for factor VII/VIIa (FVII/VIIa). It is constitutively expressed by cells surrounding blood vessels. TF is also expressed by tumor cells and contributes to a variety of pathologic processes, such as thrombosis, metastasis, tumor growth, and tumor angiogenesis.[10] Some studies have reported that endothelial cells in the tumor vasculature express TF and this may enhance angiogenesis.[11] MMAE-mediated tumor cell killing is the dominant mechanism of action of tisotumab vedotin in vivo. Upon binding to human TF-expressing cells, tisotumab vedotin is internalized, where it undergoes lysosomal degradation resulting in release of the cytotoxic payload. After intracellular release, MMAE disrupts tubulin polymerization and causes cell cycle arrest. Free MMAE may also diffuse out of the target cell and penetrate surrounding 'bystander' cells to cause cell death, potentially increasing antitumor efficacy but also contributing to off-target toxicity.

- *Regulatory history:* Tisotumab vedotin has not received marketing authorization. A pre-IND/EOP1 meeting between Genmab[3] and FDA was held on 15-Aug-2017. At the time, the sponsor submitted preliminary evidence of clinical benefit (ORR 32%) observed in the 34 patients enrolled in the cervical cancer expansion cohort in GEN701study. Based on Agency feedback, the study protocol for GEN701 was amended to enroll additional patients in the cervical cancer cohort, for a maximum of 55 patients, to better assess efficacy and safety in this population.

7. **Information related to endpoints used in the available clinical data:**

a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

The endpoint used for the BTDR request is objective response rate (ORR), which is also the primary endpoint of the ongoing phase 2 study (GCT1015-04). This endpoint demonstrates direct antitumor activity, since tumor shrinkage would not be expected in the context of ineffective therapy. ORR has been a surrogate used for accelerated approval of anticancer agents, and in the case of cemiplimab, regular approval, because of this demonstration of antitumor efficacy.

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval)

[3] Tisotumab vedotin is being co-developed by Seattle Genetics, Inc. and Genmab A/S. Genmab was the original sponsor of IND (b) (4) and IND 135476 for tisotumab vedotin for the treatment of cervical cancer (b) (4) On 29-Jun- 2018, the sponsorship of both INDs was transferred to Seattle Genetics. Genmab continues to serve as the study sponsor for cervical cancer studies being conducted under the INDs, including GEN701 and the pivotal GCT1015-04 study.

The ORR is reasonably likely to predict clinical benefit of a drug in the setting of recurrent or metastatic cervical cancer. ORR is directly attributable to drug effect, and single-arm trials conducted in patients with recurrent or metastatic tumors where no available standard of care therapy exists provide an accurate assessment of ORR. Of note, pembrolizumab recently received accelerated approval (June 2018) with an ORR of 14.3% (7.4, 24.1) for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1).

Another important supportive endpoint in these studies is the duration of the response. In the setting of metastatic disease that is not amenable to surgery or radiation, chemotherapy is used. In the first-line metastatic setting, the treatment of choice in the US, is platinum-based chemotherapy with bevacizumab.[12] For women who progress after first line treatment, sequential single agent chemotherapy is commonly used (response rates range from 8-21%; see Table 1) and the response durations for these agents tend to be short (see Table 1). A clinically significant outcome would be a higher ORR and/or a longer duration of response with a milder or non-overlapping toxicity profile compared with the available cytotoxics.

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

None.

8. **A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population.**

Patients with recurrent or metastatic cervical cancer have limited therapeutic options following the front-line standard-of-care (SoC) treatment with a platinum-based chemotherapy with bevacizumab.[12] Upon progression/recurrence after initial SoC therapy, no consensus exists for the next line of treatment. Usually, in the second and third line setting, single agent chemotherapy agents, including irinotecan, premetrexed, nab-paclitaxel are used. In June, 2018, pembrolizumab received accelerated approval for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) (ORR 14%, 95% CI 7.4, 24.1).[9] Median duration of response (DOR) had not been reached with a median 11.7 months of follow up.

Table 1: Treatment options for recurrent and/or metastatic Cervical Cancer after first-line therapy

Study	Drug	Prior lines of chemotherapy	Overall Response Rate	Median Duration of Response/Time to progression
Sutton 1989[13]	Ifosfamide (N=30)	Recurrent after RT or surgery and refractory to first-line	11% (3 PR)	Range 10-16 m (median not reported)
Irvin 1998[14]	Irinotecan (N=16)	Second line, platinum resistant	0	N/A
Verschr-aegen 1997[15]	Irinotecan (N=42)	Refractory first-line chemotherapy; up to 4 lines	21% (1 CR, 2 PR)	3 m
Coronel 2009[16]	Topotecan (N=22)	≥1 prior line; all had 1-2 prior lines	0	N/A
Fiorica 2009[17]	Topotecan (N=27)	1 prior line +/- radiosensitizer with chemoradiation	0	N/A
Lorusso 2011[18]	Topotecan (N=21)	1 prior line; included only chemoradiation	0	N/A

Study	Drug	Prior lines of chemotherapy	Overall Response Rate	Median Duration of Response/Time to progression
Garcia 2007[19]	Docetaxel (N=27; 23 evaluable)	Not more than 1 prior line	8.7% (2 PR)	TTP: 3.8 m (range 1.2-11.7m)
Lorusso 2010[20]	Pemetrexed (n=43)	1 prior platinum based chemotherapy +/- RT	13.9% (6 PR)	DOR:7weeks; PFS: 10weeks; OS: 35weeks
Miller 2008[21]	Pemetrexed (n=29)	1 prior line	15% (4 PR)	DOR:4.4m; PFS: 3.1m; OS: 7.4m
Monk 2009[22]	Bevacizumab (N=46)	1-2 prior lines; 73% one prior chemo	11% (5 PR)	DOR:6.2m; PFS: 3.4m; OS: 7.3m
FDA label[9]	*Pembrolizumab (N=77)*	*64% had 1 or 2 prior regimens*	*14.3% (2CR; 9PR)*	*NR (range 4.1 to 18.6 m+)*
Alberts 2012[23]	*Nab-paclitaxel (N=37; 35 evaluable)*	*1 prior line (excluded patients who had received prior taxanes)*	*28.6% (10 PR)*	*6m (range 1.5-9.2m)*

RT: radiotherapy; TTP: Time to progression; DOR: Duration of response; PFS: Progression free survival; OS: Overall survival; Pembrolizumab and nab-paclitaxel not considered available therapy as pembrolizumab has accelerated approval and nab-paclitaxel trial excluded patients who had previously received paclitaxel, which is part of the SoC regimen for front-line therapy.

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[4].

None.

11. Information related to the preliminary clinical evidence:

GEN701 is a first-in-human , open-label, multicenter phase 1/2 dose-escalation and expansion safety trial of tisotumab vedotin dosed every three weeks (Q3W) in multiple solid tumor types known to express the TF target. The GEN701 expansion cohort enrolled 168 patients with select relapsed, advanced, and/or metastatic tumor types, including cervical cancer. The primary objective was to establish the tolerability of tisotumab vedotin and the recommended Phase 2 dose (RP2D), which was determined to be 2.0 mg/kg, administered every 3 weeks.

The safety (n=55) and efficacy (n=51)[5] of tisotumab vedotin at the RP2D is being assessed in cervical cancer in the expansion cohort portion of the study. As of the data cut date of 30-Sep-2018, all cervical cancer patients had the opportunity for at least 18 weeks of follow up with a median follow up of 3.5 months (range, 0.6 to 11.8 months).

Efficacy data: 51 cervical cancer patients who received a standard-of-care therapy in the first line were included in the analyses of efficacy.[5] All 51 patients had received prior systemic anticancer therapy and progressed; the median number of prior therapies in the recurrent or metastatic setting was 2, with a range of 0 to 4. The median duration of treatment was 2.4 months (range, 0.03 to 10.7 months) and the median number of cycles received was 4 (range, 1 to 14). The majority of patients had received prior taxanes (50; 91%), bevacizumab (40; 73%) and/or bevacizumab as part of a GOG 240 regimen[6] (37; 67%).

[4] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.
[5] Four patients did not receive standard of care therapy in the 1L because they were refractory to treatment administered for early stage disease (concurrent chemoradiation therapy or neoadjuvant therapy).
[6] GOG 240 regimen: combination treatment with either cisplatin + paclitaxel OR paclitaxel + topotecan with bevacizumab

Among the 51 patients, 12 confirmed PRs were observed and the primary efficacy endpoint of ORR was 24% (95% CI: 13%, 38%). Of the 12 responses, 8 (22%) patients has received a prior GOG 240 regimen, and 11 (28%) patients had received either 1or 2 prior lines of therapy. Only one of the confirmed PRs was observed in a patient who had previously been treated with pembrolizumab in the 2L, was treated with topotecan approximately 6 months after disease progression on pembrolizumab, and subsequently received tisotumab vedotin in the 4L setting (response lasted for 4.1 months). The median duration of response was 4.2 months (95% CI: 1.0–9.7 months).

Reduction in target lesions of 30% or more occurred in 33% of patients (17 out of 51) on at least one scan. Two patients demonstrated CRs in all target lesions, however a new lesion was detected in one of these subjects and persistent non-target lesions were present in both patients.

A confirmed PR was also observed in 1 of the 4 patients who were refractory to early stage disease treatment (not included in the efficacy ananlysis) and received tisotumab vedotin in the first-line.[5] This response lasted for 3.0 months.

Of the 51 patients with cervical cancer, 38 (75%) experienced PFS events and 13 patients (25%) were censored. Median PFS was 4.2 months (95% CI: 2.1–4.4 months) and PFS at 6 months was approximately 26% (95% CI: 14%–41%).

Table 2: Summary of efficacy data from Cervical Cancer Cohort (GEN701)

2L+ Cervical Cancer Expansion Cohort Population	**N=51** **n (%)**
Confirmed PR n (%)	12 (24%)
Stable Disease n (%)	20 (39%)
Progressive Disease n (%)	16 (31%)
Nonevaluable n (%)	3 (6%)
Confirmed ORR (CR + PR), n (%)	**12 (24%)**
[95% CI]	[13%–38%]
Duration of Objective Response	
Median (95% CI), months	4.2 (1.0, 9.7)
Progression- Free Survival (PFS)	
Median (95% CI), months	4.2 (2.1, 4.4)
PFS at 6months (95% CI)	26 (14%, 41%)

Data cutoff date: 30 Sep 2018.

Safety data: The preliminary safety profile of tisotumab vedotin suggests a reasonable safety profile for a cytotoxic anticancer therapy. Based on drug administration data, 56.4% (n=31) of patients had at least 1 Grade 3 or 4 TEAE, and 18.2% (n=10) discontinued tisotumab vedotin due to an adverse event (AE). The summary of safety data is outlined in Table 3. The most common of TEAEs were epistaxis and fatigue in 28 patients each (51%), nausea in 27 patients (49%), and conjunctivitis in 23 patients (42%). The vast majority of these events were Grade 1 or 2. Grade 3 or higher TEAEs were experienced by 31 patients (56%). The most common Grade 3 or higher TEAEs were anemia in 6 patients (11%), fatigue in 5 patients (9%), and vomiting in 4 patients (7%).

Adverse Events of Special Interest (AESI): Bleeding events, neuropathy, and ocular events (including conjunctivitis, ulceration, keratitis, and symblepharon) have been identified as AESIs in the GEN701 study. Bleeding events were experienced by 40 patients (73%). Three patients (6%) had events of maximum Grade 3. Most bleeding events were Grade 1 epistaxis. Peripheral neuropathy events were experienced by 30 patients (55%). Grade 3 peripheral neuropathy events were recorded in 6 patients (11%). Ocular toxicities were experienced by 35 patients (64%). One event of maximum Grade 3 (conjunctivitis) was observed. More than half of patients with conjunctivitis experienced resolution of their events while on study.

Table 3: Summary of safety data from Cervical Cancer Cohort (GEN701)

	Cervical Cancer (N=55) n (%)
Patients with at least 1 Treatment-Emergent Adverse Events	55 (100.0)
Patients with any TEAEs with CTCAE Grade 3 or 4	31 (56.4)
Patients with any serious AEs	29 (52.7)
Patients with fatal TEAEs	2 (3.6)
TEAEs leading to study drug dose reduction	7 (12.7)
TEAEs leading to study drug interruption	10 (18.2)
TEAEs leading to study drug discontinuation	10 (18.2)

Data cutoff date: 30 Sep 2018.

12. Division's recommendation and rationale (pre-MPC review):

☐ GRANT :

Provide brief summary of rationale:

Preliminary clinical data submitted by the applicant in support of the request for breakthrough therapy designation suggest that tisotumab vedotin may have anti-tumor activity in the second-line treatment of women with recurrent/metastatic cervical cancer. Based on a review of the literature, currently available therapies provide an ORR of 8%-21%, with median durations of <2-16months. The data provided by the sponsor demonstrate a reported ORR (24%); this ORR does not appear to represent a substantial improvement over available therapies, especially given the relatively short duration of response of 4.2 months. As a result, the Division of Oncology Products 1 is recommending that FDA deny this breakthrough therapy designation request.

13. Division's next steps and sponsor's plan for future development:

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

14. List references, if any:

1. Villa LL, et al. Prophylactic quadrivalent human papilloma virus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomized double-blind placebo-controlled multicenter phase II efficacy trial. Lancet Oncol 2005; 6: 271-278.
2. Ault KA. Effect of prophylactic human papilloma virus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: a combined analysis of four randomized clinical trials. Lancet 2007; 369: 1861-1868.
3. Quadrivalent vaccine against human papilloma virus to prevent high-grade cervical lesions. N Engl J Med 2007; 356: 1915-1927.
4. Ries LAG, et al. SEER Cancer Statistics Review, 1975-2004. National Cancer Institute; Bethesda, MD 2007.
5. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KAe (2017). SEER Cancer Statistics Review, 1975-2014, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER web site, April 2017.
6. National Cancer Institute (2018). SEER Cancer Stat Facts: cervical cancer. https://seer.cancer.gov/statfacts/html/cervix.html
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9. Keytruda (pembrolizumab) [US Package Insert]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp.; December 2018.
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11. Contrino J, Hair G, Kreutzer DL, et al: In situ detection of tissue factor in vascular endothelial cells: Correlation with the malignant phenotype of human breast disease. Nat Med 2:209-215, 1996.
12. Tewari KS, Sill MW, Long HJ, 3rd, Penson RT, Huang H, Ramondetta LM, Landrum LM, Oaknin A, Reid TJ, Leitao MM, Michael HE, Monk BJ (2014). Improved survival with bevacizumab in advanced cervical cancer. N Engl J Med 370(8): 734-43.
13. Sutton, et al. Phase II study of ifosfamide and mesna in patients with previously-treated carcinoma of the cervix. A gynecologic oncology group study. Invest New Drugs. 1989 Nov; 7 (4): 341-3.
14. Irvin, et al. A phase II study of irinotecan (CPT-11) in patients with advanced squamous cell carcinoma of the cervix. Cancer. 1998 Jan 15; 82(2): 328-33.
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15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

16. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☐
Deny Breakthrough Therapy Designation ☒

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Revised 6/12/18/M. Raggio

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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01/11/2019 12:11:57 PM

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