CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761310Orig1s000

OTHER REVIEW(S)

SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: VENTANA FOLR1 (FOLR-2.1) RxDx Assay

Device Trade Name: VENTANA FOLR1 (FOLR-2.1) RxDx Assay

Device Procode: QUL

Applicant's Name and Address: Ventana Medical Systems Inc.
1910 E. Innovation Park Drive,
Tucson, AZ 85755

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P220006

Date of FDA Notice of Approval: November 14, 2022

II. INDICATIONS FOR USE

VENTANA FOLR1 (FOLR1-2.1) RxDx Assay is a qualitative immunohistochemical assay using mouse monoclonal anti-FOLR1, clone FOLR1-2.1, intended for use in the assessment of folate receptor alpha (FOLR1) protein in formalin-fixed, paraffin-embedded epithelial ovarian, fallopian tube or primary peritoneal cancer tissue specimens by light microscopy. This assay is for use with OptiView DAB IHC Detection Kit for staining on a BenchMark ULTRA instrument.
FOLR1 expression clinical cut-off is ≥ 75% viable tumor cells (TC) with membrane staining at moderate and/or strong intensity levels.
This assay is indicated as an aid in identifying patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer who may be eligible for treatment with ELAHERE (mirvetuximab soravtansine).
Test results of the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay should be interpreted by a qualified pathologist in conjunction with histological examination, relevant clinical information, and proper controls.
This product is intended for *in vitro diagnostic* (IVD) use.

III. CONTRAINDICATIONS

There are no known contraindications.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay labeling.

V. DEVICE DESCRIPTION

A. Device Kit Components

VENTANA FOLR1 (FOLR1-2.1) RxDx Assay contains optimized reagents required to complete an immunohistochemical staining procedure for formalin-fixed paraffin embedded (FFPE) specimens on the BenchMark ULTRA automated staining instrument visualized using the OptiView DAB IHC Detection Kit. VENTANA FOLR1 (FOLR1-2.1) RxDx Assay utilizes a mouse monoclonal hybridoma antibody produced against a recombinant protein as a cell culture supernatant, purified using protein G. The antibody and detection reagents are provided as ready-to-use dispensers and each dispenser contains sufficient reagent for 50 tests. A Stain Intensity Reference (SIR) slide is required for assay interpretation. The VENTANA FOLR1 (FOLR1-2.1) RxDx Assay Components and description is provided in the table below.

Table 1: VENTANA FOLR1 (FOLR1-2.1) RxDx Assay Components

Components	Packaged Form	Description
VENTANA FOLR1 (FOLR1-2.1) Mouse Monoclonal Primary Antibody	1 Flo-Lok Dispenser: 50 tests	One 5 mL dispenser FOLR1 reagent contains approximately 28µg of a mouse monoclonal FOLR1-2.1 antibody (approximately 5.6 µg/mL). The antibody is diluted in 0.05 M Tris- HCL with carrier protein and 0.10% ProClin 300, a preservative.
OptiView DAB IHC Detection Kit	Set of 6 Flo-Lok dispensers, packaged in a kit: 250 tests	OptiView Peroxidase Inhibitor contains 3.0% hydrogen peroxide solution.
		OptiView HQ Universal Linker contains a cocktail of HQ-labeled (HQ is a proprietary hapten covalently attached to the goat antibodies) antibodies (goat anti-mouse IgG, goat anti-mouse IgM, and goat anti-rabbit) (<50 µg/mL) in a buffer containing protein with ProClin 300, a preservative.
		OptiView HRP Multimer contains a mouse monoclonal anti-HQ- labeled HRP tertiary antibody (<40 µg/mL) in a buffer containing protein with ProClin 300, a preservative.
		OptiView H_2O_2 contains 0.04% hydrogen peroxide in a phosphate buffer solution.
		OptiView DAB contains 0.2% 3, 3′- diaminobenzidine tetrahydrochloride (DAB) in a proprietary stabilizer solution with a proprietary preservative.
		OptiView Copper contains copper sulfate (5.0 g/L) in an acetate buffer with a proprietary preservative.

BenchMark ULTRA automated staining instrument and Ventana System Software (VSS) software	Instrument installed with the VSS host system software, Version 12.3 and 12.3.1	A personal computer (PC) that runs on Microsoft Windows and controls the BenchMark ULTRA instrument via the host operating software.
Negative Control (Monoclonal)	1 Flo-Lok dispenser: 250 tests	A mouse monoclonal antibody intended for laboratory use as a control for nonspecific binding of the primary antibody in sections of FFPE tissue. One 25 mL dispenser contains approximately 25 µg (1 µg/mL) of mouse monoclonal antibody. The antibody is diluted in phosphate buffered saline containing carrier protein and ProClin 300, a preservative.
VENTANA Stain Intensity Reference (SIR) Slide	2 SIR slides packed in a slide mailer	Intended to be used as an aid when assessing the stain intensity of DAB in FOLR1 tumor cell staining in epithelial ovarian, fallopian tube or primary peritoneal cancer tissue. A section of normal fallopian tube tissue embedded on a glass slide and stained with FOLR1 Assay

Table 2: Ancillary Reagents Required for VENTANA FOLR1 (FOLR1-2.1) RxDx Assay

Reagents
EZ Prep (10x)
Reaction Buffer (10x)
ULTRA Liquid CoverSlip (LCS), pre-dilute
ULTRA Cell Conditioning Solution (CC1)
Hematoxylin II counterstain
Bluing Reagent

B. Device Instrumentation and Software

The VENTANA FOLR1 (FOLR1-2.1) RxDx Assay is performed on the BenchMark ULTRA automated staining instrument using VSS versions 12.3 or 12.3.1. The VENTANA FOLR1 (FOLR1-2.1) RxDx Assay staining protocol is assay specific. To ensure that all system reagents are used together, the software has been designed to recognize and group reagents required for staining per the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay staining protocol.

C. Specimen Preparation

Routinely processed FFPE tissues are suitable for use with the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay. Tissue is fixed in 10% neutral buffered formalin (NBF) for 12 to 72 hours. Use of alcohol-formalin-acetic acid (AFA), 95% alcohol, PREFER fixatives and Zinc Formalin or Z-5 are not recommended due to loss of specific FOLR1 protein expression.

Tissue sections should be cut at approximately 4 µm thickness and mounted on positively-charged glass slides. Slides should be stained immediately, as antigenicity of

cut tissue sections may diminish over time. See device labeling (package insert) for additional details.

D. Quality Control Procedures

Run controls are included in each staining run to establish the validity of the test results. The following controls must be run with the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay.

1. **Positive/Negative Tissue Control:** Normal Fallopian tube is used as a positive control tissue for this antibody. Positive and negative staining elements for the FOLR1 protein present in fallopian tube tissue are used to confirm that the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay functioned properly. Positive tissue controls should be utilized only for monitoring performance of reagents and instruments, not as an aid in determining specific diagnosis of test samples. The interpretation of the FOLR1 staining in normal fallopian tube when used as a positive/negative tissue control is given in the table below.

Table 3: Positive Control Tissue Evaluation, Normal Fallopian Tube

Status	Staining Pattern
Acceptable	Predominately moderate circumferential* FOLR1 membrane staining in the epithelium of normal Fallopian tube and absence of specific staining in normal Fallopian tube stroma.
Not Acceptable	Absence of staining, or predominantly weak or strong circumferential* FOLR1 membrane staining in the epithelium of normal Fallopian tube and/or Non-Specific FOLR1 background staining that interferes with interpretation.

* Note: Apical staining of the first layer of the luminal cells must not be considered in evaluating the acceptability o fallopian tube FOLR1 staining.

2. **Negative Reagent Control:** A matched negative reagent control slide should be run for every specimen to aid in the interpretation of results. Negative Reagent (Monoclonal), a negative reagent control antibody, is specifically matched for this VENTANA FOLR1 (FOLR1-2.1) RxDx Assay and is used in place of the primary antibody to evaluate nonspecific staining in the patient tissue that may result from a reaction with the detection chemistry and not the anti-FOLR1 primary antibody.

E. Principles of Operation

The VENTANA FOLR1 (FOLR1-2.1) RxDx Assay is fully automated for use on the BenchMark ULTRA automated slide stainer from deparaffinization through counterstaining. Patient FFPE tissue specimens are cut to approximately 4 µm thickness and mounted on positively charged glass slides. These slides are loaded into the Benchmark ULTRA instrument. This system first removes the paraffin wax from the tissue (deparaffinization), and then subjects the tissue to heated antigen retrieval (cell conditioning). Endogenous peroxidases that could potentially react with the horseradish peroxidase conjugates (HRP) are blocked with OptiView Inhibitor (3% H_2O_2). After the endogenous peroxidase block, the VENTANA FOLR1 (FOLR1-2.1) Mouse Monoclonal Primary Antibody is dispensed during the antibody incubation

step and allowed to bind to its antigen. The slides are then incubated with the reagents in the OptiView DAB IHC Detection Kit, which is an indirect, biotin-free system for detecting mouse IgG, mouse IgM, and rabbit primary antibodies and which produces a visible dark brown precipitate (3,3'-Diaminobenzidine) via a horseradish peroxidase (HRP) enzymatic reaction at the antigen site. Slides are then counterstained using Hematoxylin II and Bluing Reagent to create brown/blue contrast to aid the pathologist when reviewing the slides using bright field microscopy. The VENTANA FOLR1 (FOLR1-2.1) RxDx Assay staining protocol is shown in the table below.

Table 4: VENTANA FOLR1 (FOLR1-2.1) RxDx Assay Staining Protocol on BenchMark ULTRA Instrument

Procedure Type	Protocol Parameter
Baking	Optional, maybe performed off-line
Deparaffinization	4 minutes (default), 72°C
Cell Conditioning (Antigen Unmasking) Pre-Primary Peroxidase Inhibitor	ULTRA CC1, 64 minutes, 100°C 4 minutes, 36°C
Antibody (Primary)	Ventana FOLR1-2.1 RxDx Assay Ab (32 minutes, 36°C) Or Negative Control Ab (32 minutes, 36°C)
OptiView HQ Linker	8 minutes, 36°C
OptiView HRP Multimer	8 minutes, 36°C
Counterstain	Hematoxylin II, 4 minutes, 36°C
Post Counterstain	Bluing, 4 minutes, 36°C

F. Slide Review and Interpretation of FOLR1 Staining

The cellular staining pattern for VENTANA FOLR1 (FOLR1-2.1) RxDx Assay is membranous and cytoplasmic in epithelial ovarian, fallopian tube or primary peritoneal cancer tissue, with varying ranges of stain intensity; only membranous staining is evaluated for the determination of FOLR1 status. Membrane staining pattern may be apical or circumferential (partial or complete).

i. **Hematoxylin & Eosin (H&E) Slide:**
The pathologist will determine whether the H&E slide contains sufficient tumor tissue (it is recommended that approximately 100 viable tumor cells are present) consistent with epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer to allow interpretation of the case-matched IHC slides. If the H&E is not acceptable, the case-matched NRC and FOLR1 slides will not be evaluated.

ii. **System-level Control Slide(s)-Positive and Negative Tissue Control Slide(s):**
Normal fallopian tube tissue contains both positive-staining and negative-staining elements with VENTANA FOLR1 (FOLR1-2.1) RxDx Assay. Normal fallopian tube tissue stained with VENTANA FOLR1 (FOLR1-2.1) RxDx Assay contains both specific FOLR1 staining in the luminal surface of the epithelial cells and absence of FOLR1 staining in the stroma, both of which

should be evaluated to confirm that the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay is performing correctly.

iii. **Negative Reagent Control (NRC) Slide:**
The NRC slide is evaluated based on the level of non-specific staining (background). If the NRC slide is not acceptable, slide will not be evaluated, and the assay should be repeated.

iv. **SIR Slide:**
FOLR1 staining percentage at each intensity is determined by a trained pathologist using the FOLR1 SIR slide as the baseline for moderate stain intensity. Each FOLR1 SIR slide contains at least one region of 10 or more contiguous cells expressing moderate (2+) circumferential membrane staining. Prior to utilizing the FOLR1 SIR slide as a stain intensity reference tool for interpreting epithelial ovarian, fallopian tube or primary peritoneal cancer cases stained with the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay, pathologists should first review the FOLR1 SIR slide for a moderate staining region. After locating the moderate staining region in the FOLR1 SIR slide, the pathologist should use this region to aid in the identification of moderate and stronger staining in epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer slides. These tissues must be evaluated according to the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay scoring algorithm, provided in Table 5. Refer to the Interpretation Guide for additional instructions.

v. **Patient Tissue Slide:**
FOLR1 status will only be assigned if the H&E slide, the system-level control slide, the NRC slide, and the FOLR1 slide (including background, morphology, and overall staining) are all acceptable. Patient specimens should have approximately 100 viable tumor cells identified on the H&E in order to determine FOLR1 status. The percentage of tumor cells staining at each intensity (negative, weak, moderate, strong) will be assessed but only moderate and strong stain intensities will contribute to the FOLR1 status determination using the scoring method. Epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer tissue cases are considered positive for FOLR1 status if ≥ 75% of viable tumor cells (TC) demonstrate moderate and/or strong membrane staining.

Due to the histological characteristics of epithelial ovarian carcinoma, primary peritoneal adenocarcinoma and primary fallopian tube carcinoma they are grouped together as epithelial ovarian cancer (EOC) in this document. The scoring algorithm for the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay is provided in the table below.

Table 5: VENTANA FOLR1 (FOLR1-2.1) RxDx Assay Scoring Algorithm for EOC

FOLR1 Status	Staining Description
Positive*	≥ 75% of viable tumor cells with moderate (2+) and/or strong (3+) membrane staining
Negative*	< 75% of viable tumor cells with moderate (2+) and/or strong (3+) membrane staining
Not Evaluable	Artifacts making interpretation not possible.

* Re-reading by Additional Pathologists for FOLR1 Scoring

Re-reading by Additional Pathologists for FOLR1 Scoring: To decrease variability of FOLR1 results for cases with %TC near the threshold of 75% [65% to 85%], re-reading of the slide by a second pathologist is recommended. The case result with %TC between 65-85% by a pathologist should be adjudicated by one or two independent pathologists. In these cases, the patient's result with regard to FOLR1 status (positive/negative) should be obtained by either a majority rule or by consensus among the pathologists.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There is currently no alternative FDA-cleared or approved assay available for detection of FOLR1 in FFPE epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer tissues to estimate the likelihood of response for patients treated with ELAHERE (mirvetuximab soravtansine).

VII. MARKETING HISTORY

The VENTANA FOLR1 (FOLR1-2.1) RxDx Assay has not been marketed in the United States or any foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

VENTANA FOLR1 (FOLR1-2.1) RxDx Assay is intended for in vitro diagnostic (IVD) use only. As with any IVD test, the potential risks are associated with an incorrect test result or incorrect interpretation of results. Failure of the device to perform as expected or failure to correctly interpret test results may lead to improper patient management decisions.

IX. SUMMARY OF NON-CLINICAL STUDIES

A. Laboratory Studies

Non-clinical studies were performed using the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay to establish analytical performance of the device in epithelial ovarian cancer, fallopian tube cancer and primary peritoneal cancer. These studies were performed using the BenchMark ULTRA instrument using the VSS software version 12.3 and 12.3.1. These studies were conducted to characterize the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay, demonstrate the impact of pre-analytical variables on assay performance, evaluate assay precision and robustness and establish assay stability. The study results detailed below establish assay sensitivity, specificity, precision, robustness, stability, external reproducibility, and other performance characteristics of the device.

1. Analytical Sensitivity

Analytical sensitivity of the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay was assessed based on the prevalence of FOLR1 staining on a sample set which included 953 unique EOC cancer resection tissue cases. The slides were read by one pathologist and scored using the scoring method specified in Table 5 above.

FOLR1 positive status was observed in 28.75% (274/953) of cases in the commercial cohort of EOC resection tissues for prevalence reporting. FOLR1 negative status was observed in 71.25% (679/953) of cases and FOLR1 borderline status was observed in 224 of 953 cases. Borderline status is defined as 75% ± 10% tumor cell (TC) staining. Positive borderline accounted for 15.95% (152/953) of cases and 7.56% (72/953) cases as negative borderline. Results are also provided in the table below.

Table 6: Prevalence of FOLR1 in EOC stained with VENTANA FOLR1 (FOLR1-2.1) Assay

FOLR1 Status	Prevalence at 75% Cutoff (% n/N)	Borderline Prevalence (% n/N)
Positive	28.75% (274/953)	15.95% (152/953)
Negative	71.25% (679/953)	7.56% (72/953)

Note: In different populations, prevalence of FOLR1 IHC scores may be different from the prevalence presented in the above table.

2. Analytical Specificity

The antibody used in the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay is Mouse Anti-Human FOLR1 Monoclonal Antibody (Clone FOLR1-2.1). The FOLR1 antibody detects the glycosylated form of the FOLR1 protein, which has a molecular weight of 40 kDa. The following studies were conducted with FOLR1 (FOLR1-2.1) antibody to establish antibody specificity.

a. Western Blot Studies

Western blot (WB) analysis was performed on whole cell lysates from 4 cell lines with varying expression levels of FOLR1. The 4 cell lines were KB (Epithelial Carcinoma), Igrov-1 (Ovarian Adenocarcinoma), Ishikawa (Endometrial Adenocarcinoma) and Calu-3 (Lung Adenocarcinoma). VENTANA FOLR1 (FOLR1-2.1) reacted with a ~40kD band in cell lysates prepared from the KB cells (Epithelial Carcinoma) which expresses high levels of FOLR1 protein by IHC staining (3+); (Ovarian Adenocarcinoma), Igrov-1 cells (2+); and (Endometrial Adenocarcinoma) Ishikawa cells (1+). No band of this size was observed in the IHC negative Calu-3 (Lung Adenocarcinoma) cell line (0+). Independent confirmation of the relative expression levels was based on assessment of mRNA expression levels for FOLR1. No unexpected staining or background was observed in any of the whole cell lysates. An additional WB analysis was performed to ensure that VENTANA FOLR1 (FOLR1-2.1) antibody is specific for FOLR1 and does not cross-react with the other FOLR proteins. VENTANA FOLR1 (FOLR1 2.1) antibody showed no reactivity for human FOLR2 or FOLR3 proteins in the WB assay.

b. Blast Results for FOLR1 Epitope

An NCBI Blast search comparison of FOLR1 with FOLR2 and FOLR3 protein sequences showed that these proteins share 77-85% sequence identity. However, sequence analysis surrounding the Asn 69 N-linked glycosylation site in FOLR1 show this potential glycosylation site does not exist in FOLR2 or FOLR3, as the motif Asn-X-Ser/Thr is

absent in this region of FOLR2 and FOLR3. Both of these proteins do contain additional potential N-linked glycosylation sites downstream.

c. Immunoreactivity in Human Tissues [Tour of Body (TOB) and Tour of Tumor (TOT)]

The purpose of this study was to assess the analytical specificity (Tour of Body and Tour of Tumor) including non-specific staining, background and cross-reactivity of VENTANA FOLR1 (FOLR1-2.1) RxDx Assay on non-neoplastic (TOB) and neoplastic tissue (TOT) samples. One lot each of VENTANA FOLR1 (FOLR1-2.1) RxDx Assay and Negative Control reagent were used to stain slides containing multi-tissue arrays (TMA) of non-neoplastic and neoplastic tissue. Slides were evaluated by a FOLR1 trained pathologist for FOLR1 reactivity, acceptable background staining and stain intensity, and potential cross reactivity of the assay.

TOB: In this study, 128 non-neoplastic tissues along with 99 cores of non-neoplastic TMA and 2 Non-neoplastic Bladder Single-Tissue Cases were analyzed.

Result: FOLR1 reactivity was observed in 6 out of 128 non-neoplastic tissues, occurring in adrenal gland, kidney, and larynx tissues. FOLR1 reactivity was observed in 57 out of 148 neoplastic tissues, 0 of 2 individual bladder tissues, 4 of 99 TOB cores occurring in kidney and ovary tissues. FOLR1 reactivity was not observed in non-neoplastic bladder or parathyroid tissue cases. Results for non-neoplastic tissues are shown in the table below.

Table 7: VENTANA FOLR1 (FOLR1-2.1) RxDx Assay Staining of FFPE Non-neoplastic Tissues

Tissue	Number of positive/total cases	Tissue	Number of positive/total cases
Cerebrum	0/4	Stomach	0/4
Cerebellum	0/4	Small Intestine	0/4
Adrenal gland	1/4	Colon	0/4
Ovary	0/9	Liver	0/4
Pancreas	0/4	Salivary gland	0/4
Parathyroid gland	0/3	Kidney	4/4
Hypophysis	0/3	Prostate	0/4
Testis	0/4	Endometrium	0/4
Thyroid	0/4	Cervical	0/4
Breast	0/4	Skeletal Muscle	0/3
Spleen	0/3	Skin	0/4
Tonsil	0/3	Peripheral (Nerve)	0/3
Thymus gland	0/3	Mesothelium	0/3
Myeloid (Bone)	0/3	Retina	0/3
Lung	0/4	Larynx	1/3
Heart	0/3	Bladder	0/3
Esophagus	0/4	Rectal	0/1

TOT: In this study, 148 neoplastic tissues along with 95 cores of neoplastic TMA were analyzed.

Result: FOLR1 reactivity was observed in 57 out of 148 neoplastic cores/cases and 4 of 95 cores from the TOT arrays. Results for neoplastic tissues are shown in **Table 8.**

Table 8: VENTANA FOLR1 (FOLR1-2.1) RxDx Assay Staining of FFPE Neoplastic Tissues

Pathology	Number of positive/ total cases
Meningioma, fibroblastic (Cerebrum)	0/1
Astrocytoma (Cerebrum)	0/1
Meningioma, fibroblastic (Cerebellum)	0/1
Malignant meningioma (Cerebellum)	0/1
Adenoma, cortical (Adrenal Gland)	0/1
Adrenocortical carcinoma (Adrenal Gland)	0/1
Adenocarcinoma (Pancreas)	0/1
Seminoma (Testis)	0/2
Adenoma (Thyroid)	0/2
Follicular carcinoma (Thyroid)	0/1
Follicular papillary adenocarcinoma (Thyroid)	0/1
Fibroadenoma (Breast)	0/2
Invasive ductal carcinoma (Breast)	0/3
Osteosarcoma (Bone)	0/1
Chondrosarcoma (Bone)	0/1
Squamous cell carcinoma (Lung)	0/2
Adenocarcinoma (Lung)	0/1
Small cell carcinoma (Lung)	0/1
Metastatic cancer from gastrointestinal site (Lung)	0/1
Squamous cell carcinoma (Esophagus)	0/3
Adenocarcinoma (Stomach)	0/3
Adenoma (Small Intestine)	0/1
Adenocarcinoma (Small Intestine)	0/1
Adenoma (Colon)	0/1
Adenocarcinoma (Colon)	0/3
Hepatocellular carcinoma (Liver)	0/4
Metastatic colon adenocarcinoma (Liver)	0/1
Pleomorphic adenoma (Salivary Gland)	0/1
Adenoid cystic carcinoma (Salivary Gland)	0/1
Adenocarcinoma (Oral Cavity)	0/1
Squamous cell carcinoma (Oral Cavity)	0/1
Nasopharyngeal carcinoma, NPC (Nasopharynx)	0/1
Melanoma (Nasal cavity)	0/1
Clear cell carcinoma (Kidney)	1/2
Adenocarcinoma (Prostate)	0/2
Adenocarcinoma (Endometrium)	0/2
Squamous cell carcinoma (Cervix)	0/2
Squamous cell carcinoma (Skin)	0/1
Transitional cell carcinoma (Bladder)	0/2
Adenocarcinoma (Rectum)	0/3
Reactive (Lymph node)	0/1

Hodgkin lymphoma (Lymph node)	0/1
Non-Hodgkin B-cell lymphoma (Lymph node)	0/1
Anaplastic large cell lymphoma (Lymph node)	0/2
Metastatic breast ductal carcinoma (Lymph node)	0/1
Metastatic esophagus squamous cell carcinoma (Lymph node)	0/1
Granulosa cell tumor (Ovary)	0/1
Adenocarcinoma (Ovary)	0/1
Endometrioid adenocarcinoma (Ovary)	9/16
Metastatic colon signet ring cell carcinoma (Ovary)	0/1
Serous adenocarcinoma (Ovary)	39/42
Clear cell carcinoma (Ovary)	5/8
Mucinous adenocarcinoma (Ovary)	3/10

3. Precision:

Precision of the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay on BenchMark ULTRA was evaluated in three studies: Intermediate Precision study, Reader (pathologist) Precision study and Inter-Laboratory and Inter-Reader Precision (Reproducibility) study.

a. Intermediate Precision

Twenty-four unique EOC tissue specimens were enrolled (12 FOLR1 positive and 12 FOLR1 negative) in the intermediate precision study. The study design for evaluation of precision of the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay included:

- Three lots of FOLR1 antibody
- Three BenchMark ULTRA instruments
- Three OptiView DAB IHC Detection Kits
- Study performed over three non-consecutive days
- One pathologist reader
- 2 replicates per condition

All slides were blinded and randomized and then evaluated using the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay scoring algorithm specified in table 5 above. Each case had 18 results and a majority FOLR1 result was assigned based on 18 results. For each case, the median %TC and the range of %TC of 18 results were calculated. In addition, percent positive (%TC≥75%, "Eligible" with regard to FOLR1 therapy) results was calculated. Results are summarized in the tables below.

Table 9. Median and Range of %TC for Samples in the Intermediate Precision Study

Sample ID	Majority FOLR1 Result	Median %TC	Range %TC (Min to Max)	Percent Positive Results	Percent Agreement with Majority FOLR1 Result
1	Negative	10.0	10 to 10	0 (0/18)	100 (18/18)
2	Negative	20.0	20 to 25	0 (0/18)	100 (18/18)
3	Negative	25.0	25 to 25	0 (0/18)	100 (18/18)
4	Negative	25.0	25 to 25	0 (0/18)	100 (18/18)
5	Negative	30.0	25 to 30	0 (0/18)	100 (18/18)
6	Negative	35.0	35 to 35	0 (0/18)	100 (18/18)

7	Negative	45.0	45 to 50	0 (0/18)	100 (18/18)
8	Negative	45.0	45 to 45	0 (0/18)	100 (18/18)
9	Negative	50.0	45 to 50	0 (0/18)	100 (18/18)
10	Negative	55.0	55 to 55	0 (0/18)	100 (18/18)
11	Negative	65.0	60 to 75	5.6 (1/18)	94.4 (17/18)
12	Negative	70.0	60 to 70	0 (0/18)	100 (18/18)
13	Positive	75.0	70 to 75	94.4 (17/18)	94.4 (17/18)
14	Positive	80.0	80 to 85	100 (18/18)	100 (18/18)
15	Positive	90.0	90 to 90	100 (18/18)	100 (18/18)
16	Positive	90.0	90 to 90	100 (18/18)	100 (18/18)
17	Positive	90.0	90 to 90	100 (18/18)	100 (18/18)
18	Positive	90.0	90 to 90	100 (18/18)	100 (18/18)
19	Positive	90.0	90 to 90	100 (18/18)	100 (18/18)
20	Positive	90.0	90 to 90	100 (18/18)	100 (18/18)
21	Positive	90.0	90 to 90	100 (18/18)	100 (18/18)
22	Positive	90.0	90 to 90	100 (18/18)	100 (18/18)
23	Positive	95.0	95 to 95	100 (18/18)	100 (18/18)
24	Positive	98.0	98 to 98	100 (18/18)	100 (18/18)

Table 10: Precision Components for Samples in Intermediate Precision Study

					Standard Deviation					
Sample ID	**Majority Call FOLR1 Result**	**Number of Results**	**Median %TC**	**Range %TC (Min to Max)**	**Repeatability (Within Run)**	**Between Day**	**Between Antibody Lot**	**Between Detection Kit**	**Between Instrument**	**Total**
1	Negative	18	10.0	10 to 10	0	0	0	0	0	0
2	Negative	18	20.0	20 to 25	1.16	0	0	0	0	1.16
3	Negative	18	25.0	25 to 25	0	0	0	0	0	0
4	Negative	18	25.0	25 to 25	0	0	0	0	0	0
5	Negative	18	30.0	25 to 30	0	0	0	0	1.01	1.01
6	Negative	18	35.0	35 to 35	0	0	0	0	0	0
7	Negative	18	45.0	45 to 50	0	1.00	1.00	0	0	1.42
8	Negative	18	45.0	45 to 45	0	0	0	0	0	0
9	Negative	18	50.0	45 to 50	1.16	0	0	0	0	1.16
10	Negative	18	55.0	55 to 55	0	0	0	0	0	0
11	Negative	18	65.0	60 to 75	0	2.21	0	0.81	0	2.36
12	Negative	18	70.0	60 to 70	0	0	0	0	2.01	2.01
13	Positive	18	75.0	70 to 75	0	1.29	0	0	0	1.29
14	Positive	18	80.0	80 to 85	0	0	0	0.85	0	0.85
15	Positive	18	90.0	90 to 90	0	0	0	0	0	0
16	Positive	18	90.0	90 to 90	0	0	0	0	0	0
17	Positive	18	90.0	90 to 90	0	0	0	0	0	0
18	Positive	18	90.0	90 to 90	0	0	0	0	0	0
19	Positive	18	90.0	90 to 90	0	0	0	0	0	0
20	Positive	18	90.0	90 to 90	0	0	0	0	0	0

					Standard Deviation					
Sample ID	Majority Call FOLR1 Result	Number of Results	Median %TC	Range %TC (Min to Max)	Repeatability (Within Run)	Between Day	Between Antibody Lot	Between Detection Kit	Between Instrument	Total
21	Positive	18	90.0	90 to 90	0	0	0	0	0	0
22	Positive	18	90.0	90 to 90	0	0	0	0	0	0
23	Positive	18	95.0	95 to 95	0	0	0	0	0	0
24	Positive	18	98.0	98 to 98	0	0	0	0	0	0

In addition, a qualitative analysis of different components was performed. Results are summarized in the table below.

Table 11: Intermediate Precision of VENTANA FOLR1 (FOLR1-2.1) RxDx Assay

Repeatability/ Precision	Agreement			
	Type	n/N	%	95% CI
Between- Antibody Lots	PPA	72/72	100.0	(94.9, 100.0)
	NPA	72/72	100.0	(94.9, 100.0)
	OPA	144/144	100.0	(97.4, 100.0)
Between-Instruments (BenchMark ULTRA)	PPA	72/72	100.0	(94.9, 100.0)
	NPA	71/72	98.6	(97.2, 100.0)
	OPA	143/144	99.3	(98.6, 100.0)
Between-Detection Kits	PPA	71/72	98.6	(97.2, 100.0)
	NPA	72/72	100.0	(94.9, 100.0)
	OPA	143/144	99.3	(98.6, 100.0)
Between-Day	PPA	71/72	98.6	(97.2, 100.0)
	NPA	71/72	98.6	(97.2, 100.0)
	OPA	142/144	98.6	(97.2, 100.0)
Within-Run	PPA	107/108	99.1	(98.1, 100.0)
	NPA	107/108	99.1	(98.1, 100.0)
	OPA	214/216	99.1	(98.1, 100.0)

Positive Percent Agreement (PPA), Negative Percent Agreement (NPA), Overall Percent Agreement (OPA)

b. Reader Precision Study

In the Reader Precision study for VENTANA FOLR1 (FOLR1-2.1) RxDx Assay, Within-Reader and Between-Reader components of precision for EOC tissue reads were evaluated. The study included 100 unique EOC specimens (50 FOLR1 positive and 50 FOLR1 negative) that were stained with VENTANA FOLR1 (FOLR1-2.1) RxDx Assay. Specimens were blinded and randomized prior to evaluation for FOLR1 status using the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay scoring algorithm specified in table 5 above. The study included three readers (pathologists). Readers scored all sample twice, with a minimum of two-week wash-out period between reads. Each sample had 6 reads (2 reads by each of three readers). Variability of %TC values for 100 cases was evaluated and following precision components were calculated: within-reader, between-reader and total. Results are summarized in the tables 12 and 13 below:

Table 12: Precision Components for Samples in Reader Precision Study

				Standard Deviation			
Sample Category	**#Samples**	**# Read**	**Range of Median %TC**	**Within Reader**	**Between Reader**	**Total**	**Percent Positive Results**
Negative	30	180	0 to 20	3.57	2.23	4.21	0.0 (0/180)
	7	42	21 to 40	12.1	8.68	14.9	0.0 (0/42)
	6	36	41 to 64	8.36	9.44	12.6	0.0 (0/36)
Borderline Negative	7	42	65 to 74	7.82	10.6	13.2	14.3 (6/42)
Borderline Positive	17	102	75 to 85	5.75	6.77	8.88	90.2 (92/102)
Positive	22	132	86 to 95	6.52	5.21	8.35	99.2 (131/132)
	11	66	96 to 100	2.58	4.55	5.24	100.0 (66/66)

In addition, a qualitative analysis of different precision components was performed. The agreement rates for these studies are summarized in the table 13 below.

Table 13: Within-Reader and Between-Reader Precision of VENTANA FOLR1 (FOLR1-2.1) RxDx Assay

Precision	**Agreement**			
	Type	**n/N**	**%**	**95% CI**
Within-Reader	APA	286/295	96.9	(95.1, 98.6)
	ANA	296/305	97.0	(95.1, 98.7)
	OPA	291/300	97.0	(95.0, 98.7)
Between-Reader	APA	276/296	93.2	(89.4, 96.8)
	ANA	284/304	93.4	(89.9, 96.8)
	OPA	280/300	93.3	(90.0, 96.7)

Average Positive Agreement (APA), Average Negative Agreement (ANA), Overall Percent Agreement (OPA)

4. External Reproducibility (Inter-Laboratory) Study

The Inter-laboratory Reproducibility (ILR) study for the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay was conducted to evaluate reproducibility of the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay on the BenchMark ULTRA. The study included 28 EOC samples (14 FOLR1 positive and 14 FOLR1 negative) run across three BenchMark ULTRA instruments on each of 5 non-consecutive days at three external laboratories. Each set of 5 stained slides per sample per staining day was randomized and evaluated by a total of 12 readers (4 readers per site). Each case had 20 results per site (60 results in total). Data showed that the performance of one of 12 readers (8.3%) was significantly different from other eleven readers. Performance of 11 readers (4 readers at site A, 3 readers at site B, and 4 readers at site C) was evaluated and following precision components were calculated: between-reader, between-day, between-site and total. Results are presented in the table below.

Table 14. Precision Components for Samples in the Inter-Laboratory Reproducibility Study

				Standard Deviation (SD)				Percent Positive Results			
Sample ID	Majority Call, FOLR1 Status	Median %TC	Range %TC (Min to Max)	Between Reader	Between Day	Between Site	Total	Site A	Site B	Site C	Overall
1	Negative	0.0	0 to 85	1.3	0.0	0.0	1.3	5% (1/20)	0% (0/15)	0% (0/20)	2% (1/55)
2	Negative	10.0	3 to 25	3.4	1.5	0.0	3.8	0% (0/20)	0% (0/15)	0% (0/20)	0.0% (0/55)
3	Negative	25.0	5 to 60	0.0	0.0	10.4	10.4	0% (0/20)	0% (0/15)	0% (0/20)	0.0% (0/55)
4	Negative	25.0	5 to 50	5.5	0.0	9.0	10.6	0% (0/20)	0% (0/15)	0% (0/20)	0.0% (0/55)
5	Negative	40.0	15 to 70	0.0	0.0	7.2	7.2	0% (0/20)	0% (0/15)	0% (0/20)	0.0% (0/55)
6	Negative	45.0	20 to 70	0.0	0.0	2.0	2.0	0% (0/20)	0% (0/15)	0% (0/20)	0.0% (0/55)
7	Negative	50.0	30 to 75	2.1	0.0	5.4	5.8	15% (3/20)	0% (0/15)	0% (0/20)	5% (3/55)
8	Negative	50.0	20 to 75	1.7	3.2	5.2	6.3	10% (2/20)	0% (0/15)	0% (0/20)	4% (2/55)
9	Negative	50.0	15 to 75	3.3	0.0	4.7	5.8	10% (2/20)	0.0% (0/15)	0.0% (0/20)	4% (2/55)
10	Negative	50.0	0 to 75	8.9	12.1	18.3	23.7	10% (2/20)	0% (0/15)	0% (0/20)	4% (2/55)
11	Negative	60.0	25 to 85	3.9	1.8	7.2	8.4	25% (5/20)	0% (0/15)	0% (0/20)	9% (5/55)
12	Negative	60.0	40 to 75	1.9	0.0	0.0	1.9	5% (1/20)	0% (0/15)	0% (0/20)	2% (1/55)
13	Negative	60.0	30 to 75	0.4	0.0	0.0	0.4	35% (7/20)	0% (0/15)	0% (0/20)	13% (7/55)
14	Negative	65.0	22 to 80	1.3	8.0	0.0	8.1	20% (4/20)	0.0% (0/15)	35% (7/20)	20% (11/55)
15	Positive	75.0	55 to 100	8.8	0.0	14.4	16.8	90% (18/20)	80% (12/15)	35% (7/20)	67% (37/55)
16	Positive	75.0	40 to 95	12.0	0.0	12.6	17.4	80% (16/20)	73% (11/15)	40% (8/20)	64% (35/55)
17	Positive	75.0	40 to 95	11.9	4.2	20.1	23.7	75% (15/20)	80% (12/15)	50% (10/20)	67% (37/55)
18	Positive	80.0	0 to 90	3.6	23.9	20.3	31.6	95% (19/20)	93% (14/15)	58% (11/19)	81% (44/54)

				Standard Deviation (SD)				Percent Positive Results			
Sample ID	Majority Call, FOLR1 Status	Median %TC	Range %TC (Min to Max)	Between Reader	Between Day	Between Site	Total	Site A	Site B	Site C	Overall
19	Positive	80.0	75 to 100	5.0	0.0	10.7	11.8	100% (20/20)	100% (15/15)	100% (20/20)	100% (55/55)
20	Positive	80.0	65 to 95	3.4	0.0	7.4	8.1	100% (20/20)	93% (14/15)	80% (16/20)	91% (50/55)
21	Positive	85.0	70 to 100	8.1	0.0	13.3	15.5	100% (20/20)	100% (15/15)	85% (17/20)	95% (52/55)
22	Positive	90.0	70 to 100	3.9	1.8	8.4	9.4	100% (20/20)	100% (15/15)	95% (19/20)	98% (54/55)
23	Positive	90.0	75 to 100	5.3	0.0	2.4	5.9	100% (20/20)	100% (15/15)	100% (20/20)	100% (55/55)
24	Positive	90.0	80 to 98	6.4	1.2	7.4	9.9	100% (20/20)	100% (15/15)	100% (20/20)	100% (55/55)
25	Positive	90.0	0 to 100	0.0	2.5	0.0	2.5	95% (19/20)	100% (15/15)	100% (20/20)	98% (54/55)
26	Positive	95.0	75 to 100	2.2	0.0	2.3	3.2	100% (20/20)	100% (15/15)	100% (20/20)	100% (55/55)
27	Positive	95.0	60 to 100	1.7	0.0	0.0	1.7	100% (20/20)	93% (14/15)	100% (20/20)	98% (54/55)
28	Positive	95.0	0 to 100	2.6	23.7	3.2	24.1	100% (20/20)	100% (15/15)	80% (16/20)	93% (51/55)

Performance for 28 cases by 11 readers is also summarized in the table below:

Table 15: Percent of Positive and Negative FOLR1 Results for Different Ranges of %TC

%TC Range (Median Values)	Number of Samples	Percent Positive Results	Percent Negative Results
<50	6	0.3%	99.7%
(50-75)	8	7.5%	92.5%
75	3	66.1%	33.9%
(75-85)	4	89.9%	10.1%
>85	7	99.2%	0.8%

Performance of one of the twelve readers was significantly different from the other 11 readers which showed a high percent of positive results for slides with median %TC values larger than 40%. In addition, a qualitative analysis of different precision components was performed for 28 cases and 12 readers. Results of the analysis are summarized in the table below.

Table 16. Inter-Laboratory Reproducibility for VENTANA FOLR1 (FOLR1-2.1) RxDx Assay

		Agreement for 11 Readers			Agreement for 12 Readers		
External Reproducibility	**Type**	**n/N**	**%**	**95% CI**	**n/N**	**%**	**95% CI**
Overall*	PPA	688/769	89.5	(82.6, 95.6)	758/839	90.3	(84.0, 95.9)
	NPA	736/770	95.6	(94.0, 97.0)	763/840	90.8	(88.3, 93.3)
	OPA	1424/1539	92.5	(89.0, 95.6)	1521/1679	90.6	(87.1, 93.7)
Within-Site	PPA	678/739	91.7	(86.3, 96.2)	748/809	92.5	(87.5, 96.5)
	NPA	756/800	94.5	(92.2, 96.5)	783/870	90.0	(87.3, 92.7)
	OPA	1434/1539	93.2	(90.1, 95.8)	1531/1679	91.2	(88.2, 93.9)
Within-Reader	PPA	696/734	94.8	(91.9, 97.3)	805/849	94.8	(92.3, 97.0)
	NPA	779/805	96.8	(95.6, 97.9)	800/830	96.4	(95.3, 97.4)
	OPA	1475/1539	95.8	(94.2, 97.3)	1605/1679	95.6	(94.1, 97.0)

Positive Percent Agreement (PPA), Negative Positive Agreement (NPA), Overall Percent Agreement (OPA).
*0.06% (1 out of 1680) results was not evaluable.

In addition, pairwise comparison calculations were performed for Between-Site, Between-Reader and Between-Day for FOLR1 status. The data in the table below indicates VENTANA FOLR1 (FOLR1-2.1) RxDx Assay reproducibility across 3 days, 3 sites, and 12 readers.

Table 17: External reproducibility, Pairwise Comparison Results

External Reproducibility	**Agreement**			
	Type	**n/N**	**%**	**95% CI**
Between-Sites	APA	(27990/33362)	83.9	(77.5, 89.1)
	ANA	(28386/33758)	84.1	(79.7, 88.4)
	OPA	(28188/33560)	84.0	(78.7, 88.7)
Between-Readers	APA	(2134/2505)	85.2	(79.5, 89.9)
	ANA	(2158/2529)	85.3	(81.2, 89.4)
	OPA	(2146/2517)	85.3	(80.5, 89.6)
Between-Days	APA	(3088/3337)	92.5	(89.5, 95.1)
	ANA	(3126/3375)	92.6	(90.5, 94.8)
	OPA	(3107/3356)	92.6	(90.1, 94.9)

5. Robustness:

a. Tissue Thickness

Tissue thickness was evaluated using 5 unique EOC specimens. Duplicate sections at 2, 3, 4, 5, 6, and 7 microns were tested for each case. A 4-micron thick sample was used as a reference for each case. Three, 4-, 5-, 6- and 7-micron thick sections demonstrated concordant FOLR1 status and acceptable background staining when stained with VENTANA FOLR1 (FOLR1-

2.1) RxDx Assay and compared to the reference of 4 microns. Sections that were 2 microns thick exhibited a change in FOLR1 status compared to the reference. Specimens should be cut at 4 microns for staining with VENTANA FOLR1 (FOLR1-2.1) RxDx Assay.

b. Protocol Limitations and Failure Modes:

The purpose of this study was to identify protocol conditions (protocol parameters and simulated dispense errors) that might lead to a potential false positive, false negative, or unacceptable result and prevent these conditions from affecting the end user.

The test conditions included

- One lot of VENTANA FOLR1 (FOLR1-2.1) RxDx Assay
- One lot of OptiView DAB IHC Detection Kit
- Three BenchMark ULTRA instrument systems
- Replicates: 2 per condition stained with VENTANA FOLR1 (FOLR1-2.1) RxDx Assay
- One Negative Reagent Control per case per test condition
- One SIR Slide
- One Pathologist (Reader)
- Six EOC samples (Three FOLR1 positive cases (including one borderline positive case) and three FOLR1 negative cases (including one borderline negative case) were enrolled

Parameters tested included Offline baking, On Instrument Baking (Low/mid/high), Counterstain and Post-Counterstain (Bluing, Hematoxylin II, Bluing/Hematoxylin II Stacked) for different time durations, Multimer Over/Under Dispense and Peroxidase Inhibitor Over/Under Dispense and Antibody Over/Under Dispense at different concentrations (1/2, 1/4, 2X or 4X). Other assay parameters were locked and not used as test conditions in this study.

The result of each test sample was compared to its respective sample stained with the final locked staining protocol. Based on the data, there were differences in staining results between the final locked staining protocol parameters and the modified parameters. Therefore, the final staining protocol specified in Table 4should be followed. Refer to the Labeling (Package Insert) for additional instructions.

6. Stability Studies:

a. Cut Slide Stability

This study evaluated the stability of FOLR1 antigen in FFPE tissue that had been sectioned onto positively charged glass microscope slides and stored for an extended duration of time at 5±3°C and 30±5°C. Cut slide stability was evaluated on seven EOC samples with staining that spanned the range of FOLR1 expression. Slides sectioned and stained at the Day 0 time point served as the baseline comparator for the remainder of the time points tested. Tissue was sectioned from each of the seven cases and separated into two different storage conditions for the duration of the study. One set of slides was stored at the refrigerated temperature condition (5±3°C) and one at the incubator temperature condition (30±5°C). Slides were stained at each pre-defined designated time

and staining results for each time point were compared to the Day 0 baseline slides. Based on the study results, the recommended cut slide stability is 45 days at both the 5±3ºC and 30±5ºC storage conditions.

b. Reagent/Ship Stress Stability

The objective of this study was to assess the stability (shelf-life and in-use) and shipping category of the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay. Three final lots of VENTANA FOLR1 (FOLR1-2.1) RxDx Assay were subjected to different stress conditions and then placed at the intended storage condition (2-8°C). The conditions tested were as follows:

i. Intended Storage (2-8°C)
ii. Hot Ship Stress Cat. A (33°C±3ºC 192 hours)
iii. Hot Ship Stress Cat. B (18°C±3ºC 192 hours)
iv. Hot Ship Stress Cat. F (37°C±2ºC 192 hours)
v. Cold Ship Stress Freeze/Thaw (-20°C±5ºC 192 hours)
vi. Cold Ship Stress Freeze/Thaw (-25°C±5ºC 192 hours)

Based on the study results, the stability dating for the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay device is 24 months when stored at 2-8°C and shipping categories A and F.

c. Real-time and Ship Stress Stability of the VENTANA FOLR1 Stain Intensity Reference (Normal Fallopian Tube) Slide:

This study evaluated the stability of IHC staining intensity of the DAB signal across a range of staining on normal fallopian tube tissue when stained with the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay. The study design encompassed 14 test conditions [type of storage container (plastic box, card box slide storage box, open slide flat), type of coverslip types (glass, film), type of lighting (fluorescent, dark, intermittent exposure)], 9 total normal fallopian tube tissue samples with two replicates, 1 reader, 1 lot of the VENTANA FOLR1 (FOLR1-2.1) RxDx antibody, 2 lots of OptiView DAB IHC Detection Kit, 6 BenchMark ULTRA Instruments and 9 testing time points; Slides were stained and read at Day 0 and the same slides were read again at months between 1 thru 6, and month 9 and month 12.

Acceptance criteria was as follows: At each time point, slides shall exhibit assay overall stain intensity that is equal to but no more than 1.0 point different compared to the Day 0 stained slide score.

Acceptance criteria for this study were met. Based on the study results, the stability dating for the SIR slide is 9 months when stored in room temperature conditions (15-30˚C).

B. Animal Studies

None

C. Additional Studies

1. Tissue Heterogeneity

This study evaluated the prevalence of tissue heterogeneity in EOC tissue blocks from the same case (multiple blocks from the same case, as well as heterogeneity within a block) when stained with VENTANA FOLR1 (FOLR1-2.1) RxDx Assay on the BenchMark ULTRA instrument.

a. Within-Block Heterogeneity

The intent of this study was to evaluate FOLR1 tumor cell expression level across multiple sections from the same tissue block when stained with VENTANA FOLR1 (FOLR1-2.1) RxDx Assay. Eight FFPE EOC samples encompassing the FOLR1 expression range from negative to positive were enrolled in the study. The case distribution consisted of 3 positive cases (all borderline) and 5 negative cases (inclusive of 1 borderline negative case). For each block, approximately every 10th section was stained with VENTANA FOLR1 (FOLR1-2.1) RxDx Assay. Cases were sectioned to exhaustion. Six out of eight cases maintained the FOLR1 expression level throughout the block. Both cases with inconsistent FOLR1 expression level were borderline cases - 1 borderline positive and 1 borderline negative. This demonstrates that some heterogeneity may be observed in the FOLR1 expression level within each EOC tissue block from the same case when stained with the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay.

b. Within-Case Heterogeneity

The intent of this study was to evaluate EOC case heterogeneity when multiple blocks from the same patient case were stained with VENTANA FOLR1 (FOLR1-2.1) RxDx Assay. Twenty-seven cases with two blocks per case and 2 cases with four blocks per case were evaluated in this study. Twenty-six (26) out of 29 patient cases (89.7%) displayed no case level heterogeneity for the 75% cutoff. Case level heterogeneity was observed in 3 out of 29 cases (10.3%) for the 75% cut-off. This demonstrates that variation may be observed in the FOLR1 expression level of different EOC tissue blocks from the same patient case when stained with the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay.

2. Impact of Tissue Specimen Preparation and Treatment Studies/ Effect of Fixative Type, Time and Delay to Fixation on FOLR1 antigenicity in DU-145 Xenografts:

a. Ischemia Study (Time to Fixation)

The objective of this study was to evaluate the effects of ischemic time on FOLR1 antigenicity as detected by staining with VENTANA FOLR1 (FOLR1-2.1) RxDx Assay. This study examined the effects of delay to fixation (Ischemia) for DU-145 xenograft samples at zero hours, 0.5 hours, 1 hour, 2 hours, 6 hours, and 24 hours post excision. All samples were fixed in 10% NBF for 24 hours after being delayed for fixation at their various ischemia time points. The study demonstrated concordant FOLR1 staining results for all samples tested. However, it is recommended that samples are fixed immediately in 10% NBF.

b. Fixation Study

The objective of this study was to evaluate the effects of fixative type and fixation time on FOLR1 antigenicity as detected by staining with VENTANA FOLR1 (FOLR1-2.1) RxDx Assay. Six DU-145 Xenograft blocks were fixed for 1, 6, 12, 24, 48 and 72 hours in 6 fixatives: 10%

NBF, Zinc formalin, 95% alcohol, AFA, Z-5, and PREFER for a total of 36 samples. The data were then compared to the reference standard of 10% NBF for 24 hours.
Tissues fixed in AFA, PREFER fixative, 95% EtOH and zinc formalin were unacceptable when stained with VENTANA FOLR1 (FOLR1-2.1) RxDx Assay and therefore are not recommended fixatives. Based on results of this study, specimens for testing with the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay should be fixed immediately post-excision in 10% NBF for 12-72 hours.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The objective of this study was to evaluate the performance of VENTANA FOLR1 (FOLR1-2.1) RxDx Assay as a companion diagnostic (CDx) device to identify patients for treatment with ELAHERE (mirvetuximab soravtansine) in patients with platinum-resistant epithelial ovarian cancer, primary peritoneal, or fallopian tube cancer.

A. Study Design

Immunogen Study IMGN853-0417 (NCT04296890) was a Phase 3, single-arm trial to evaluate the efficacy and safety of ELAHERE in patients with Folate Receptor (FRα) positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer. Patients were permitted to receive up to three prior lines of systemic therapy. All patients were required to have received prior bevacizumab. The trial enrolled patients whose tumors were positive for FRα expression (i.e., ≥ 75% of viable TC demonstrated FOLR1 membrane staining at moderate and/or strong staining intensity) as determined by the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay at a central site. The efficacy evaluable population included 104 patients with platinum-resistant disease, who had measurable disease, and received at least one dose of ELAHERE.

1. Clinical Inclusion and Exclusion Criteria

a. Key Trial Inclusion Criteria

Patients had to meet all the following criteria to enter the enrollment phase and receive ELAHERE in this study:

i. Patients must have a confirmed diagnosis of high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer
ii. Patients must have had platinum-resistant disease
iii. Patients must have progressed radiographically on or after their most recent line of anticancer therapy
iv. Patients must be willing to provide an archival tumor tissue block or slides, or undergo procedure to obtain a new biopsy using a low-risk, medically routine procedure for immunohistochemistry (IHC) confirmation of FRα positivity
v. Patient's tumor must be positive for FRα expression as defined by the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay
vi. Patients must have received at least 1 but no more than 3 prior systemic lines of anticancer therapy

b. Key Trial Exclusion Criteria

Patients who met any of the following criteria were excluded from study enrollment:

i. Patients with endometrioid, clear cell, mucinous, or sarcomatous histology, mixed tumors containing any of the above histologies, or low-grade/borderline ovarian tumor
ii. Patients with primary platinum-refractory disease, defined as disease that did not respond to (CR or PR) or has progressed within 3 months of the last dose of first-line platinum-containing chemotherapy
iii. Patients with prior wide-field radiotherapy (RT) affecting at least 20% of the bone marrow
iv. Patients with > Grade 1 peripheral neuropathy per Common Terminology Criteria for Adverse Events (CTCAE)
v. Patients with a history of other malignancy within 3 years prior to enrollment

2. Follow-up Schedule

The median follow-up time was approximately 3 months.

3. Primary Clinical Efficacy Endpoints

Primary objective of the IMGN853-0417 study was to evaluate the efficacy of ELAHERE in patients with platinum-resistant epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer and high FRα expression by assessing the ORR, which includes best response of complete response (CR) or partial response (PR) as assessed by the Investigator.

B. Accountability of PMA Cohort

A total of 467 patients were screened, and a total of 106 patients were enrolled into IMGN853-0417 study. Of the 467 patients screened for entry into Study IMGN853-0417, 25 cases failed enrollment criteria associated with study IMGN853-0417 prior to testing and 4 cases were associated with a diagnostic testing (Dx) screen failure (cases did not have an acceptable H&E slide). Tissue specimens from the remaining 438 patients were tested with VENTANA FOLR1 (FOLR1-2.1) RxDx Assay. Out of the 438 patients, 332 patients were not enrolled because they failed enrollment criteria related to Study IMGN853-0417, 1 patient was enrolled who did not have efficacy results and one patient was excluded from the efficacy evaluable population as this patient did not have platinum-resistant disease. The remaining 104 cases comprised the efficacy population. Patient accountability is summarized in the below table.

Table 18: Accountability of IMGN853-0417 Study PMA Cohort

Patient Disposition for Study IMGN853-0417	N
Total number of patients screened	**467**
-Samples did not meet the study eligibility criteria (prior to testing)	25
-Dx testing screen failure (case did not have an acceptable H&E slide)	4
Number tested with the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay	**438**
Failed enrollment criteria related to ImmunoGen Study IMGN853-0417	334
Final number of patients in the trial	**104**

Sixty-six cases were associated with a Dx protocol deviation (specimen slides were scored based on digital slide image reads instead of glass slides). These 66 cases were re-scored using glass slides by same readers at same sites (as in digital reads), with a minimum wash-out period of 2 months. Pairwise comparison was used to calculate the agreement rates between the digital image reads and glass slide reads. The overall concordance between the digital image reads and glass slide reads was 93.9 % (95% CI: 87.7, 98.5). Of the 66 patients who were screened using digital reads, 29 were FOLR1-positive. Of those 29 patients, 27 were enrolled to the trial, with the other 2 being excluded due to other inclusion/exclusion criteria not related to FOLR1 clinical status. None of the remaining 37 patients were enrolled into the clinical trial.

C. Study Population Demographics and Baseline Parameters

Table below summarizes patient demographic and specimen characteristic information.

Table 19: Study Population Demographics and Baseline Parameters-Patient Characteristic

	Enrolled (N=104)	Not Enrolled (N=334)	Overall (N=438)
Age (years)			
Mean (SD)	61.7 (9.73)	62.5 (10.43)	62.3 (10.27)
Median	62	63	63
Min - Max	35 - 85	30 - 87	30 - 87
Missing	0	4	4
Age Group			
18-64	59 (56.7%)	182 (54.5%)	241 (55.0%)
>=65	45 (43.3%)	148 (44.3%)	193 (44.1%)
Missing	0	4 (1.2%)	4 (0.9%)
Sex			
Female	104 (100.0%)	334 (100.0%)	438 (100.0%)
Race			
Asian	2 (1.9%)	10 (3.0%)	12 (2.7%)
Black Or African American	0	7 (2.1%)	7 (1.6%)
White	100 (96.2%)	276 (82.6%)	376 (85.8%)
Not Reported	2 (1.9%)	30 (9.0%)	32 (7.3%)
Missing	0	11 (3.3%)	11 (2.5%)
Ethnicity			
Hispanic or Latino [b]	2 (1.9%)	18 (5.4%)	20 (4.6%)

Not Hispanic or Latino	97 (93.3%)	276 (82.6%)	373 (85.2%)
Unknown	1 (1.0%)	4 (1.2%)	5 (1.1%)
Not Reported	4 (3.8%)	25 (7.5%)	29 (6.6%)
Missing	0	11 (3.3%)	11 (2.5%)
Stage at Initial Diagnosis			
IA	0	2 (0.6%)	2 (0.5%)
IB	0	3 (0.9%)	3 (0.7%)
IC	2 (1.9%)	10 (3.0%)	12 (2.7%)
IIA	0	2 (0.6%)	2 (0.5%)
IIB	0	3 (0.9%)	3 (0.7%)
IIC	0	6 (1.8%)	6 (1.4%)
IIIA	5 (4.8%)	23 (6.9%)	28 (6.4%)
IIIB	5 (4.8%)	20 (6.0%)	25 (5.7%)
IIIC	51 (49.0%)	149 (44.6%)	200 (45.7%)
IV	40 (38.5%)	92 (27.5%)	132 (30.1%)
Missing	1 (1.0%)	24 (7.2%)	25 (5.7%)
Histology at Diagnosis			
Carcinosarcoma	0	1 (0.3%)	1 (0.2%)
Clear Cell	0	1 (0.3%)	1 (0.2%)
Endometrioid	0	5 (1.5%)	5 (1.1%)
High Grade Serous	104 (100.0%)	274 (82.0%)	378 (86.3%)
Low Grade Serous	0	7 (2.1%)	7 (1.6%)
Mucinous	0	1 (0.3%)	1 (0.2%)
Serous Adenocarcinoma	0	18 (5.4%)	18 (4.1%)
Squamous	0	2 (0.6%)	2 (0.5%)
Other	0	14 (4.2%)	14 (3.2%)
Missing	0	11 (3.3%)	11 (2.5%)
Sample Characteristic			
Sample Collection Method			
Biopsy	19 (18.3%)	88 (26.3%)	107 (24.4%)
Excision/Resection	85 (81.7%)	246 (73.7%)	331 (75.6%)
Tumor Type			
Locoregional Recurrence	22 (21.2%)	82 (24.6%)	104 (23.7%)
Metastasis	8 (7.7%)	47 (14.1%)	55 (12.6%)
Primary	74 (71.2%)	205 (61.4%)	279 (63.7%)
Location (Sample Origin of Primary Tumor)			
Fallopian Tube	5 (4.8%)	12 (3.6%)	17 (3.9%)
Ovary	53 (51.0%)	160 (47.9%)	213 (48.6%)
Peritoneum	15 (14.4%)	29 (8.7%)	44 (10.0%)
Not Applicable*	31 (29.8%)	133 (39.8%)	164 (37.4%)

[a] Patients are classified as Hispanic or Latino if they are Mexican/Hispanic American, Mexican National, Central American, Puerto Rican, Cuban, South American, Caribbean, or Other Hispanic or Latino Origin

*Metastasis or Locoregional Recurrence

C. Safety and Effectiveness Results

1. Safety Results

No adverse events associated with use of VENTANA FOLR1 (FOLR1-2.1) RxDx Assay under study IMGN853-0417 protocol occurred during the clinical study.

2. Effectiveness Results

The major efficacy outcome measures were investigator-assessed ORR (primary endpoint) and DOR (secondary endpoint) evaluated according to RECIST, version 1.1. The primary endpoint of ORR was calculated based on the Efficacy Evaluable (EE; n=104) population. The ORR was 31.7% (22.9, 41.6) with 4.8% of patients showing complete response and 26.9% of patients showing partial response. Considering the 66 patients who were screened using digital slide reading and then re-scored using glass slides, 3 patients had positive FOLR1-2.1 RxDx Assay results based on digital slide reading and negative results based on glass slides reading. Two of the 3 patients were included in the efficacy population. After excluding these 2 patients, the observed ORR for patients had positive FOLR1-2.1 RxDx Assay results based on glass slide reading was 32.4% (23.5, 42.2) with 4.9% of patients showing complete response and 27.5% of patients showing partial response. In addition, one patient with negative result based on digital slide image but positive result based on glass slide re-read may be eligible but was not enrolled into the Study 0417 and therefore not available for CDx efficacy analysis. Efficacy results for IMGN853-Study 0417 are summarized in Table 20.

Table 20: Efficacy Results from Study IMNG853-0417 by Investigator

	ELAHERE (N=104)[b]
Confirmed Overall Response [a] (n) (%; 95% CI)	N=33 (31.7%; 22.9, 41.6)
Complete response (n) (%)	5 (4.8%)
Partial response (n) (%)	28 (26.9%)
Duration of Response	N=33
Median Duration of Response, months (95% CI)	6.9 (5.6, 9.7)

[a] Investigator assessment

[b] The CDx efficacy population excluded 2 subjects from the drug efficacy population who are digital slide read positive, but glass slide re-read negative. In addition, one subject with digital slide read negative result but glass slide re-read positive result may be eligible but was not enrolled into the clinical trial and therefore not available for CDx efficacy analysis

Response assessment results using independent radiology review were consistent with investigator assessment.

3. Subgroup Analyses

There were no subgroup analyses performed in this trial.

4. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

D. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study investigators did not report any financial conflicts of interest for this study.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Not applicable.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Hematology and Pathology Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA did not raise any new safety and effectiveness questions compared with information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The primary efficacy data in conjunction with the staining performance support the reasonable assurance of safety and effectiveness of use of VENTANA FOLR1 (FOLR1-2.1) RxDx Assay as a companion diagnostic device for ELAHERE treatment in the target EOC patient population. The IMGN853-0417 primary efficacy analysis demonstrated a clinically meaningful ORR for patients with advanced stage EOC whose tumors have high FOLR1 expression as determined by the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay. The performance of the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay was also supported by the analytical performance validation studies.

B. Safety Conclusions

The risks of the device are based on data collected in the clinical study conducted to support PMA approval as described above.

The VENTANA FOLR1 (FOLR1-2.1) RxDx Assay is an *in vitro* diagnostic device which is used to test FFPE tumor specimens collected from patients with EOC. No adverse events associated with the diagnostic testing procedure were reported during this study. The process of testing on FFPE tumor specimens does not present additional significant safety concerns, as the required biopsies are obtained using a medically routine sampling procedure that does not present a significant risk to the patient.

C. Benefit-Risk Determination

The probable benefits of the device are based on data collected in the clinical study IMGN853-0417 conducted to support the PMA approval as described above. The clinical performance of the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay was demonstrated in the clinical validation studies. As shown in Table 20 above, the ORR among patients selected by the VENTANA FOLR1 (FOLR1- 2.1) RxDx Assay in study IMGN853-0417 was 31.7% with a duration of response of 6.9 months. The studies demonstrated that VENTANA FOLR1 (FOLR1-2.1) RxDx assay appropriately and reproducibly detects FOLR1 antigen in EOC carcinoma tissue and can aid in the assessment of these patients being considered for treatment with ELAHERE.

The primary risk of the VENTANA FOLR1 (FOLR1-2.1) RxDx assay is obtaining a false result. A false positive result could lead to the treatment with reduced probability of benefit. This could unnecessarily expose the patient to toxicity of the drug. A false negative result could deprive a patient of the potential benefit of ELAHERE (mirvetuximab soravtansine) targeted treatment. There is also a risk of delayed results, which may lead to a delay in treatment with ELAHERE (mirvetuximab soravtansine) or other approved therapy depending on the FOLR1 testing result. In conclusion, given the available information above, the data support the use of VENTANA FOLR1 (FOLR1-2.1) RxDx Assay for determination of eligibility for ELAHERE (mirvetuximab soravtansine) treatment in patients with advanced EOC who progressed on previous chemotherapy treatments, who are more likely to benefit from treatment with ELAHERE (mirvetuximab soravtansine) monotherapy, as the probable benefits outweigh the probable risks.

D. Patient Perspective

This PMA submission did not include specific information on patient perspectives for this device.

E. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The provided study data support the use of the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay as a companion diagnostic to identify patients with epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer, for treatment with (mirvetuximab soravtansine) ELAHERE.

XIV. CDRH DECISION

CDRH issued an approval order on November 14, 2022.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

Clinical Inspection Summary

Date	September 8, 2022
From	Yang-Min (Max) Ning, M.D., Ph.D. Min Lu, M.D., M.P.H. Jenn Seller, M.D., Ph.D. GCPAB/OSI/CDER/FDA
To	Mirat Shah, M.D. Asma Dilawari, M.D. Gwynn Ison, M.D. Laleh Amiri-Kordestani, M.D. Alice Lee, RPM DO1/OOD/CDER/FDA
BLA #	761310
Applicant	ImmunoGen, Inc.
Drug	Mirvetuximab soravtansine-xxxx
New Molecular Entity	Yes
Therapeutic Classification	Antibody-drug conjugate
Proposed Indication	Treatment of patients with folate receptor alpha positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received one to three prior systemic treatment regimens
Consultation Request Date	April 29, 2022
Inspection Summary Date	September 9, 2022
Action Goal Date	October 14, 2022
PDUFA Date	November 28, 2022

I. OVERALL ASSESSMENT OF INSPECTIONAL FINDINGS AND RECOMMENDATIONS

Clinical data from an ongoing Phase 3 trial [Protocol IMGN853-0417] were submitted to the Agency in support of a new Biologics License Application (BLA) for mirvetuximab soravtansine-xxxx for the proposed indication as listed above. Three participating clinical investigators [Drs. Jason Konner (Site 026), Domenica Lorusso (Site 504), and Andrew Dean (Site 932)] and the study sponsor (ImmunoGen. Inc.) were inspected.

Inspections of these four entities identified no significant regulatory violations in the conduct of Study IMGN853-0417. Subjects enrolled at the three investigator sites met the eligibility criteria and their clinical data, submitted by the Applicant, were verified with source records reviewed at the sites. Based on these inspection results, Study IMGN853-0417 appears to have been properly conducted and the clinical data generated from these three investigator sites are acceptable for this BLA.

II. BACKGROUND

Mirvetuximab soravtansine-xxxx is the conjugate of a folate receptor-directed antibody (mirvetuximab) with a microtubule inhibitor (soravtansine). The investigational name of this product was IMGN853 or "MIRV" in the study protocol. For this BLA, the sponsor submitted clinical data from Study IMGN853-0417 and proposed an initial indication for the product for the treatment of adult patients with folate receptor-α (FRα) positive platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received one to three prior systemic treatment regimens.

Study IMGN853-0417 [NCT04296890] is an ongoing, open-label, multicenter trial of mirvetuximab soravtansine-xxxx in patients with advanced platinum-resistant serous epithelial ovarian, primary peritoneal, or fallopian tube cancer (referred as PROC) whose tumors express a high level of FRα. To be eligible for this study, subjects were required to have had: 1) confirmed diagnosis of high-grade serous epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer; 2) platinum-resistant disease that progressed radiographically on or within 6 months after their most recent line of up to three prior anticancer therapies as specified in the protocol, with bevacizumab as a required prior treatment; 3) FRα positivity in tumor specimen(s) as determined with the Ventana FOLR1 Assay at a central laboratory; 4) at least one measurable as assessed by the Investigator. Subjects with endometrioid, clear cell, mucinous, or sarcomatous histology, mixed tumors containing any of the above histological types, or low-grade/borderline ovarian tumor were to be excluded.

The primary endpoint of this study was confirmed objective response rate (ORR) as assessed by the Investigator using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1.

Subjects enrolled into the study were scheduled to receive MIRV at 6 mg/kg (adjusted ideal body weight) once every 3 weeks (21-day cycle), administered as an intravenous infusion at an initial rate of 1 mg/min. The rate was to be adjusted with subject's tolerance according to the protocol. All subjects also were to receive pre-medications as specified in the protocol, including corticosteroid eye drops. Study treatment was to be continued until disease progression as assessed by Investigator, unacceptable toxicity, withdraw consent, non-compliance with the required study visits, or death.

For the primary endpoint ORR, tumor assessments were performed with computed tomography (CT)/magnetic resonance imaging (MRI) scans of the chest, abdomen, and pelvis at baseline (within 28 days before initiation of study treatment), every 6 weeks (±1 week) for the first 36 weeks on study, and then every 12 weeks (±3 weeks) until documentation of disease progression or the start of a new anticancer therapy, whichever occurred first. For subjects who discontinued study treatment due to other reasons (e.g., unacceptable toxicity) but remained on study, imaging assessments were to be continued until disease progression or initiation of new anticancer therapy. Copies of all scans were required to be submitted to the sponsor's designated central imaging laboratory for the blinded independent central review, which was designed for conducting sensitivity

analyses. For clinical safety assessments, adverse events, protocol-required examinations (e.g., ophthalmic exam) and laboratory tests were to be collected and/or conducted according to "Schedule of Assessments" (Table 2) of the protocol. All adverse events and laboratory abnormalities were to be graded for severity using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

From 07/23/2020 through 11/16/2021 [data cutoff date for analyses included in this BLA], the study enrolled 106 subjects from 39 investigator sites in eight countries, including Australia, Belgium, Germany, Ireland, Israel, Italy, Spain, and the United States (U.S.). Of the enrolled, 24 subjects (23%) were from 13 sites the U.S. and 82 subjects (77%) from 26 sites in the above-listed foreign countries. All the 106 subjects received at least one dose of study treatment and were included in the safety analysis. Except for one subject, 105 subjects had measurable disease at baseline and were included in the efficacy analysis.

The DO1 and OSI review teams evaluated the Applicant's submitted dataset clinsite.xpt and the related investigators risk ranking for this BLA, discussed the study design and reported data by study site, and selected the above three participating investigators and the sponsor for clinical inspection. Relative to other investigator sites in Study IMGN853-0417, these three investigator sites enrolled large numbers of subjects in respective geographical regions. The reason for selection of the two foreign investigators was inadequate domestic data for the application. In addition, Dr. Dean's site was associated with a tumor response rate of 55%, higher than the reported overall response rate of 32% in this study. Inspection of the study sponsor was also requested given that this application is for a new molecular entity and that there was no prior inspection history for the sponsor.

III. RESULTS

1. **Jason Konner, M.D. (Site 026)**
   300 East 66 Street
   New York, NY 10065

   Dr. Konner was inspected on July 18-22, 2022, as a surveillance and data audit for Study IMGN853-0417. This was the first FDA inspection of the investigator.

   The site screened 17 subjects and enrolled 4 into the study. As of the data cutoff date, 3 of the 4 subjects were discontinued from study treatment due to disease progression and one subject (# (b) (6)) remained on study treatment. At the time of this inspection, Subject (b) (6) was found to have been discontinued from study treatment due to disease progression. The study was active for survival follow-up but not open for new enrollment.

   Source records for all the enrolled subjects were reviewed and compared with the Applicant's submitted data for this site. Records reviewed during the inspection included, but were not limited to, the informed consent forms, eligibility information, shipping documentation of the tumor tissue or formalin-fixed, paraffin embedded (FFPE) slides submitted to the sponsor's designated central laboratory, study treatment received,

protocol-required scans and related review reports and subsequent submissions to the central imaging laboratory, adverse events (AEs), concomitant medications, and protocol deviations. Regulatory documents related to the study administration and oversight at the site were also reviewed, including the Institutional Review Board (IRB) approvals of the protocol/amendments and related informed consents, site training for the protocol, delegation of authority log, FDA 1572s, financial disclosures, site's access to the electronic case report forms (eCRFs) system (i.e., Medidata RAVE), study monitoring activities, reports to the sponsor, control of investigation product from receipt to disposition, and retention of study records.

The inspection found no regulatory violations at the site. All the enrolled subjects were found to have had their tumor specimens submitted to the sponsor's designated central laboratory (b) (4) for evaluation of FRα expression status. These subjects met the eligibility criteria for the study and received study treatment as scheduled until disease progression. Tumor assessments were conducted per protocol and the scans were reviewed and subsequently submitted to the sponsor's designated imaging lab (b) (4) for central review. Results from the central review were found unavailable to the site.

No Form FDA 483, Inspectional Observations, was issued to Dr. Konner at the conclusion of this inspection.

2. Domenica Lorusso, M.D., Ph.D. (Site 504)
Largo Agostino Gemelli, Ala O Policlinico Gemelli
Rome, Lazio, 00168
Italy

Dr. Lorusso was inspected on July 18-22, 2022, as a surveillance and data audit for Study IMGN853-0417. For the investigator, this was the initial inspection by FDA. The site enrolled and treated 12 subjects in the study. As of the data cutoff date, 9 subjects were discontinued from study treatment due to disease progression and one subject (b) (6) due to clinical deterioration, and two subjects (# (b) (6)) continued receiving study treatment. At the time of this inspection, all the subjects were discontinued from study treatment. The study was closed to enrollment and continued to follow subjects for survival per protocol.

Source records for all the 12 subjects were reviewed and compared relevant data with the submitted clinical data for this site. Records reviewed and confirmed in the inspection included the informed consents, eligibility criteria, premedication and treatment with the investigational product, study visits, RECIST assessments and documentation, adverse events, concomitant medications, protocol deviations, and data in the eCRFs. The inspection also reviewed regulatory documentation for the administration and oversight of this study at the site, including the local Ethics Committee approvals and communication related to the study protocol and amendments, prescreening consents for testing of tissue block(s) for FRα expression, training activities and certifications, signed Form FDA 1572s, financial disclosures, access to the Medidata Rave system, control of the

investigational product, study monitoring, and reports to the sponsor.

The inspection revealed no significant regulatory deficiencies, with no Form FDA 483 issued to Dr. Lorusso. All the enrolled subjects were verified for their eligibility, study-required assessments, and reported clinical data, with no notable discrepancies identified except for two AEs (Grade 1 nausea and Grade 1 vomiting) for Subject (b) (6), which were documented in the progress note but not found in the eCRF or the submitted data listings for this subject. These two AEs occurred in (b) (6) and were attributed to study treatment based on the clinical assessment. In addition, Subject (b) (6) was verified to have received an additional treatment with nab-paclitaxel plus relacoritant from (b) (6) through (b) (6) following disease progression on the third prior line treatment nab-paclitaxel alone from (b) (6) to (b) (6) while the subject participated in another clinical trial. The investigator acknowledged these findings, which were also discussed at the close of this inspection.

Reviewer's Comments: The unreported Grade 1 nausea and Grade 1 vomiting for Subject (b) (6) *appear to be isolated since nausea and vomiting were reported for other subjects from the same site. In addition, both AEs were already included in the study report and the proposed label. It is less likely that the two unreported AEs can affect the safety profile of mirvetuximab soravtansine-xxxx in the study disease setting. For Subject* (b) (6)*, the additional treatment with nab-paclitaxel plus relacoritant, as described above, should be deemed another line of prior therapy per protocol. This was reported as a protocol deviation in the study report. Given that relacoritant, a glucocorticoid receptor antagonist, was intended to overcome resistance to chemotherapy in an investigational manner, nab-paclitaxel appears to represent the backbone chemotherapy in this combination treatment.*

3. Andrew Dean, M.D. (Site 932)
12 Salvado Road
Subiaco, WA 6008
Australia

Dr. Dean was inspected on August 1-5, 2022, as a data audit for Study IMGN853-0417. This was the second FDA inspection of the investigator. The first one was conducted in August 2015 for another new drug application and was classified as No Action Indicated.

For the current inspection, the established inspection report is not available as of 9/7/2022. Based on the inspector's preliminary summary, Dr. Dean's site enrolled 11 subjects into the study. All the 11 subjects received study treatment following enrollment. As of the data cutoff, 5 of the 11 subjects were discontinued from study treatment due to disease progression or adverse event(s) and the remaining 6 subjects continued receiving study treatment. At the time of this inspection, one subject died from disease progression and 10 subjects were on survival follow-up.

The inspection audited source records for all the 11 subjects at the site and compared the Applicant's submitted data with source data. There were no discrepancies identified for

subjects' eligibility and clinical data. Protocol-required efficacy assessments and investigator-reported tumor responses were verifiable with source data reviewed. There was no evidence of under-reporting of adverse events.

No Form FDA 483 was issued to Dr. Dean at the conclusion of this inspection.

Reviewer's Note: An addendum to this summary will be made if the Establishment Inspection Report for Dr. Dean contains substantial differences that can alter the current assessment of his conduct and/or reported data for Study IMGN853-0417.

4. ImmunoGen, Inc. (Study Sponsor)
830 Winter Street
Waltham, MA 02451

The study sponsor was inspected from 7/20/2022 through 7/28/2022 to evaluate its conduct and oversight of Study IMGN853-0417. This was the first FDA inspection of this firm.

The inspection was performed in accordance with the FDA Compliance Program #7348.810 for sponsor and contract research organizations (CROs). The inspection focused on sponsor's responsibilities for Study IMGN853-0417, with a comprehensive review of records and procedures used for the conduct of this study. Records reviewed during the inspection included the sponsor's organizational chart, standard operational procedures, transfer of regulatory and obligations and related agreements, selection of clinical investigators and monitors for the study and related training, investigator agreements and financial disclosures, selection of CROs and oversight plans, study monitoring plans and reports, data collection and handling as well as related data transfers, reporting of adverse events and protocol deviations, investigational product accountability and quality assurance.

The inspection found no objectionable regulatory deficiencies in the sponsor's conduct and oversight of Study IMGN853-0417, with no Form FDA-483 issued at the conclusion of this inspection. The study was found to be ongoing at the time of this inspection. No investigators were terminated for non-compliance or placed on enrollment hold. Key participating CROs in the study and their roles were reviewed, including (b) (4) for central testing of FRα expression levels and (b) (4) for qualification of investigator sites and training under the sponsor's oversight and final approval per Clinical Monitoring Plan. Clinical data were collected from study sites using the Medidata RAVE system and were managed by (b) (4) under the sponsor's oversight per the Data Management Plan and Data Review Plan. For the current submission, the database lock date of 11/16/2021 was verified.

{See appended electronic signature page}

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

CONCURRENCE: {See appended electronic signature page}

Min Lu, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Jenn Seller, M.D., Ph.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Review Division /Division Director
Review Division /Project Manager
Review Division /Clinical Team Lead
Review Division/Medical Officer
OSI/DCCE/GCPAB Reviewer
OSI/Office Depute Director
OSI/DCCE/Division Director
OSI/DCCE/GCPAB Branch Chief
OSI/DCCE/GCPAB Team Lead
OSI/GCP Program Analyst
OSI/Database PM

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/

YANGMIN NING
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JENN W SELLERS
09/08/2022 12:53:38 PM

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

PATIENT LABELING REVIEW

Date:	August 29, 2022
To:	Alice Lee Regulatory Project Manager **Division of Oncology I (DO1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Koung Lee, RPh, MSHS Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	ELAHERE (mirvetuximab soravtansine-gynx)
Dosage Form and Route:	injection, for intravenous use
Application Type/Number:	BLA 761310
Applicant:	ImmunoGen, Inc.

1 INTRODUCTION

On March 28, 2022, ImmunoGen, Inc., submitted for the Agency's review an original Biologics License Application (BLA) 761310 for ELAHERE (mirvetuximab soravtansine-gynx) injection, for intravenous use. ELAHERE is a folate receptor-alpha directed antibody and microtubule inhibitor conjugate proposed for the treatment of adult patients with folate receptor-alpha positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received one to three prior systemic treatment regimens.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology1 (DO 1) on April 6, 2022, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for ELAHERE (mirvetuximab soravtansine-gynx) injection, for intravenous use.

2 MATERIAL REVIEWED

- Draft ELAHERE (mirvetuximab soravtansine-gynx) injection MG received on March 28, 2022, and received by DMPP and OPDP on August 22, 2022.
- Draft ELAHERE (mirvetuximab soravtansine-gynx) injection Prescribing Information (PI) received on March 28, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 22, 2022.

3 REVIEW METHODS

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

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

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

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

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

SUSAN W REDWOOD
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KOUNG U LEE
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BARBARA A FULLER
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LASHAWN M GRIFFITHS
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

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

Memorandum

Date: August 26, 2022

To: Alice Lee, Regulatory Project Manager, Division of Oncology 1 (DO1)

From: Koung Lee, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Rachael Conklin, Team Leader, OPDP

Subject: OPDP Labeling Comments for ELAHERE™ (mirvetuximab soravtansine-gynx) injection, for intravenous use

BLA: 761310

Background:
In response to DO1's consult request dated April 6, 2022, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide, and carton and container labeling for the original BLA 761310 submission for ELAHERE™ (mirvetuximab soravtansine-gynx) injection, for intravenous use (Elahere).

PI/Medication Guide:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on August 22, 2022, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Koung Lee at 240-402-8686 or Koung.lee@fda.hhs.gov.

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/s/

KOUNG U LEE
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Medical Officer's Review of BLA 761310
Ophthalmology Consultation

BLA 761310

Submission date: 3/28/2022
Consult Request: 4/ 5/2022
Review date: 7/8/2022

Sponsor: ImmunoGen, Inc.

Drug Name: ELAHERE (mirvetuximab soravtansine)

Indications: Treatment of adult patients with folate receptor-alpha (FRα) positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received one to three prior systemic treatment regimens. Select patients for therapy based on an FDA-approved test [*see Dosage and Administration (2.1)*].

Consult Request: We request ophthalmology reviewer to assist with review of the ocular disorder data associated with mirvetuximab, including the proposed plan to include Ocular disorders in W&P section 5.1 of product labeling. The safety reviewer for the clinical team is Asma Dilawari; Mirat Shah is the efficacy reviewer. Once consultant is assigned, the clinical team would like to meet to discuss review plans and answer any questions to assist in conducting the consultation. EDR: \\CDSESUB1\evsprod\BLA761310\0001
Planning meeting: April 8, 2022. Filing meeting: May 5, 2022

Clinical Studies:

Study IMGN853-0401: First-In-Human Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of IMGN853 in Adults with Ovarian cancer and Other FOLR-1-Positive Solid Tumors

Open-label, Phase 1, non-randomized, safety, PK, and pharmacodynamic study of mirvetuximab soravtansine in adult patients with solid tumors that had relapsed and were refractory to standard therapies. The estimated study duration was intended to be approximately 50 months for patient accrual, dosing, and follow-up. Approximately 209 patients were planned to be enrolled in the study. The study consisted of a dose-escalation phase that evaluated 2 dosing schedules of mirvetuximab soravtansine and up to 5 dose-expansion groups at the MTD. The primary intent of dose escalation was to evaluate the safety and tolerability of mirvetuximab soravtansine, to identify the MTD, and to characterize the PK profile of mirvetuximab soravtansine when administered IV on 2 dosing schedules:

Schedule A (Q3W): The dose was escalated as detailed in Section 9.1.1.1. Once the MTD was identified (6 mg/kg Q3W adjusted ideal body weight [AIBW]), enrollment to MTD dose expansion Cohorts 1 and 2 began. The use of Schedule A in Cohorts 3, 4, and 5 was determined after the CRC reviewed the data for both dosing regimens.

Schedule B (modified weekly): The dose was escalated as detailed in Section 9.1.1.3. The MTD was determined to be 2.0 mg/kg (AIBW). The CRC reviewed safety, PK, and anti-tumor activity data from the dose-escalation cohorts, as well as available data from patients treated on Schedule A.

Ophthalmologic Exclusion Criteria
Any active or chronic corneal disorder, including but not limited to the following: Sjogren's syndrome, Fuchs corneal dystrophy (requiring treatment), history of corneal transplantation, active herpetic keratitis, and also active ocular conditions requiring ongoing treatment/monitoring, such as wet age-related macular degeneration requiring intravitreal injections, active diabetic retinopathy with macular edema, presence of papilledema, or acquired monocular vision.

Lubricating Artificial Tears
Beginning with Protocol Amendment 7, patients were required to use preservative-free, lubricating artificial tears on a daily basis, as directed by the product label or the treating physician.

Corticosteroid Eye Drops
All patients enrolled in Cohort 5 were required to self-administer corticosteroid eye drops (1% prednisolone; Pred Forte® or generic equivalent) during active study treatment. Patients recorded their eye drop administration in a patient diary, which was entered on the eCRF.

Table 39: Treatment-Related TEAEs by SOC and PT Occurring in >10% Patients, per SOC, in Patients with EOC, Platinum Resistant EOC, IMGN853-0403 Eligible EOC, and Endometrial Cancer (Safety Population - Expansion)

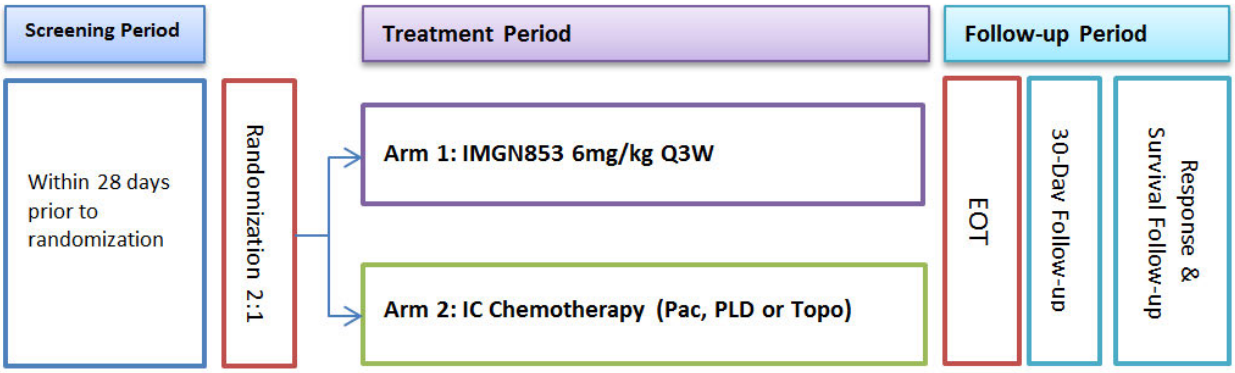
System Organ Class Preferred Term	All EOC Patients (n=113)	Pt Resistant EOC Patients (n=96)	IMGN853 0403-Eligible EOC Patients[a] (n=36)	Endometrial Cancer Patients (n=24)
Eye disorders	66 (58)	57 (59)	21 (58)	10 (42)
Vision blurred	48 (42)	40 (42)	13 (36)	6 (25)
Dry eye	17 (15)	15 (16)	6 (17)	4 (17)
Keratopathy	16 (14)	13 (14)	2 (6)	2 (8)
Keratitis	12 (11)	8 (8)	3 (8)	2 (8)
Punctate keratitis	10 (9)	10 (10)	1 (3)	1 (4)
Corneal epithelial microcysts	7 (6)	7 (7)	4 (11)	1 (4)

Study IMGN853-0403: Title: FORWARD 1: A Randomized, Open-label Phase 3 Study to Evaluate the Safety and Efficacy of Mirvetuximab Soravtansine (IMGN853) Versus Investigator's Choice of Chemotherapy in Women with Folate Receptor α−positive Advanced Epithelial Ovarian Cancer, Primary Peritoneal Cancer or Fallopian Tube Cancer

Approximately 333 patients were to be randomized 2:1, MIRV (Arm 1) to IC chemotherapy (Arm 2). Patients enrolled in Arm 1 received MIRV at 6 mg/kg AIBW administered IV on Day 1 of a 3-week cycle. Patients in Arm 2 received a dose of IC chemotherapeutic agent calculated using body surface area (BSA).

- Paclitaxel administered at 80 mg/m^2 as a 1-hour IV infusion on Days 1, 8, 15, and 22 of a 4-week cycle; OR
- Topotecan administered at 4 mg/m^2 over 30 minutes on Days 1, 8, and 15 of a 4-week cycle. Alternatively, topotecan could have been administered at 1.25 mg/m^2 over 30 minutes on Days 1 to 5 of a 3-week cycle; OR
- Pegylated liposomal doxorubicin administered at 40 mg/m^2 as a 1 mg/min IV infusion on Day 1 of a 4-week cycle. After Cycle 1, if tolerated, pegylated liposomal doxorubicin could have been administered as a 1-hour infusion.

Phase 3 Study Design Schema



Abbreviations: EOT = end of treatment, IC=Investigator' choice, Pac=paclitaxel; PLD = pegylated liposomal doxorubicin; Topo = topotecan.

Schedule of Clinical Assessments: Arm 1 (MIRV) and Arm 2 (IC: Topotecan) – Q3W

Activity	Screening	Cycle 1			Cycle 2			Cycle 3			Cycles ≥ 4		EOT	30-Day Follow-up (+ 14 Days)
		Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 8		
Ophthalmic examinations [h]	•[c]	Every other cycle (from point at which treatment-emergent eye disorder was first reported) [h]											•[h]	•[h]
Ocular symptom assessment [i]	•[c]	•			•			•			•		•	•
MIRV administration, Arm 1		•			•			•			•			
Topotecan administration, Arm 2		•[l]			•[l]			•[l]			•[l]			
AE and SAE assessments	•	•	•	•	•	•	•	•	•	•	•		•	•
Record concomitant medications	•	•	•	•	•	•	•	•	•	•	•		•	•

Abbreviations: AE = adverse event; MIRV = mirvetuximab soravtansine; SAE = serious adverse event.

[c] Within 14 days before the start of Cycle 1 Day 1.

[h] Baseline ophthalmic exams will be performed by an ophthalmologist within 14 days before first dose and will include the following: visual acuity (with/without corrective lens; whichever best reflects the patient's usual functioning), slit lamp examination, intraocular pressure measurement, Schirmer test, and indirect fundoscopy. All patients will have a complete ophthalmologic exam performed at the EOT visit or 30-Day Follow-up visit.

[i] Ocular symptom assessment will be performed before the start of each cycle by the treating physician or other qualified individual. For patients reporting > Common Terminology Criteria for Adverse Events Grade 1 ocular symptoms, treatment will be held until the patient is evaluated by an ophthalmologist for a complete examination.

[l] Topotecan administered daily on Days 1-5; no assessments performed on Days 2-5.

Schedule of Clinical Assessments: Arm 2 (IC: Pegylated Liposomal Doxorubicin, Paclitaxel, and Topotecan Q4W

Activity	Screening	Cycle 1			Cycle 2			Cycle 3			Cycles ≥ 4			EOT	30-Day Follow-up (+ 14 Days)
		Day 1	Days 8 and 15	Day 22	Day 1	Days 8 and 15	Day 22	Day 1	Days 8 and 15	Day 22	Day 1	Days 8 and 15	Day 22		
Ophthalmic examinations [i]	•[c]	Every other cycle (from point at which treatment-emergent eye disorder was first reported) [i]												•[i]	•[i]
Ocular symptom assessment [j]	•[c]	•			•			•			•			•	•
Topotecan administration		•			•			•			•				
AE and SAE assessments	•	•	•	•	•	•	•	•	•	•	•			•	•
Record concomitant medications	•	•	•	•	•	•	•	•	•	•	•			•	•

Abbreviations: AE = adverse event; MIRV = mirvetuximab soravtansine; SAE = serious adverse event.

[c] Within 14 days before the start of Cycle 1 Day 1.

[i] Baseline ophthalmic exams will be performed by an ophthalmologist within 14 days before first dose and will include the following: visual acuity (with/without corrective lens; whichever best reflects the patient's usual functioning), slit lamp examination, intraocular pressure measurement, Schirmer test, and indirect fundoscopy. All patients will have a complete ophthalmologic exam performed at the EOT visit or 30-Day Follow-up visit.

[j] Ocular symptom assessment will be performed before the start of each cycle by the treating physician or other qualified individual. For patients reporting > Common Terminology Criteria for Adverse Events Grade 1 ocular symptoms, treatment will be held until the patient is evaluated by an ophthalmologist for a complete examination.

Prophylactic Use of Corticosteroid Eye Drops

Patients receiving MIRV were mandated to use corticosteroid eye drops as prescribed by the treating physician unless the risk outweighed the benefit per the ophthalmologist/physician. All patients enrolled were instructed to self-administer 1% prednisolone 6 times daily on Days 1 through 4, and 4 times daily on Days 5 through 8 of each cycle during the study. For individual patients who could not tolerate the preservative contained in 1% prednisolone, other corticosteroid eye drops may have been substituted and administered on Days 1 through 8 of each cycle at a frequency prescribed by the ophthalmologist.

Reviewer's Comments: *Topical ophthalmic corticosteroids are labeled to be used only after examination of the cornea with magnification such as a slit lamp (first Rx and every refill) and, if used for more than 10 days, to have intraocular pressure checked on a regular basis.*

Lubricating Artificial Tears

Patients receiving MIRV were mandated to use preservative-free, lubricating artificial tears on a daily basis (as directed by the product label or the treating physician). Patients were advised to wait at least 15 minutes after corticosteroid eye drop administration before administering lubricating eye drops.

Reviewer's Comments: *Acceptable.*

Ocular Symptom Assessment and Ophthalmic Examination

Ocular symptom assessment was performed by the treating physician or other qualified individual. An ophthalmology assessment form was used to assess the patient to enable consistent evaluation. For patients reporting > CTCAE Grade 1 ocular symptoms, treatment was held until the patient was evaluated by an ophthalmologist for a complete examination.

An ophthalmic examination was performed by an ophthalmologist and included the following: distant visual acuity, best corrected visual acuity, slit lamp examination, intraocular pressure measurement, Schirmer test, and indirect fundoscopy. Patients who experienced ocular TEAEs while on study had a complete ophthalmologic exam at the emergence of the symptoms and at every other cycle thereafter.

Reviewer's Comments: *The use of ocular symptoms as the trigger to start performing ophthalmic examinations is not considered sufficient to accurately monitor ophthalmic events. There are multiple ophthalmic events which would not be initially noticed by the patient but could lead to blindness. Elevated intraocular pressure, such as that caused by the use of topical ophthalmic corticosteroids is one example. The use of ocular symptoms as a trigger can also be expected to reduce the reported incidence of ocular adverse events.*

Distant visual acuity is not helpful in assessing visual acuity unless it is a corrected distance visual acuity, preferably best corrected distance visual acuity. Best corrected visual acuity is not helpful in assessing visual acuity in individuals under the age of 40 unless it is best corrected distance visual acuity.

Visual Acuity/IOP/Fundoscopy/ Schirmer's

Shift of Both Eye Best Corrected Visual Acuity from Baseline to Worst Post- baseline – Safety Population

	Worst Post-baseline Categories				
Baseline Categories	**≥20/40**	**<20/40 and ≥20/200**	**≥20/200**	**Missing**	**Total**
MIRV (N=243), n (%)					
≥20/40	93 (38)	12 (5)	0	65 (27)	170 (70)
<20/40 and ≥20/200	0	0	0	1 (<1)	1 (<1)
Missing	18 (7)	2 (1)	0	52 (21)	72 (30)
Total	111 (46)	14 (6)	0	118 (49)	243 (100)
Total IC Chemotherapy (N=109), n (%)					
≥20/40	31 (28)	1 (1)	1 (1)	40 (37)	73 (67)
<20/40 and ≥20/200	0	0	0	1 (1)	1 (1)
Missing	1 (1)	0	0	34 (31)	35 (32)
Total	32 (29)	1 (1)	1 (1)	75 (69)	109 (100)

Abbreviations: IC = investigator's choice; MIRV = mirvetuximab soravtansine. Note: The both eye best corrected visual acuity is categorized ≥ 20/40, < 20/40 and ≥ 20/200, and < 20/200. These categories correspond to ≤ 40, > 40 and ≤ 200, and > 200, respectively. the number of patients in the Safety population. Source: 14.3.10.3.4 and Listing 16.2.9.3.2.

Reviewer's Comments: *Noted on the table are 138 (57%) of the visual acuity measurement entries for MIRV listed as missing.*

Shift Changes in Intraocular Eye Pressure – Safety Population

Category of Highest Right/Left Eye Baseline	**≤22**	**>22**	**Missing**	**Total**
MIRV (N=243), n (%)				
≤22	145 (60)	8 (3)	78 (32)	231 (95)
>22	0	0	1 (<1)	1 (<1)
Missing	7 (3)	1 (<1)	3 (1)	11 (5)
Total	152 (63)	9 (4)	82 (34)	243 (100)
Total IC Chemotherapy (N=109), n (%)				
≤22	50 (46)	0	55 (50)	105 (96)
>22	0	0	0	0
Missing	1 (1)	0	3 (3)	4 (4)
Total	51 (47)	0	58 (53)	109 (100)

IC = investigator's choice; MIRV = mirvetuximab soravtansine. Source: 14.3.10.3.5 and Listing 16.2.9.3.3.

Reviewer's Comments: *Noted on the table are 90 (37%) of the intraocular pressure measurements for MIRV listed as missing.*

Left Eye Fundoscopy

Visit Name	Within Normal Limits	Abnormal, Not Clinically Significant	Abnormal, Clinically Significant
IMGN853 (N=243)			
Screening (N=4)	4 (100%)	0	0
End Of Treatment (N=0)	0	0	0
30-Day Follow Up (N=0)	0	0	0
Total IC Chemo (N=109)			
Screening (N=2)	2 (100%)	0	0
End Of Treatment (N=0)	0	0	0
30-Day Follow Up (N=0)	0	0	0
IC Chemo: Pac (N=32)			
Screening (N=1)	1 (100%)	0	0
End Of Treatment	0	0	0
30-Day Follow Up	0	0	0
IC Chemo: PLD (N=50)			
Screening (N=1)	1 (100%)	0	0
End Of Treatment (N=0)	0	0	0
30-Day Follow Up (N=0)	0	0	0
IC Chemo: Topo (N=27)			
Screening (N=0)	0	0	0
End Of Treatment (N=0)	0	0	0
30-Day Follow Up (N=0)	0	0	0

Right Eye Fundoscopy

Visit Name	Within Normal Limits	Abnormal, Not Clinically Significant	Abnormal, Clinically Significant
IMGN853 (N=243)			
Screening (N=4)	4 (100%)	0	0
End Of Treatment (N=0)	0	0	0
30-Day Follow Up (N=0)	0	0	0
Total IC Chemo (N=109)			
Screening (N=2)	2 (100%)	0	0
End Of Treatment (N=0)	0	0	0
30-Day Follow Up (N=0)	0	0	0
IC Chemo: Pac (N=32)			
Screening (N=1)	1 (100%)	0	0
End Of Treatment	0	0	0
30-Day Follow Up	0	0	0
IC Chemo: PLD (N=50)			
Screening (N=1)	1 (100%)	0	0
End Of Treatment (N=0)	0	0	0
30-Day Follow Up (N=0)	0	0	0
IC Chemo: Topo (N=27)			
Screening (N=0)	0	0	0
End Of Treatment (N=0)	0	0	0
30-Day Follow Up (N=0)	0	0	0

IC = investigator's choice. The number of patients at the visit.Data Source: Listing 16.2.9.2

Reviewer's Comments: *Evaluation of only 4 subjects who have taken IMGN853 does not provide sufficient monitoring of the effects on the fundus.*

Left Eye Dilated Slit Lamp

Visit Name	Within Normal Limits	Abnormal, Not Clinically Significant	Abnormal, Clinically Significant
IMGN853 (N=243)			
Screening (N=4)	4 (100%)	0	0
End Of Treatment (N=0)	0	0	0
30-Day Follow Up (N=0)	0	0	0
Total IC Chemo (N=109)			
Screening (N=2)	1 (50%)	1 (50%)	0
End Of Treatment (N=0)	0	0	0
30-Day Follow Up (N=0)	0	0	0
IC Chemo: Pac (N=32)			
Screening (N=1)	0	1 (100%)	0
End Of Treatment	0	0	0
30-Day Follow Up	0	0	0
IC Chemo: PLD (N=50)			
Screening (N=1)	1 (100%)	0	0
End Of Treatment (N=0)	0	0	0
30-Day Follow Up (N=0)	0	0	0
IC Chemo: Topo (N=27)			
Screening (N=0)	0	0	0
End Of Treatment (N=0)	0	0	0
30-Day Follow Up (N=0)	0	0	0

Right Eye Dilated Slit Lamp

Visit Name	Within Normal Limits	Abnormal, Not Clinically Significant	Abnormal, Clinically Significant
IMGN853 (N=243)			
Screening (N=4)	4 (100%)	0	0
End Of Treatment (N=0)	0	0	0
30-Day Follow Up (N=0)	0	0	0
Total IC Chemo (N=109)			
Screening (N=2)	1 (50%)	1 (50%)	0
End Of Treatment (N=0)	0	0	0
30-Day Follow Up (N=0)	0	0	0
IC Chemo: Pac (N=32)		0	
Screening (N=1)	0	1 (100%)	0
End Of Treatment	0	0	0
30-Day Follow Up	0	0	0
IC Chemo: PLD (N=50)		0	
Screening (N=1)	1 (100%)		0
End Of Treatment (N=0)	0	0	0
30-Day Follow Up (N=0)	0	0	0
IC Chemo: Topo (N=27)		0	
Screening (N=0)	0		0
End Of Treatment (N=0)	0	0	0
30-Day Follow Up (N=0)	0	0	0

Reviewer's Comments: *Evaluation of only 4 subjects who have taken IMGN853 does not provide sufficient monitoring of the effects on ocular structures.*

Left Eye Intraocular Pressure

Visit Name	Within Normal Limits	Abnormal, Not Clinically Significant	Abnormal, Clinically Significant
IMGN853 (N=243)			
Screening (N=4)	4 (100%)	0	0
End Of Treatment (N=0)	0	0	0
30-Day Follow Up (N=0)	0	0	0
Total IC Chemo (N=109)			
Screening (N=2)	2 (100%)	0	0
End Of Treatment (N=0)	0	0	0
30-Day Follow Up (N=0)	0	0	0
IC Chemo: Pac (N=32)			
Screening (N=1)	1 (100%)	0	0
End Of Treatment	0	0	0
30-Day Follow Up	0	0	0
IC Chemo: PLD (N=50)			
Screening (N=1)	1 (100%)	0	0
End Of Treatment (N=0)	0	0	0
30-Day Follow Up (N=0)	0	0	0
IC Chemo: Topo (N=27)			
Screening (N=0)	0	0	0
End Of Treatment (N=0)	0	0	0
30-Day Follow Up (N=0)	0	0	0

Right Eye Intraocular Pressure

Visit Name	Within Normal Limits	Abnormal, Not Clinically Significant	Abnormal, Clinically Significant
IMGN853 (N=243)			
Screening (N=4)	4 (100%)	0	0
End Of Treatment (N=0)	0	0	0
30-Day Follow Up (N=0)	0	0	0
Total IC Chemo (N=109)			
Screening (N=2)	2 (100%)	0	0
End Of Treatment (N=0)	0	0	0
30-Day Follow Up (N=0)	0	0	0
IC Chemo: Pac (N=32)			
Screening (N=1)	1 (100%)	0	0
End Of Treatment	0	0	0
30-Day Follow Up	0	0	0
IC Chemo: PLD (N=50)			
Screening (N=1)	1 (100%)	0	0
End Of Treatment (N=0)	0	0	0
30-Day Follow Up (N=0)	0	0	0
IC Chemo: Topo (N=27)			
Screening (N=0)	0	0	0
End Of Treatment (N=0)	0	0	0
30-Day Follow Up (N=0)	0	0	0

Reviewer's Comments: *Evaluation of only 4 subjects who have taken IMGN853 does not provide sufficient monitoring of the effects on intraocular pressure.*

Left Eye Schirmer Test

Visit Name	Within Normal Limits	Abnormal, Not Clinically Significant	Abnormal, Clinically Significant
IMGN853 (N=243)			
Screening (N=4)	4 (100%)	0	0
End Of Treatment (N=0)	0	0	0
30-Day Follow Up (N=0)	0	0	0
Total IC Chemo (N=109)			
Screening (N=2)	2 (100%)	0	0
End Of Treatment (N=0)	0	0	0
30-Day Follow Up (N=0)	0	0	0
IC Chemo: Pac (N=32)			
Screening (N=1)	1 (100%)	0	0
End Of Treatment	0	0	0
30-Day Follow Up	0	0	0
IC Chemo: PLD (N=50)			
Screening (N=1)	1 (100%)	0	0
End Of Treatment (N=0)	0	0	0
30-Day Follow Up (N=0)	0	0	0
IC Chemo: Topo (N=27)			
Screening (N=0)	0	0	0
End Of Treatment (N=0)	0	0	0
30-Day Follow Up (N=0)	0	0	0

Right Eye Schirmer Test

Visit Name	Within Normal Limits	Abnormal, Not Clinically Significant	Abnormal, Clinically Significant
IMGN853 (N=243)			
Screening (N=4)	4 (100%)	0	0
End Of Treatment (N=0)	0	0	0
30-Day Follow Up (N=0)	0	0	0
Total IC Chemo (N=109)			
Screening (N=2)	2 (100%)	0	0
End Of Treatment (N=0)	0	0	0
30-Day Follow Up (N=0)	0	0	0
IC Chemo: Pac (N=32)			
Screening (N=1)	1 (100%)	0	0
End Of Treatment	0	0	0
30-Day Follow Up	0	0	0
IC Chemo: PLD (N=50)			
Screening (N=1)	1 (100%)	0	0
End Of Treatment (N=0)	0	0	0
30-Day Follow Up (N=0)	0	0	0
IC Chemo: Topo (N=27)			
Screening (N=0)	0	0	0
End Of Treatment (N=0)	0	0	0
30-Day Follow Up (N=0)	0	0	0

Reviewer's Comments: *Evaluation of only 4 subjects who have taken IMGN853 does not provide sufficient monitoring of the effects on tear production.*

Visual Acuity Cont'd

Reviewer's Comments: *The following visual acuity values appear to have been entered into the database in error. An explanation and/or correction should be provided.*

USUBJID	OESEQ	OETESTCD	OEORRES	OESTRESC	OESTRESN	FOCID	VISITNUM	VISIT	OEDTC	OEDY
IMGN853-0403-(b) (6)	1	BCVA	0	0	0	OD	1000	SCREENING	(b) (6)	-3
IMGN853-0403-(b) (6)	18	BCVA	2	2	2	OU	1006.01	UNSCHEDULED 1006.0101		150
IMGN853-0403-(b) (6)	1	BCVA	3	3	3	OD	1000	SCREENING		-7
IMGN853-0403-(b) (6)	2	BCVA	4	4	4	OS	1000	SCREENING		-7
IMGN853-0403-(b) (6)	1	BCVA	5	5	5	OD	1000	SCREENING		-5
IMGN853-0403-(b) (6)	4	BCVA	5	5	5	OU	1000	SCREENING		-5
IMGN853-0403-(b) (6)	1	BCVA	6	6	6	OD	1000	SCREENING		-5
IMGN853-0403-(b) (6)	3	BCVA	6	6	6	OS	1000	SCREENING		-5
IMGN853-0403-(b) (6)	1	BCVA	6	6	6	OD	1994	30-DAY FOLLOW UP		181
IMGN853-0403-(b) (6)	2	BCVA	6	6	6	OS	1994	30-DAY FOLLOW UP		181
IMGN853-0403-(b) (6)	1	BCVA	6	6	6	OD	1000	SCREENING		-5
IMGN853-0403-(b) (6) 8	2	BCVA	6	6	6	OS	1000	SCREENING		-5
IMGN853-0403-(b) (6)	1	BCVA	6	6	6	OD	1000	SCREENING		-8
IMGN853-0403-(b) (6) 9	2	BCVA	6	6	6	OS	1000	SCREENING		-8
IMGN853-0403-(b) (6)	1	BCVA	6	6	6	OD	1000	SCREENING		-13
IMGN853-0403-(b) (6)	2	BCVA	6	6	6	OS	1000	SCREENING		-13
IMGN853-0403-(b) (6)	1	BCVA	6	6	6	OD	1000	SCREENING		-11
IMGN853-0403-(b) (6)	2	BCVA	6	6	6	OS	1000	SCREENING		-11
IMGN853-0403-(b) (6)	1	BCVA	6	6	6	OD	1000	SCREENING		-12
IMGN853-0403-(b) (6)	2	BCVA	6	6	6	OS	1000	SCREENING		-12
IMGN853-0403-(b) (6)	2	BCVA	9	9	9	OD	1994	30-DAY FOLLOW UP		189
IMGN853-0403-(b) (6)	4	BCVA	9	9	9	OS	1994	30-DAY FOLLOW UP		189

Adverse Events:

Ocular Inflammation

IMGN853-0403- (b) (6)	Uveitis	Uveitis	Possibly related	Recovered/Resolved	Grade 1	(b) (6)
IMGN853-0403- (b) (6)	Ocular Inflammation	Uveitis	Not related	Not Recovered/Resolved	Grade 1	
IMGN853-0403- (b) (6)	Sympathetic Uveitis, Both eyes	Sympathetic uveitis	Possibly related	Recovered/Resolved	Grade 2	
IMGN853-0403- (b) (6)	Uveitis, Left eye	Uveitis	Possibly related	Recovered/Resolved	Grade 1	
IMGN853-0403- (b) (6)	Right eye uveitis	Uveitis	Possibly related	Recovered/Resolved	Grade 1	
IMGN853-0403- (b) (6)	Uveitis	Uveitis	Possibly related	Recovered/Resolved	Grade 1	

Reviewer's Comments: *Although the summary text in the application claims that the product does not cause ocular inflammation, ocular inflammation (uveitis) was reported in 4 patients.*

Summary TEAEs Occurring in ≥ 10% of Patients in Any Analysis Population by SOC and PT

System Organ Class	**Study 0417 N=106**	**EOC Patients (6 mg/kg AIBW Q3W) (N=464)**	**All Patients (6 mg/kg AIBW Q3W) (N=488)**
	n (%)	**n (%)**	**n (%)**
Patients with TEAEs	105 (>99)	462 (>99)	486 (>99)
Eye Disorders	63 (59)	283 (61)	295 (60)
Vision Blurred	49 (46)	206 (44)	213 (44)
Keratopathy	32 (30)	126 (27)	128 (26)
Dry Eye	29 (27)	119 (26)	123 (25)
Cataract	19 (18)	69 (15)	70 (14)
Visual Acuity Reduced	4 (4)	61 (13)	61 (13)
Photophobia	18 (17)	59 (13)	59 (12)
Eye Pain	10 (9)	49 (11)	49 (10)

Reviewer's Comments: *With the exception of cataracts, the ocular events are explained by cornea "failings."*

Vision Blurred and Keratopathy TEAEs

	Study 0417 N=106 n (%)	**EOC Patients (6 mg/kg AIBW Q3W) (N=464) n (%)**
Vision Blurred and Keratopathy All Grades	55 (52)	231 (50)
Grade 1	20 (19)	95 (20)
Grade 2	23 (22)	113 (24)
Grade 3	11 (10)	22 (5)
Grade 4	1 (<1)	1 (<1)
Vision Blurred All Grades	49 (46)	206 (44)
Grade 1	23 (22)	100 (22)
Grade 2	19 (18)	92 (20)
Grade 3	7 (7)	14 (3)
Keratopathy All Grades	32 (30)	126 (27)
Grade 1	11 (10)	59 (13)
Grade 2	12 (11)	55 (12)
Grade 3	8 (8)	11 (2)
Grade 4	1 (<1)	1 (<1)
Keratitis All Grades	4 (4)	25 (5)
Grade 1	2 (2)	8 (2)
Grade 2	1 (<1)	15 (3)
Grade 3	1 (<1)	2 (<1)
Punctate Keratitis All Grades	9 (8)	24 (5)
Grade 1	5 (5)	15 (3)
Grade 2	4 (4)	9 (2)
Corneal Epithelial Microcysts All Grades	2 (2)	12 (3)
Grade 1	1 (<1)	8 (2)
Grade 2	1 (<1)	4 (<1)
Corneal Deposits All Grades	1 (<1)	11 (2)
Grade 1	0	7 (2)
Grade 2	0	3 (<1)
Grade 3	1 (<1)	1 (<1)
Corneal Disorder All Grades	1 (<1)	5 (1)
Grade 1	1 (<1)	4 (<1)

	Study 0417 N=106 n (%)	EOC Patients (6 mg/kg AIBW Q3W) (N=464) n (%)
Grade 2	0	0
Grade 3	0	1 (<1)
Corneal Cyst All Grades	0	4 (<1)
Grade 1	0	2 (<1)
Grade 2	0	2 (<1)
Corneal Epithelium Defect All Grades	2 (2)	2 (<1)
Grade 1	2 (2)	2 (<1)
Corneal Opacity All Grades	0	1 (<1)
Grade 1	0	1 (<1)
Keratitis Interstitial All Grades	0	1 (<1)
Grade 1	0	0
Grade 2	0	1 (<1)
Limbal Stem Cell Deficiency All Grades	0	1 (<1)
Grade 1	0	1 (<1)

Abbreviations: AIBW = adjusted ideal body weight; EOC = epithelial ovarian cancer; Q3W = every 3 weeks; SOC = system organ class; TEAE = treatment-emergent adverse event. Keratopathy data reflect grouped PTs, including corneal cyst, corneal deposits, corneal disorder, corneal epithelial microcysts, corneal epithelium defect, corneal erosion, corneal opacity, corneal pigmentation, keratitis, keratitis interstitial, keratopathy, limbal stem cell deficiency, and punctate keratitis. Note: Coding was performed using Med MedDRA (Medical Dictionary for Regulatory Activities), Version 24.0, Data cut-off date for study IMGN853-0401: 13FEB2018; IMGN853-0403: 18MAR2020; IMGN853-0417: 16NOV2021. Source: 5.3.5.3 ISS Table 4.12.1.

Reviewer's Comments: *While reported in the table above, the grading system used for the events is based on symptoms. Symptom based reporting systems for ocular events is misleading because events such as corneal ulcers can be without symptoms until the time that the perforate. Corneal perforation can lead to complete loss of visual function.*

An ophthalmic exam was performed at baseline for all patients enrolled in studies of mirvetuximab soravtansine. Ocular symptoms assessment was performed by the treating physician or other qualified individual before the start of each cycle. For patients reporting NCI-CTCAE Grade > 1 ocular symptoms, treatment was held until the patient was evaluated by an ophthalmologist for a complete examination which was then performed every other cycle thereafter including 30 days beyond end of treatment and/or until resolution (Study 0417). Ocular assessment included questions regarding symptoms, i.e., visual acuity, eye pain, dry eye, or other, and impact on ADLs. Strict protocol-driven guidance for dose delay and reduction was provided to ensure safety and confirm resolution of any eye-related event(s).

Reviewer's Comments: *As identified earlier in this review, very few subjects had dilated slit lamp examination, fundus examination, intraocular pressure examinations or evaluations of tear production.*

Dosing Modifications during Clinical Trials

The most common actions taken for ocular TEAEs (vision blurred and keratopathy) in all patients in the primary analysis population were dose delayed, interrupted, or not given (91 patients; 20%) and dose reduced (54 patients; 12%). Most commonly reported worst outcomes were dose reduced (54 patients; 12%) and dose delayed, interrupted, or not given (42 patients; 9%). No action was taken in 132 patients (28%).

The median time to onset of vision blurred was 41.5 days (range: 1 to 394). The most common actions taken for patients with vision blurred TEAEs were dose delayed, interrupted, or not given (69 patients; 15%) and dose reduced (42 patients; 9%). Most commonly reported worst outcomes were dose reduced (42 patients; 9%) and dose delayed, interrupted, or not given (33 patients; 7%). No action was taken in 129 patients (28%).

The median time to onset of keratopathy was 50.0 days (range: 23 to 394). The most common actions taken for patients with keratopathy TEAEs were dose delayed, interrupted, or not given (54 patients; 12%) and dose reduced (27 patients; 6%). Most commonly reported worst outcomes were dose delayed, interrupted, or not given (30 patients; 6%) and dose reduced (27 patients; 6%). No action was taken in 107 patients (23%).

Severity Grade (NCI-CTCAE v5.0)	**Management**	**Guidelines for MIRV Dose Modifications**
Grade 1	Complete eye exam as outlined in Schedule of Assessments. Monitor for worsening symptoms.	Continue MIRV dosing.
Grade 2	Complete eye exam as outlined in Schedule of Assessments. Repeat complete exam as clinically indicated. Patients should have weekly symptomatic ocular assessments by the investigator until the symptoms resolve to Grade 1 or baseline or are deemed to be irreversible by the investigator.	Hold MIRV dosing until AE has resolved to Grade 1 or better. Patients with ocular symptoms lasting < 14 days may be allowed to resume MIRV at the same dose level. Patients with ocular symptoms lasting ≥ 14 days but no more than 28 days may resume MIRV at one lower dose level. Recurrence of Grade 2 toxicity on subsequent cycles despite best supportive care will require a MIRV dose reduction of one dose level.

Grade 3	Complete eye exam as outlined in Schedule of Assessments. Repeat complete exam as clinically indicated. Patients should have weekly symptomatic ocular assessments by the investigator until the symptoms resolve to Grade 1 or baseline or are deemed to be irreversible by the investigator.	Hold MIRV dosing Patients may be allowed to resume MIRV at a lower dose after AE has resolved to Grade 1 or better within 28 days. Recurrence of Grade 3 toxicity on subsequent cycles despite best supportive care will require a MIRV dose reduction of one dose level.
Grade 4	Complete eye exam as outlined in Schedule of Assessments. Repeat complete exam as clinically indicated. Patients should have weekly symptomatic ocular assessments by the investigator until the symptoms resolve to Grade 1 or baseline or are deemed to be irreversible by the investigator.	Permanently discontinue MIRV.

Reviewer's Comments: *Disagree with the use of NCI-CTCAE for grading ophthalmic adverse events. Grading of ocular events based purely on symptoms can lead to a failure to recognize important ocular events and ultimately lead to significant permanent vision loss.*

The following grading system and dose modification recommendations are recommended for ophthalmic anterior segment findings:

Ocular Adverse Reactions

Adverse Reaction	***Severity***	***Grade***	***Change in dosing***
Corneal keratitis	*Clear cornea, no epithelial defects*	*Grade 0*	*Dosing not interrupted*
Corneal keratitis	*Nonconfluent superficial keratitis*	*Grade 1*	*Dosing not interrupted*
Corneal keratitis	*Confluent superficial keratitis, a cornea epithelial defect, or 3-line or more loss in best corrected distance visual acuity*	*Grade 2*	*Delay dose until resolved to nonconfluent superficial keratitis, then maintain dose.*
Corneal keratitis	*Corneal ulcer or stromal opacity or best corrected distance visual acuity 20/200 or worse*	*Grade 3*	*Delay dose until resolved, then reduce dose by 1 level.*
Corneal keratitis	*Corneal perforation*	*Grade 4*	*Discontinue participant from study treatment*
Iritis	*Clear anterior chamber*	*Grade 0*	*Dosing not interrupted*
Iritis	*Rare cell in anterior chamber*	*Grade 1*	*Dosing not interrupted*

Iritis	*1-2+ Cell or Flare in anterior chamber*	*Grade 2*	*Delay dose until resolved to Grade 0 or 1 and then maintain dose.*
Iritis	*3+ Cell or Flare in anterior chamber*	*Grade 3*	*Delay dose until resolved to Grade 0 or 1, then reduce dose by 1 level.*
Iritis	*Hypopyon*	*Grade 4*	*Discontinue participant from study treatment*

Prophylactic use of topical ophthalmic corticosteroids
Overall, ocular events in the primary analysis population described above were similar in frequency across all analysis populations. Primary prophylactic use of topical corticosteroid eye drops resulted in fewer ocular AE-related dose reductions in patients who received mirvetuximab soravtansine. In Study 0401 Cohorts 1 and 3, where no prophylactic eye drops were used, 15% of patients (11/73) required dose reductions, whereas in Dose Expansion Cohort 5, with primary prophylactic corticosteroid eye drops, 5% of patients (2/40) required dose reductions (5.3.3.2 Study 0401 CSR, Table 14.3.3.11). For this reason, use of prophylactic steroid eye drops was implemented into Study 0403 and Study 0417 and is currently recommended for patients receiving mirvetuximab soravtansine.

Reviewer's Comments: *It is recommended that along with recommending the use of topical ophthalmic corticosteroids, labeling include recommendations that are consistent with the labeling of topical ophthalmic corticosteroid medications including: Topical ophthalmic corticosteroids should be prescribed only after examination of the cornea with magnification such as a slit lamp (first Rx and every refill) and, if used for more than 10 days, intraocular pressure should be checked on a regular basis.*

It was observed that both frequency and severity of ocular TEAEs was not affected by the addition of prophylactic steroid eye drop use initiated in Study 0417 at Day -1 compared with administration beginning on Day 1 in Study 0403. Therefore, the proposed prescribing information will recommend prophylactic steroid eye drop use beginning on Day 1 through Day 8, as was done in Study 0403.

Reviewer's Comments: *No objection.*

Summary Comments

1. *The following visual acuity values appear to have been entered into the database in error. The applicant should provide an explanation and/or correction:*

USUBJID	OESEQ	OETESTCD	OEORRES	OESTRESC	OESTRESN	FOCID	VISITNUM	VISIT	OEDTC	OEDY
IMGN853-0403-(b) (6)	1	BCVA	0	0	0	OD	1000	SCREENING	(b) (6)	-3
IMGN853-0403-(b) (6)	18	BCVA	2	2	2	OU	1006.01	UNSCHEDULED 1006.0101		150
IMGN853-0403-(b) (6)	1	BCVA	3	3	3	OD	1000	SCREENING		-7
IMGN853-0403-(b) (6)	2	BCVA	4	4	4	OS	1000	SCREENING		-7
IMGN853-0403-(b) (6)	1	BCVA	5	5	5	OD	1000	SCREENING		-5
IMGN853-0403-(b) (6)	4	BCVA	5	5	5	OU	1000	SCREENING		-5
IMGN853-0403-(b) (6)	1	BCVA	6	6	6	OD	1000	SCREENING		-5
IMGN853-0403-(b) (6)	3	BCVA	6	6	6	OS	1000	SCREENING		-5
IMGN853-0403-(b) (6)	1	BCVA	6	6	6	OD	1994	30-DAY FOLLOW UP		181
IMGN853-0403-(b) (6)	2	BCVA	6	6	6	OS	1994	30-DAY FOLLOW UP		181
IMGN853-0403-(b) (6)		BCVA	616	616	616			SCREENING		
IMGN853-0403-(b) (6)	2	BCVA	6	6	6	OS	1000	SCREENING		-5
IMGN853-0403-(b) (6)	1	BCVA	6	6	6	OD	1000	SCREENING		-8
IMGN853-0403-(b) (6)	2	BCVA	6	6	6	OS	1000	SCREENING		-8
IMGN853-0403-(b) (6)	1	BCVA	6	6	6	OD	1000	SCREENING		-13
IMGN853-0403-(b) (6)	2	BCVA	6	6	6	OS	1000	SCREENING		-13
IMGN853-0403-(b) (6)	1	BCVA	6	6	6	OD	1000	SCREENING		-11
IMGN853-0403-(b) (6)	2	BCVA	6	6	6	OS	1000	SCREENING		-11
IMGN853-0403-(b) (6)	1	BCVA	6	6	6	OD	1000	SCREENING		-12
IMGN853-0403-(b) (6)	2	BCVA	6	6	6	OS	1000	SCREENING		-12
IMGN853-0403-(b) (6)	2	BCVA	9	9	9	OD	1994	30-DAY FOLLOW UP		189
IMGN853-0403-(b) (6)	4	BCVA	9	9	9	OS	1994	30-DAY FOLLOW UP		189

2. *Visual acuities were measured in each eye separately and both eyes together. The visual acuity of both eyes together is expected to be at least as good as the better seeing eye separately, however there were a number of visits in which this was not the case. The applicant should quality check the values and if necessary provide a correction:*

Patient	*Visit*	*Date of Exam*	*Right Eye*	*Left Eye*	*Both Eyes*
(b) (6)	*UNS*	(b) (6)	*80*	*40*	*50*
	C11d1		*40*	*100*	*50*
	SCR		*20*	*40*	*25*
	EOT		*20*	*10*	*15*

Patient	*Visit*	*Date of Exam*	*Right Eye*	*Left Eye*	*Both Eyes*
(b) (6)	*SCR*	(b) (6)	*40*	*40*	*70*
	SCR		*80*	*40*	*50*
	SCR		*25*	*16*	*20*
	UNS		*40*	*32*	*63*
	C15D1		*100*	*40*	*50*
	UNS		*160*	*40*	*60*
	UNS		*20*	*50*	*25*
	SCR		*32*	*40*	*40*
	SCR		*22*	*22*	*25*
	EOT		*20*	*15*	*20*
	C2D15		*2*	*2*	*30*
	SCR		*40*	*70*	*50*
	SCR		*6*	*10*	*16*
	EOT		*32*	*50*	*50*
	SCR		*40*	*50*	*63*
	EOT		*20*	*80*	*25*
	SCR		*25*	*70*	*40*
	30D FU		*40*	*200*	*50*
	SCR		*100*	*60*	*100*
	30D FU		*10*	*10*	*20*

3. *The use of ocular symptoms as the trigger to start performing ophthalmic examinations is not considered sufficient to accurately monitor ophthalmic events and can reduce the incidence of reported ocular adverse events. There are multiple ophthalmic events which would not be initially noticed by the patient but could lead to blindness. One example is elevated intraocular pressure, such as caused by the use of topical ophthalmic corticosteroids. It is recommended that this procedure not be continued in future clinical trials.*

4. *With the exception of cataracts, the reported ocular events are explained by cornea failings and/or a decrease in tear production. The shift tables for best corrected visual acuity, and intraocular pressure are not interpretable because of the large number of missing values. Assessments of fundoscopy, dilated slit lamp and evaluation of tear production are not interpretable due to the large number of missing values. The following reported ocular adverse events are considered underestimates of the frequency of ophthalmic events that can be expected with use of the product.*

Eye Disorders	>60%
Vision Blurred	>45%
Keratopathy	>25%
Dry Eye	>25%
Visual Acuity Reduced	>15%
Photophobia	>12%
Eye Pain	>10%
Iritis	>1%

5. *The use of NCI-CTCAE for grading ophthalmic adverse events is not recommended. Grading of ocular events based purely on symptoms can lead to a failure to recognize important ocular events. Corneal ulcers for example can be without symptoms until the time that it perforates and ultimately lead to significant permanent vision loss.*

   The following grading system and dose modification recommendations are recommended for ophthalmic anterior segment findings:

Ocular Adverse Reactions

Adverse Reaction	**Severity**	**Grade**	**Change in dosing**
Corneal keratitis	Clear cornea, no epithelial defects	Grade 0	Dosing not interrupted
Corneal keratitis	Nonconfluent superficial keratitis	Grade 1	Dosing not interrupted
Corneal keratitis	Confluent superficial keratitis, a cornea epithelial defect, or 3-line or more loss in best corrected distance visual acuity	Grade 2	Delay dose until resolved to nonconfluent superficial keratitis, then maintain dose.
Corneal keratitis	Corneal ulcer or stromal opacity or best corrected distance visual acuity 20/200 or worse	Grade 3	Delay dose until resolved, then reduce dose by 1 level.
Corneal keratitis	Corneal perforation	Grade 4	Discontinue participant from study treatment
Iritis	Clear anterior chamber	Grade 0	Dosing not interrupted
Iritis	Rare cell in anterior chamber	Grade 1	Dosing not interrupted
Iritis	1-2+ Cell or Flare in anterior chamber	Grade 2	Delay dose until resolved to Grade 0 or 1 and then maintain dose.
Iritis	3+ Cell or Flare in anterior chamber	Grade 3	Delay dose until resolved to Grade 0 or 1, then reduce dose by 1 level.
Iritis	Hypopyon	Grade 4	Discontinue participant from study treatment

6. *Ophthalmic corticosteroids were given as routine care without the appropriate ophthalmic examinations. The use of topical ophthalmic corticosteroids increases the risk of ocular hypertension, glaucoma, corneal melting, corneal perforations and ocular infections. While a decrease in ocular adverse events was observed following the use of topical ophthalmic corticosteroids, the use puts patients at risk from corticosteroid related adverse events. It is recommended that topical ophthalmic corticosteroids continue to be used, but labeling include recommendations that are consistent with the labeling of topical ophthalmic corticosteroid medications including: "Topical ophthalmic corticosteroids should be prescribed only after examination of the cornea with magnification such as a slit lamp (first*

Rx and every refill) and, if used for more than 10 days, intraocular pressure should be checked on a regular basis."

7. *The summary text claims that there were no inflammatory events, however there were reports of uveitis (ocular inflammation) and evidence of remaining cells on the back of the cornea in one patient.*

						(b) (6)
IMGN853-0403-(b) (6)	Uveitis	Uveitis	Possibly related	Recovered/Resolved	Grade 1	
IMGN853-0403-(b) (6)	Ocular Inflammation	Uveitis	Not related	Not Recovered/Resolved	Grade 1	
IMGN853-0403-(b) (6)	Sympathetic Uveitis, Both eyes	Sympathetic uveitis	Possibly related	Recovered/Resolved	Grade 2	
IMGN853-0403-(b) (6)	Uveitis, Left eye	Uveitis	Possibly related	Recovered/Resolved	Grade 1	
IMGN853-0403-(b) (6)	Right eye uveitis	Uveitis	Possibly related	Recovered/Resolved	Grade 1	
IMGN853-0403-(b) (6)	Uveitis	Uveitis	Possibly related	Recovered/Resolved	Grade 1	

It is likely that the incidence would have been much higher if the ophthalmic corticosteroids had not been given.

Wiley A. Chambers, MD
Supervisory Physician, Ophthalmology

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/

WILEY A CHAMBERS
07/08/2022 03:03:17 PM

Memorandum

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

Date: June 30, 2022

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Norman Stockbridge, MD, PhD
Division Director, DCN

To: Alice Lee
DO1

Subject: QT Consult to BLA761310 (SDN 001)

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

This memo responds to your consult to us dated 4/14/2022 regarding the sponsor's proposel label. We reviewed the following materials:

- Previous IRT review(s) for IND 111915 dated 12/20/2018 in DAARTS; and
- Sponsor's proposed labelling (BLA761310/SDN001; link);

1 Responses for the review division

Question from the review division: Review division is asking for our review and comments on the sponsor's proposed labeling for Mirvetuximab

IRT's response: Below are the proposed edits to the sponsor's proposed label in BLA761310/SDN001.

Our changes are highlighted (addition, ~~deletion~~). Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4) *M*irvetuximab soravtansine-xxxx ~~did~~ *does* not cause *a* mean increase~~s~~ *in the QTc interval >*~~10 msec~~ *20 milliseconds* ~~in the QTc interval~~ *at 6 mg/Kg adjusted ideal body weight administered as an intravenous infusion every 3 weeks (the approved recommended dose).*

We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.

2 Internal Comments for the Division

- *None*

3 BACKGROUND

In the previous IRT review of QT effects in Study IMGN853-0401 (IND111915), mirvetuximab soravtansine was found to have no significant QT prolongation effects (i.e., > 20 ms).

In the current BLA 761310, the sponsor has proposed a labelling language on QT effects of mirvetuximab soravtansine in the Cardiac Electrophysiology section of the label.

We have therefore proposed edits to the sponsor's label based on findings from the previous IRT review.

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

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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/

ELIFORD N KITABI
06/30/2022 09:25:14 AM

JOSE VICENTE RUIZ
06/30/2022 09:57:53 AM

NORMAN L STOCKBRIDGE
06/30/2022 10:24:51 AM

LABEL AND LABELING REVIEW

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

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Date of This Review:	June 22, 2022
Requesting Office or Division:	Division of Oncology 1 (DO1)
Application Type and Number:	BLA 761310
Product Name, Dosage Form, and Strength:	Elahere (mirvetuximab soravtansine-xxxx)[a] injection, 100 mg/20 mL (5 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Immunogen Inc.
FDA Received Date:	March 28, 2022 and May 13, 2022
OSE RCM #:	2022-640
DMEPA 2 Safety Evaluator:	Sarah Thomas, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD, BCCCP

[a] The nonproprietary name for this BLA has not yet been determined; therefore, the placeholder, mirvetuximab soravtansine-xxxx, is used throughout this review to refer to the nonproprietary name for this product.

1 REASON FOR REVIEW

As part of the approval process for Elahere (mirvetuximab soravtansine-xxxx) injection, the Division of Oncology 1 (DO1) requested that we review the proposed Elahere prescribing information (PI), medication guide (MG), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Review

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

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the proposed container label and carton labeling, as well as the proposed PI and MG for Elahere identified areas where the label and labeling may be improved to promote the safe use of the product.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed Elahere PI, MG, container label and carton labeling may be improved to promote the safe use of the products as described in Sections 4.1 and 4.2.

4.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 1 (DO1)

A. General Recommendations

1. Since the proposed product is considered an "injection", we recommend revising the dosage form presentation from (b) (4) to "injection" across the labeling.

B. Prescribing Information

1. Dosage and Administration Section, Highlights

    a. We recommend revising the route of administration statement (b) (4) (b) (4) to specify that the proposed product should be diluted prior to intravenous infusion, as follows: "Administer Elahere as an intravenous infusion only after dilution in 5% Dextrose Injection, USP." Additionally, consider removing the statement, (b) (4) (b) (4) We recommend this revision due to post-marketing reports that negative statements (b) (4) may have the opposite of the intended meaning (b) (4) (b) (4) and the warning may be misinterpreted as an affirmative action.[b]

    b. We recommend adding the following statement at the end of the Highlights, Dosage and Administration section to alert the end-user that there is additional preparation and administration instructions and dosage modifications for adverse reactions provided in the Dosage and Administration section of the full PI: "See full Prescribing Information for preparation and administration instructions and dose modifications for adverse reactions."

2. Dosage and Administration Section, Full PI

    a. We recommend replacing the "IV" and "PO" abbreviations with the routes of administration "intravenous" and "oral", respectively, in Table 1, as the routes of administration should generally be described without abbreviation.[c]

    b. Clarify if the dose reduction doses provided in Table 2 should be administered once every 3 weeks (21-day cycle) as an intravenous infusion similar to the recommended dose. If so, we recommend adding this as a footnote to Table 2 or alternatively in the introductory sentence in Section 2.4.

    c. See Appendix G.3 for edits to Section 2.5 of the full PI, Instructions for Preparation and Administration. Proposed edits are recommended to reduce redundancy, improve readability, remove negative or non-

[b] Institute for Safe Medication Practices. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Med Saf Alert Acute Care. 2010;15(16):1-3.
[c] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2022. Available from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors

affirmative statements that can be misinterpreted[d], and clearly describe routes of administration without abbreviation[e].

3. How Supplied/Storage and Handling Section

   a. We recommend adding the mg/mL concentration (5 mg/mL) after the 100 mg/20 mL strength[f] in section 16, in accordance with USP General Chapter <7> Labeling. Additionally, consider revising the format of the How Supplied section as follows for improved readability:

      Each ELAHERE (mirvetuximab soravtansine-xxxx) injection carton (NDC XXXXX-XXX-XX) contains:

      - One single-dose vial containing 100 mg of mirvetuximab soravtansine-xxxx in 20 mL (5 mg/mL) of clear to slightly opalescent, colorless to slightly brown or slightly yellow sterile solution

   b. We note instructions in Section 16 to store vials in the original carton in order to protect from light. Clarify whether or not the intravenous infusion bag containing the diluted Elahere product needs to be protected from light as well during storage and administration. If so, we recommend providing instruction for this in Section 2.

4. Patient Counseling Information Section

   a. We note (b) (4) in the first sentence of the Patient Counseling Information, when we only note a Medication Guide was submitted (b) (4) We recommend deleting (b) (4) (b) (4)

C. Medication Guide (MG)

1. We recommend removing the statement (b) (4) in the first bullet under the section "How will I receive ELAHERE?" since this is a potentially misleading statement, as it is not all encompassing and can be confusing (b) (4) (b) (4)

[d] Institute for Safe Medication Practices. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Med Saf Alert Acute Care. 2010;15(16):1-3.

[e] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2022. Available from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors

[f] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2022. Available from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors

4.2 RECOMMENDATIONS FOR IMMUNOGEN INC.

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

A. General Comments (Container label & Carton Labeling)

1. We note the nonproprietary name "mirvetuximab soravtansine-xxxx" is difficult to read on the principal display panel of the container label and carton labeling. We recommend adjusting the color, font, and/or increase the font size of the nonproprietary name to increase readability.[g]
2. We recommend adding the statement "Dispense the enclosed Medication Guide to each patient." prominently displayed on the principal display panel (PDP) of the container label, if space allows, and the carton labeling in accordance with 21 CFR 208.24(d).
3. We recommend replacing the warning (b) (4) with "Warning: Hazardous Drug", in order to ensure consistency with the similar warning present in Section 16 of the PI.
4. Ensure the presentation of the nonproprietary name is provided as "mirvetuximab soravtansine-xxxx" across the label and labeling.
5. Since the proposed product is considered an "injection", we recommend revising the dosage form presentation from (b) (4) to "injection" across the label and labeling.
6. We recommend revising the statement (b) (4) (b) (4) to the following, in order to ensure consistency with the PI: "For Intravenous Infusion after Dilution in 5% Dextrose Injection, USP".
7. We recommend revising the storage instructions (b) (4) (b) (4) (b) (4) (on carton labeling) to the following, in order to ensure consistency with the storage information presented in the PI: "Store vial upright in a refrigerator at 2°- 8°C (36°- 46°F) and in the original carton in order to protect from light." In addition, we recommend bolding this statement to increase the prominence of this important information and minimize the risk of the storage information being overlooked.
8. To ensure consistency with the PI, we recommend revising the (b) (4) statement on the container label and carton labeling ("Dosage: See Prescribing

[g] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2022. Available from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors

Information.") to the following: "Recommended Dosage: See prescribing information.".

9. We recommend presenting the proprietary name, proper name, and dosage form on the container label and carton labeling similar to the example below with the dosage form located below the proper name[h], followed by the strength statement:

ELAHERE

mirvetuximab soravtansine-xxxx

Injection

10. Consider adjusting the presentation of the concentration 100 mg/20 mL (5 mg/mL) to ensure the quantity per total volume (100 mg/20 mL) is the primary and prominent expression on the principal display panel (PDP) by bolding or by some other means of increasing prominence, followed in close proximity by the quantity per milliliter enclosed by parenthesis.[i] For example,

100 mg/20 mL

(5 mg/mL)

B. Container Label

1. Clarify if the barcode in the following image is the linear barcode containing the NDC number:

If so, ensure the barcode is surrounded by sufficient white space to allow scanners to correctly read the barcode in accordance with 21 CFR 201.25(c)(i).

[h] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2022. Available from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors

[i] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2022. Available from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Elahere received on May 13, 2022 from Immunogen Inc.

Table 2. Relevant Product Information for Elahere	
Initial Approval Date	N/A
Nonproprietary Name	mirvetuximab soravtansine-xxxx
Indication	Treatment of adult patients with FRα positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received one to three prior systemic treatment regimens. Select patients for therapy based on the presence of FRα tumor expression using an FDA-approved test.
Route of Administration	intravenous
Dosage Form	injection
Strength	100 mg/20 mL (5 mg/mL)
Dose and Frequency	The recommended dose of ELAHERE is 6 mg/kg adjusted ideal body weight administered (b) (4) (b) (4) until disease progression or unacceptable toxicity. The total dose of ELAHERE is calculated based on each patient's AIBW using the following formula: AIBW = Ideal Body Weight (IBW [kg]) + 0.4*(Actual weight (kg) – IBW) Female IBW (kg) = 0.9*height(cm) – 92 See Section 2.4 for dose modifications for adverse reactions.
How Supplied	(b) (4)
Storage	Store ELAHERE vials upright in a refrigerator at (2°- 8°C) (36°-46°F) until the time of preparation. *Do not freeze or shake.* (b) (4)
Container Closure	20 mL (b) (4) clear (b) (4) glass vial, stopper, and an over-seal

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[j] along with postmarket medication error data, we reviewed the following Elahere label and labeling submitted by Immunogen Inc.

- Container label received on March 28, 2022
- Carton labeling received on March 28, 2022
- Prescribing Information (Image not shown) received on May 13, 2022, available from \\CDSESUB1\evsprod\bla761310\0008\m1\us\114-label\1141-draft-label\draft-labeling-text-word.docx
- Medication Guide received on March 28, 2022, available from \\CDSESUB1\evsprod\bla761310\0001\m1\us\114-label\1141-draft-label\medication-guide-word.docx

G.2 Label and Labeling Images

Container Label

(b) (4)

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

3 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

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