CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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MULTI-DISCIPLINE REVIEW

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

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Biologics License Application (BLA), 351 (a)
Application Number(s)	761310
Priority or Standard	Priority
Submit Date(s)	March 28, 2022
Received Date(s)	March 28, 2022
PDUFA Goal Date	November 28, 2022
Division/Office	DO1/OOD/OND/CDER
Review Completion Date	*Electronic Stamp Date*
Established/Proper Name	Mirvetuximab soravtansine-gynx
(Proposed) Trade Name	Elahere™
Pharmacologic Class	Antibody-drug conjugate
Applicant	ImmunoGen, Inc.
Doseage form	Injection: 100 mg/20 mL (5 mg/mL) solution in single dose vial
Applicant proposed Dosing Regimen	6 mg/kg adjusted ideal body weight (AIBW) intravenous infusion every 3 weeks
Applicant Proposed Indication(s)/Population(s)	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
Recommendation on Regulatory Action	*Accelerated Approval*
Recommended Indication(s)/Population(s) (if applicable)	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 upon an FDA-approved test.
Recommended Dosing Regimen	6 mg/kg adjusted ideal body weight (AIBW) intravenous infusion every 3 weeks

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations

OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

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OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Mirvetuximab soravtansine-gynx is a folate receptor-alpha (FRα)- directed antibody-drug conjugate (ADC). It contains a chimeric IgG1 directed against FRα, a cleavable linker, and a DM4 payload. DM4 is a microtubule-disrupting agent. This product is not approved for any indication worldwide.

The Applicant proposed the following indication for BLA 761310:

[TRADENAME] is indicated for the 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.

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

The recommended indication for accelerated approval is:

ELAHERE™ is indicated for the 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.

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

The recommended dose of mirvetuximab soravtansine is 6 mg/kg adjusted ideal body weight (AIBW) administered once every 3 weeks (21-day cycle) as an intravenous infusion 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

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends accelerated approval of mirvetuximab soravtansine-gynx for treatment of patients with FRα-positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received one to three prior systemic treatment regimens, in accordance with 21 Code of Federal Regulations (CFR) Part 601.41, Subpart E for Biological Products Licensing Regulations. This recommendation is primarily based on efficacy and safety data from Study 0417 (SORAYA, NCT04296890), a single arm trial in 106 patients with FRα-positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who had received one to three prior systemic regimens. To be eligible, patients had to have tumor tissue with "high" expression for FRα, which was determined by the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay. All patients were also required to and did receive prior bevacizumab. Patients received mirvetuximab soravtansine-gynx 6 mg/kg (based on AIBW) as an intravenous infusion every 3 weeks until disease progression or unacceptable toxicity. Tumor response assessments occurred every 6 weeks for the first 36 weeks and every 12 weeks thereafter.

The major efficacy outcome measures were confirmed overall response rate (ORR) as assessed by investigator according to response evaluation criteria in solid tumors (RECIST) v1.1 and duration of response (DOR). The efficacy evaluable population included 104 patients with platinum-resistant disease, who had measurable disease, and received at least one dose of ELAHERE. Confirmed ORR by investigator was 31.7% (95% CI: 22.9, 41.6). Median DOR was 6.9 months (95% CI: 5.6, 9.7), with a 4.8% complete response rate and a 26.9% partial response rate. Response assessment results using independent radiology review were consistent with investigator assessment.

Available therapies in this treatment setting are limited to single agent chemotherapies with ORRs ranging from 6-27%. However, these data were collected prior to establishment of a platinum-based doublet ± bevacizumab followed by maintenance treatment with bevacizumab and/or a poly(ADP-ribose) polymerase (PARP) inhibitor as standard of care for advanced ovarian cancer. More contemporary data suggest available chemotherapies have ORRs of 12-13% and median DORs of 4-7.4 months, and these data come from clinical trials where patients were less heavily pre-treated than those patients enrolled to Study 0417. It is also notable that the patient population enrolled into Study 0417 was a biomarker-defined population with FRα-expressing tumors. To date, there are no other available therapies for patients with ovarian cancer which target this biomarker.

Mirvetuximab soravtansine-gynx demonstrated acceptable tolerability for the indicated population with a serious and life-threatening disease. The most common adverse reactions (≥20 %) including laboratory abnormalities, were vision impairment, fatigue, increased aspartate aminotransferase, nausea, increased alanine aminotransferase, keratopathy, abdominal pain, decreased lymphocytes, peripheral neuropathy, diarrhea, decreased albumin,

constipation, increased alkaline phosphatase, dry eye, decreased magnesium, decreased leukocytes, decreased neutrophils, and decreased hemoglobin. Serious adverse reactions occurred in 31% of patients receiving mirvetuximab soravtansine-gynx, including intestinal obstruction (8%), ascites (4%), infection (3%), and pleural effusion (3%). Fatalities due to adverse reactions occurred in 2% of patients including small intestinal obstruction (1%) and pneumonitis (1%).

Ocular toxicity is an important safety signal related to mirvetuximab soravtansine-gynx. Ocular adverse reactions occurred in 61% of patients with ovarian cancer treated with mirvetuximab soravtansine-gynx. Nine percent (9%) of patients experienced Grade 3 ocular adverse reactions, including visual impairment, keratopathy/keratitis, dry eye, photophobia, and eye pain; and one patient (0.2%) experienced Grade 4 keratopathy. The prescribing information recommends premedication and use of lubricating and ophthalmic topical steroids eye drops during treatment with mirvetuximab soravtansine-gynx. The prescribing information also includes a Boxed Warning to advise health professionals of the risk of ocular toxicity. FDA will issue a postmarketing requirement to further characterize the incidence and severity of mirvetuximab soravtansine-related ocular adverse events and evaluate additional risk mitigation strategies for ocular adverse events.

There was limited dosage exploration for mirvetuximab soravtansine, and the product was associated with a high frequency of ocular toxicity. A different dosing schedule may have a more optimal benefit-risk profile. FDA will issue a dose-finding postmarketing requirement for evaluation of alternate dosing schedules.

A Pre-Market Approval (PMA) Application (PMA P220006) was submitted to CDRH for the Ventana FOLR1 (FOLR-2.1) RxDx Assay. The PMA will receive contemporaneous approval with the current BLA as a companion diagnostic device to identify patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer for treatment with mirvetuximab soravtansine-gynx.

Study 0416 (MIRASOL) is an ongoing randomized Phase 3 trial comparing mirvetuximab soravtansine to investigator's choice chemotherapy in patients with FRα-positive, platinum-resistant, epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received 1-3 prior lines of systemic therapy. FDA requested blinded topline interim ORR/DOR data from Study 0416, . These ORR/DOR data were supportive of the results from Study 0417.

The results of this study will serve to confirm the benefit of mirvetuximab soravtansine for this indication.

Overall, the benefit-risk profile based upon results from Study 0417 was favorable. Based on review of this application, as well as the current therapeutic landscape, the review team concludes that mirvetuximab soravtansine-gynx represents a new treatment option for patients with FRα-positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal

cancer, who have received one to three prior systemic treatment regimens. The ORR of 31.7% with a median duration of 6.9 is a surrogate endpoint that is reasonably likely to predict clinical benefit (i.e., improved survival or progression free survival) in patients with FRα-positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who had received one to three prior systemic regimens cancer. This patient population has a significant unmet medical need for better treatment options.

Therefore, the FDA review team recommends granting accelerated approval to mirvetuximab soravtansine-gynx for the following indication:

ELAHERE is a folate receptor alpha (FRα)-directed antibody and microtubule inhibitor conjugate indicated for treatment of adult patients with FRα positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cacner, who have received one to three prior systemic treatment regimens. Select patients for therapy based upon an FDA-approved test.

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

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Ovarian cancer, including fallopian tube and primary peritoneal cancer, is the fifth leading cause of cancer-related death for women in the United States. There will be an estimated 19,880 new cases of ovarian cancer and 12,810 deaths from ovarian cancer in the U.S. in 2022. Unfortunately, there is no recommended screening for ovarian cancer for the general population, and ovarian cancer is often diagnosed at an advanced stage. Five-year overall survival (OS) is only 49%.

Initial treatment for patients with advanced ovarian cancer is typically surgery and (neo)adjuvant chemotherapy with a platinum-based doublet ± bevacizumab. Patients who experience a complete response (CR) or partial response (PR) may be candidates for maintenance treatment with bevacizumab and/or a PARP inhibitor. Although most advanced ovarian cancer is initially platinum sensitive, virtually all patients ultimately develop platinum-resistant disease which is associated with a limited overall survival and few treatment options.

Patients with platinum-resistant ovarian cancer who have received only 1-2 prior lines of systemic treatment and who have not previously received bevacizumab may be candidates to receive bevacizumab in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin (PLD). If patients cannot receive this regimen, or after progression of disease on this regimen, treatment options are limited to single agent chemotherapy with paclitaxel, topotecan, PLD, gemcitabine, or other options. Historical data suggest that single agent chemotherapies have ORRs ranging from 6-27%. However, these data were collected prior to establishment of a platinum-based doublet ± bevacizumab followed by maintenance treatment with bevacizumab and/or a PARP inhibitor as standard of care for advanced ovarian cancer. More contemporary data suggest available chemotherapies have ORRs of 12-13% and median DORs of 4-7.4 months. In addition, a unique aspect of mirvetuximab soravtansine-gynx is that it targets FRα, and its activity is enhanced in tumors with higher levels of FRα expression. To this end, there are currently no other available therapies for ovarian cancer which target tumors overexpressing FRα.

The efficacy and safety assessment for mirvetuximab soravtansine-gynx was primarily based on results from SORAYA, a single-arm international trial which enrolled 106 patients with FRα-positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer. Patients had received 1-3 prior lines of therapy and all patients had received

prior bevacizumab. Patients were selected for treatment if their tumors were positive for FRα expression according to the Ventana FOLR1 (FOLR1-2.1) CDx assay. Patients received mirvetuximab soravtansine-gynx 6 mg/kg intravenously every 3 weeks until disease progression or unacceptable toxicity. Tumor response assessments occurred every 6 weeks for the first 36 weeks and every 12 weeks thereafter. The primary endpoint was confirmed ORR assessed by investigator according to RECIST v1.1. DOR was a secondary endpoint.

There were 104 patients in the efficacy evaluable population for SORAYA. Study 0417 enrolled 96% White patients, 2% Asian patients, and 2% of patients with race not reported. Only 2% of patients were Hispanic or Latino. The patient population was not representative of a U.S.-based population with platinum-resistant ovarian cancer, with respect to race and ethnicity. Because of this, FDA issued a post-marketing commitment (PMC) for the Applicant to characterize the safety and efficacy of mirvetuximab soravtansine-gynx in patients from racial and ethnic minority groups. Regarding baseline disease characteristics and prior therapies, the Study 0417 population was representative of a U.S.-based population with platinum-resistant ovarian cancer. All patients had high-grade serous cancer, and 51% of patients had visceral metastases. Ten percent of patients had received 1 prior line of systemic therapy, 39% of patients had received 2 prior lines of systemic therapy, and 50% of patients had received 3 prior lines of systemic therapy. Thirty-eight percept of patients had received prior treatment in the platinum-resistant setting. All patients had received prior bevacizumab, and 49% of patients had received a PARP inhibitor.

Confirmed ORR assessed by investigator according to RECIST v1.1 was 31.7% (95% CI: 22.9, 41.6) and median DOR was 6.9 months (95% CI: 5.6, 9.7). Confirmed ORR and DOR assessed by BICR were generally consistent with the results per investigator. In addition, FDA requested blinded topline ORR/DOR data from Study 0416, an ongoing randomized trial in a similar treatment setting to Study 0417. Study 0416 is fully enrolled. These ORR/DOR data were supportive of the results from Study 0417.

The safety profile of mirvetuximab soravtansine-gynx is generally reflective of the maytansinoid DM4 payload, which is an antimitotic agent that inhibits tubulin polymerization and microtubule assembly, resulting in cell cycle arrest and apoptosis. The main target organs for mirvetuximab soravtansine-gynx-associated toxicity include the eyes, lungs, and peripheral nerves. Fatal adverse reactions occurred in 2% of patients of the 106 patients that made up the safety population on Study 0417 and included pneumonitis and small intestinal obstruction. Serious adverse reactions occurred in 31% of patients and included intestional obstruction (8%), ascites (4%), infection (3%), and pleural effusion (3%). The most common adverse reactions (≥20%) included vision impairment, fatigue, transaminase elevation, keratopathy,

abdominal pain, decreased lymphocytes, peripheral neuropathy, diarreha, decreased albumin, constipation, increased alkaline phosphatase, dry eye, decreased magnesium, decreased leukocytes, decreased neutrophils, and decreased hemoglobin Adverse reactions leading to dose discontinuation occurred in 11% of patients, adverse reactions leading to dose interruptions occurred in 39% of patients and adverse reactions leading to dos reduction occurred in 20% of patients.

Ocular toxicity is an important safety signal associated with mirvetuximab soravtansine-gynx and affected 61% of patients enrolled to Study 0417, including 9% of patients experiencing grade 3 ocular adverse reactions and one patient who experienced grade 4 keratopathy. There is a Boxed Warning for ocular toxicity in the mirvetuximab soravtansine USPI to alert providers to the risk of developing severe ocular toxicities, including visual impairment, keratopathy, dry eye, photophobia, eye pain, and uveitis. Patients should adhere to the premedication and required eye care plan outlined in the USPI, and should be promptly referred to an eye care professional for any new or worsening ocular symptoms.

Other important safety signals associated with mirvetuximab soravtansine include pneumonitis, peripheral neuropathey, and risk of embryo-fetal toxicity, which are listed under Warnings and Precautions in the USPI.

Patients with platinum-resistant ovarian cancer, particularly those who have received prior bevacizumab, have limited treatment options consisting of single agent chemotherapies. Contemporary data suggesting these therapies have ORRs of 12-13% and median DORs of 4-7.4 months. Considering the limited therapeutic options for patients with platinum-resistant ovarian cancer who have received bevacizumab, along with the results from Study 0417, and ORR/DOR data from Study 0416, the review team considers that the efficacy of mirvetuximab soravtansine represents a meaningful advantage compared to available therapies, and these results are reasonably likely to predict clinical benefit. Safety and tolerability of mirvetuximab soravtansine-gynx were acceptable for a patient population with a serious and life-threatening illness and limited treatment options. Adverse reactions are manageable through pretreatment, supportive care, and labeling, including a Boxed Warning for ocular toxicity.

Overall, the benefit-risk assessment for mirvetuximab soravtansine-gynx is favorable. There is a post-marketing requirement (PMR) to submit results from the ongoing randomized trial, Study 0416, for confirmation of clinical benefit. This trial is comparing mirvetuximab soravatansine to investigator's choice chemotherapy in patients with FRα-positive, platinum-resistant, epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received 1-3 prior lines of

systemic therapy.

Patients should be selected for treatment with mirvetuximab soravtansine-gynx according to the Ventana FolR1 (FOLR-2.1) RxDx Assay. The assay is an Immunohistochemistry (IHC) assay indicated to select patients with epithelial ovarian, fallopian tube, or pirmaty peritoneal cancer whose tumor cells display membrane staining for the folate receptor alpha (FOLR1) at moderate and/or strong intensity levels (≥75% viable tumor cells with membrane staining). The PMA P220006 for the VENTANA FOLR1 (FOLR-2.1) RxDx Assay will be contemporaneously approved by CDRH with the BLA for mirvetuximab soravtansine-gynx.

Mirvetuximab soravtansine-gynx is recommended for accelerated approval as follows:
Mirvetuximab soravtansine is a folate receptor alpha (FRα)-directed antibody and microtubule inhibitor conjugate indicated for the 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 an FDA-approved test.

Table 1 FDA Benefit-Risk Assessment for Mirvetuximab Soravtansine

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Ovarian cancer, including fallopian tube and primary peritoneal cancer, is the fifth leading cause of cancer-related death for women in the United States. • There are 19,880 new cases of ovarian cancer and 12,810 deaths from ovarian cancer estimated in the US for 2022. • Ovarian cancer is often diagnosed at an advanced stage and has only a 49% five-year overall survival. • Almost all patients with advanced ovarian cancer develop platinum-resistant disease which is incurable and has a poor prognosis.	**Platinum-resistant ovarian cancer is incurable and is a serious and life-threatening condition.**
Current Treatment Options	• Platinum-resistant ovarian cancer is not curable and treatment is palliative. • Treatment options are limited and include single agent chemotherapies associated with relatively low ORRs and short DORs. From contemporary data, ORRs for available therapies are 12-13% with median DORs of 4-7.4 months. • There are no treatments approved specifically for patients with FRα-positive, platinum-resistant ovarian cancer.	**There is an unmet medical need for treatments that improve outcomes for patients with platinum-resistant ovarian cancer, including for patients with FRα-positive platinum-resistant ovarian cancer.**
Benefit	• In Study 0417, there were 104 patients with FRα-positive, platinum-resistant ovarian cancer who had received 1-3 prior lines of systemic treatment, including 1 line containing bevacizumab, in the efficacy evaluable population. • Confirmed ORR as assessed by investigator according to RECIST v1.1 was 31.7% (95% CI: 22.9, 41.6). • Median DOR was 6.9 months (95% CI: 5.6, 9.7). • Assessments of ORR and DOR by blinded independent central review	**Mirvetuximab soravtansine-gynx demonstrated a confirmed ORR and DOR which represent an improvement compared to available therapies for patients with FRα-positive, platinum-resistant ovarian cancer who have received 1-3 prior lines of systemic treatment, including 1 line containing bevacizumab. ORR and DOR results are**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(BICR) were consistent results as assessed by investigator.	**reasonably likely to predict clinical benefit.**
Risk and Risk Management	• In Study 0417, the most common (≥20%) adverse reactions that occurred in patients treated with mirvetuximab soravtansine-gynx were vision impairment, fatigue, increased transaminases, nausea, keratopathy, abdominal pain, decreased lymphocytes, peripheral neuropathy, diarrhea, decreased albumin, constipation, increased alkaline phosphatase, dry eye, decreased magnesium, decrased leukocytes, decreased neutrophils, and decreased hemoglobin. The most common Grade ≥3 adverse reactions were keratopathy, vision impairment, and abdominal pain. • Fatal adverse reactions occurred in 2% of patients and included small intestinal obstruction and pneumonitis. • Ocular toxicity is an important safety signal associated with mirvetuximab soravtansine-gynx, experienced by 61% patients enrolled to Study 0417. • There is a boxed warning to alert providers to the potential for severe ocular toxicity in patients receiving mirvetuximab soravtansine in the USPI. • Additional important safety signals associated with mirvetuximab soravtansine-gynx include pneumonitis, peripheral neuropathy, and risk of embryo-fetal toxicity, which are listed under Warnings and Precautions in the USPI.	**The toxicity profile of mirvetuximab soravtansine-gynx is acceptable for the indicated patient population with platinum-resistant ovarian cancer and limited therapeutic options.** **Safe use of mirvetuximab soravtansine-gynx can be managed through labeling, which includes ocular toxicity as a boxed warning and the inclusion of pneumonitis, peripheral neuropathy, and embryo-fetal toxicity under Warnings and Precautions.** **No REMS is indicated.**

1.4. Patient Experience Data

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

				Section of review where discussed, if applicable
☐	**The patient experience data that were submitted as part of the application include:**			
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
X	**Patient experience data was not submitted as part of this application.**			

X _____

Cross Disciplinary Team Leader
Gwynn Ison

2 Therapeutic Context

2.1. Analysis of Condition

Ovarian cancer is the fifth leading cause of cancer-related death for women in the United States. In 2022, there will be an estimated 19,880 new cases of ovarian cancer and 12,810 deaths from ovarian cancer. The most common type of ovarian cancer is epithelial ovarian cancer, which comprises approximately 90% of all cases. Most epithelial ovarian cancers are high-grade serous tumors which are associated with a poorer prognosis compared to other ovarian cancer subtypes. There are no recommended screening measures for ovarian cancer for the general population, and unfortunately, ovarian cancer is often detected at an advanced stage. Ovarian cancer is associated with only a 49% five-year overall survival (American Cancer Society 2022).

FRα is an isoform of the FR which is normally expressed in epithelial cells including the kidney, retina, choroid plexus, and placenta. FRα may be expressed in >80% of serous ovarian cancers. Data are conflicting regarding the association between FRα expression and tumor stage and grade. Although it is hypothesized that FRα could mediate tumor progression, it is also unclear if FRα expression is associated with prognosis for ovarian cancer. FRα expression appears to be conserved with tumor progression (Vergote 2015).

2.2. Analysis of Current Treatment Options

Initial treatment for patients with advanced ovarian cancer is typically hysterectomy/bilateral salphingo-oophorectomy with comprehensive staging and debulking. Patients then receive adjuvant chemotherapy with a platinum-based doublet. Some patients with bulky disease who are less likely to experience an optimal cytoreduction may receive neoadjuvant chemotherapy first with a platinum-based doublet ± bevacizumab, followed by an interval debulking surgery with completion hysterectomy/BSO and cytoreduction, followed by adjuvant treatment with a platinum-based doublet ± bevacizumab (NCCN 2022). Patients who experience a CR or PR (70-80% of patients) may be candidates to receive maintenance treatment with bevacizumab (if received with platinum-based chemotherapy), niraparib, olaparib, or olaparib + bevacizumab (Kemp 2013).

Most patients will experience recurrence of disease. Patients with platinum-sensitive disease can receive treatment with a platinum-based doublet (± bevacizumab) and if they experience a CR or PR, they may be candidates for maintenance treatment with bevacizumab (if received with platinum-based chemotherapy), niraparib, olaparib, or rucaparib.

Unfortunately, ultimately, almost all patients with advanced ovarian cancer develop platinum-resistant disease, which has limited survival and few treatment options. Patients who have received only 1-2 prior lines of systemic treatment and who have not previously received bevacizumab may be candidates to receive bevacizumab in combination with chemotherapy, either paclitaxel, topotecan, or pegylated liposomal doxorubicin (PLD) (AVASTIN USPI 2022). If patients cannot receive this regimen or if patients experience progression of disease (PD) on this regimen and are still candidates for systemic therapy, their treatment options are limited to single agent chemotherapy with paclixel, topotecan, PLD, gemcitabine, or other options.

There are no therapies approved specifically for patients with platinum-resistant ovarian cancer who have already received a bevacizumab-containing regimen. There are also no therapies approved specifically for patients with FRα-positive ovarian cancer. Potential treatment options for patients with platinum-resistant ovarian cancer who have already received a bevacizumab-containing regimen are summarized in Table 2.

Table 2 Summary of Available Therapies for Platinum-Resistant Ovarian Cancer

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Reference
FDA Approved Treatments						
Paclitaxel	2L treatment for ovarian cancer	1992	135 mg/m2 or 175 mg/m2 IV every 3 weeks	• ORR 14% in P3 trial, 31% in pooled P1-P2 trials for PROC • DOR not included	Neutropenia, anemia, hypersensitivity, peripheral neuropathy, mucositis	AVASTIN USPI 2022
Paclitaxel	PROC	-	80 mg/m2 IV weekly for 12 weeks, then weekly for 3 weeks out of each 4-week cycle	• ORR 20.9%	Neutropenia, anemia, hypersensitivity, peripheral neuropathy, mucositis	GOG 2006
Pegylated liposomal doxorubicin (PLD)	PROC	1999	50 mg/m2 IV every 4 weeks	• ORR 13.8% (95% CI: 8.1%, 19.3%) • Median DOR 39.4 weeks	Cardiomyopathy, infusion related reactions, hand-foot syndrome, nausea, vomiting, diarrhea, stomatitis, anorexia, r ash	DOXIL USPI 2022

Topotecan	2L+ treatment for ovarian cancer	1996	1.5 mg/m2 IV daily on Days 1-5 of each 21-day cycle	• ORR 12% • DOR not included	Interstitial lung diseases, extravasation and tissue injury, myelosuppression	HYCAMTIN USPI 2022
Other Treatments						
Gemcitabine	PROC	-	1000 mg/m2 Days 1 and 8 of each 21-day cycle	• ORR 6.1% • DOR not included	Nausea, vomiting, faituge, neutropenia, pulmonary failure, hepatic toxicity	Ferrandina 2008
Etoposide	PROC	-	50 mg/m2 daily for 21 days out of each 28-day cycle	• ORR 26.8% • Median DOR: 4.3 months (range 1.3, 8.7 months)	Neutropenia, anemia, thrombocytopenia, GI effects	Rose 1998
Docetaxel	PROC	-	100 mg/m2 IV every 3 weeks	• ORR 22.4% (95% CI: 12.5%, 35.3%) • Median DOR 2.5 months	Hypersensitivity, second primary malignancies, cutaneous reactions, asthenia, hepatotoxicity, neurologic reactions, eye disorders, fluid retention, neutropenia, anemia	Rose 2003
Control Arms for Recent Trials						
Paclitaxel, PLD, or topotecan	PROC	-	-	• ORR 13% (7%, 18%) • Median DOR 5.4 months	See other boxes	AVASTIN USPI 2002 (Control arm for AURELIA)
Gemcitabine or PLD	PROC	-	-	• ORR 13.2% • Median DOR 7.4 months	See other boxes	Hamanish 2021 (Control arm for NINJA)
PLD or topotecan	PROC	-	-	• ORR 12.7% (95% CI: 8.6%, 17.8%)	See other boxes	Gaillard 2021 (Control arm for CORAIL)

				• Median DOR 4 months (95% CI: 1.9, 5.7 months)		
Paclitaxel, PLD, or topotecan	PROC	-	-	• ORR 12% • DOR 7.3 months	See other boxes	Moore 2021 (Control arm for Study 0403 /FORWARD 1)

*PROC: platinum-resistant ovarianc cancer

Reviewer comment: *It is challenging to evaluate the efficacy data for available therapies. Trials of the single agent chemotherapies occurred prior to adoption of the current treatment paradigm for advanced ovarian cancer which includes a platinum-based doublet ± bevacizumab followed by maintenance treatment with bevacizumab or a PARP inhibitor. The efficacy results (ORR/DOR) in the table may not represent what patients would experience in the current era (2022) of treatment for advanced ovarian cancer.*

Data from the control arms for more recent trials is shown in Table 2 *to get a sense of the efficacy which could be expected with these single agent chemotherapy options in the current era of treatment. It is important to note that even these trials are not reflective of the patients enrolled to Study 0417. In AURELIA, patients only received 1-2 prior lines of treatment, and no patients had received prior bevacizumab. In CORAIL, ~75% of patients had received 1-2 prior lines of treatment, and ~40% of patients had received prior bevacizumab. In NINJA, ~60% of patients had received 1-2 prior lines of treatment and it is unclear if patients had received prior bevacizumab. In* Study 0403(*FORWARD 1), ~65% of patients had received 1-2 prior lines of treatment, and ~50% of patients had received prior bevacizumab. In general, generation of the efficacy results in the table occurred in less heavily pre-treated populatons than those patients enrolled to Study 0417.*

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Mirvetuximab soravtansine is not approved for any indication in any country worldwide.

3.2. Summary of Presubmission/Submission Regulatory Activity

Table 3 summarizes key interactions with FDA.

Table 3 Key Regulatory Activities During Clinical Development of Mirvetuximab Soravtansine for Platinum-Resistant Ovarian Cancer

July 2011	Pre- Investigational New Drug (IND) meeting held to discuss the Chemistry, Manufacturing, and Controls (CMC) plan to support initial clinical trials and design of the first-in-human clinical trial.
June 2012	Study-May-Proceed Letter issued
April 2015	Type C meeting held to discuss nonclinical development plan and nonclinical toxicology studies
April 2016	Type C meeting held to discuss CMC aspects of development. See Product Quality review(s) for additional details.
July 2016	Type B EOP2/Pre-P3 meeting held to discuss design of Study 0403 (FORWARD 1) to support a potential Biologics License Application (BLA). This trial would enroll patients with intermediate and high FRα expression.
April 2017	Type C meeting held to discuss CMC aspects of development. See Product Quality review(s) for additional details.
June 2018	Fast Track designation granted for the treatment of patients with medium to high FRα-positive platinum-resistant epithelial ovarian cancer who received at least 1 but no more than 3 prior systemic treatment regimens and for whom single-agent chemotherapy is appropriate as the next line of therapy.
November 2018	Type C meeting held to discuss which trials (Study 0401 and Study 0403) should be included in a potential BLA submission.
January 2019	Type C meeting help to discuss CMC strategy and plan to support a

	potential BLA submission. See Product Quality review(s) for additional details.
April 2019	Type C meeting held to discuss the strategy and plan for detection of anti-drug antibodies (ADAs) to support a potential BLA.
May 2019	Type C meeting help to discuss results of Study 0403 to support a potential BLA submission. Study 0403 did not meet its primary progression-free survival (PFS) endpoint. (b) (4) FDA stated that the results could not support a BLA and recommended the Applicant conduct a new trial exclusively in patients with tumors containing high FRα expression.
September 2019	Type B End-of-Phase 2 (EOP2)/Pre-Phase 3 (P3) meeting held to discuss the strategy to support submission of a potential BLA. FDA and the Applicant discussed that ORR/DOR data from a proposed single arm trial in patients with high FRα expression could support a potential accelerated approval. FDA and the Applicant discussed the design of Study 0416 (MIRASOL) which would be the confirmatory trial. FDArecommended the addition of OS as a co-primary endpoint. FDA also stated that the trial population should be representative of a U.S. based population, including with respect to prior exposure to bevacizumab. FDA reviewed the Applicant's plan for assessment of FRα expression and reiterated that the device should be locked down prior to use in the proposed trial.
April 2021	Type C meeting held to review the Applicant's plan for the content and format of a potential BLA submission based on results from Study 0417 with supportive results from Study 0401 and Study 0403 . FDA reminded the Applicant that the potential confirmatory trial should be well underway/fully enrolled at the time of a potential accelerated approval action.
January 2022	Type B pre-BLA meeting held to discuss the topline results from the Study 0417 for a BLA submission.
March 2022	BLA submitted.

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

4.1. Office of Scientific Investigations (OSI)

DO1 consulted OSI to perform an audit of the Applicant as well as of the overall trial conduct. FDA selected three sites (Site 026: Dr. Jason Konner, Site 504: Dr. Domenica Lorusso, Site 932: Dr. Andrew Dean) for clinical inspection based on enrolling large numbers of patients in their respective geographic regions and/or having a higher ORR than observed on the trial. The trial sponsor, ImmunoGen. Inc., was also selected for inspection given that mirvetuximab soravtansine is an NME, and there have been no prior inspections of this sponsor. Based on these inspections, there were no significant regulatory violations, the trial conduct for Study 0417 appears adequate, and the submitted data from the three sites appear reliable.

Clinical inspection summaries are included here:

Site 025: Dr. Jason Konner

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 [redacted] (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 [redacted] (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.

Site 504: Dr. Domenica Lorusso

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 [redacted] (b) (6) due to clinical deterioration, and two subjects (# [redacted] (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 [redacted] (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 [redacted] (b) (6) and were attributed to study treatment based on the clinical assessment. In addition, Subject [redacted] (b) (6) was verified to have received an additional treatment with nab-paclitaxel plus relacoritant from [redacted] (b) (6) through [redacted] (b) (6) following disease progression on the third prior line treatment nab-paclitaxel alone from [redacted] (b) (6) to [redacted] (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.

OSI 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.*

Site 932: Dr. Andrew Dean

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.

OSI 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.

ImmunoGen, Inc.

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.

4.2. Product Quality

The Office of Biotechnology Products, OPQ, CDER, recommended approval for ELAHERE (mirvetuximab soravtansine) manufactured by ImmunoGen, Inc. and found the data submitted were adequate to support the conclusion that the manufacture of ELAHERE is well-controlled and leads to a product that is pure and potent. The assessment of manufacturing information provided in the application and in the crossreferenced drug master file (DMF) concluded that the methodologies and processes used for the M9346A antibody intermediate, DM4 payload, sulfo-SPDB linker, drug substance, and drug product manufacturing, release and stability testing are robust and sufficiently controlled to result in a consistent and safe product. Additionally, the manufacturing site inspections were conducted, and the recommendation was for approval, based upon adequate inspection findings.

There were several PMCs included in the review including to provide results for the stability indicating product quality attributes of the IMGN853DP shipped during the summer and winter months from the (b) (4) manufacturing site, to validate a gravimetric method to test the product, and to repeat the endotoxin method verification for in process samples of drug substance.

4.3. Clinical Microbiology

The antibody intermediate and drug substance manufacturing processes are robust for removal and control of adventitious agents. No approvability issues were identified from a sterility assurance or microbiology product quality perspective. Microbial quality is controlled at each step of the manufacturing process [redacted] (b) (4) Bioburden and endotoxin samples are monitored at each critical step of the manufacturing process [redacted] (b) (4) [redacted] (b) (4) and at DS release.

Microbial control [redacted] (b) (4) is addressed [redacted] (b) (4) [redacted] Adequate controls are in place to maintain microbiological product quality during [redacted] (b) (4) and throughout the manufacturing process.

4.4. Devices and Companion Diagnostic Issues

A Pre-Market Approval (PMA) Application (PMA P220006) was submitted to CDRH for the Ventana FOLR1 (FOLR-2.1) RxDx Assay.

The Ventana FOLR1 (FOLR-2.1) RxDx Assay is a qualitative immunohistochemistry assay that can be used to assess folate receptor alpha (FOLR1) in formalin-fixed, paraffin-embedded epithelial ovarian, fallopian tube, or primary peritoneal cancer tissue specimens by light microscopy. The assay is for use with the OptiView DAB IHC Detection Kit for staining on a BenchMark ULTRA instrument.

Effectiveness of the Ventana FOLR1 (FOLR-2.1) RxDx Assay was based upon pateints enrolled to Study 0417. The eligibility for Study 0417 required that patients have tumors with positivite FRα expression. FRα positivity was defined by the PS2+ scoring method, which is the methodology in which the pathologist describes the percentage of tumor cells expressing a certain intensity of membrane staining. The intensity of interest for the current study was determined to be levels of moderate (2+) or strong (3+), and this was scored by assessing the total number of viable tumor cells these staining levels. To be considered positive for FRα expression, ≥ 75% of viable tumor cells in the specimen had to demonstrate FOLR1membrane staining at moderate and/or strong staining intensity, as determined by the assay, which was interpreted at a central site.

According to the CDRH team, the performance of the Ventana FOLR1 (FOLR1-2.1) RxDx Assay was supported by the analytical performance validation studies. It was determined that the data submitted in the PMA are supportive of approval of the Ventana FOLR1 (FOLR1-2.1) RxDx Assay as a companion diagnostic deveic to identify patients with epithelial ovarian, fallopian

tube, or primary peritoneal cancer who may be eligible for treatment with mirvetuximab soravtansine.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Mirvetuximab soravtansine (Elahere) is an antibody-drug conjugate (ADC) consisting of a humanized immunoglobulin G1 antibody (M9346A) directed against folate receptor alpha (FRα), a succinimidyl-4-(pyridine-2-yl) disulfanyl-2-sulfo-butyrate (sulfo-SPDB) linker, and maytansine microtubule inhibitor, DM4. Each antibody is conjugated to an average of 3 to 4 molecules of DM4. Mirvetuximab soravtansine is administered by intravenous (IV) infusion once every 3 weeks at the recommended dose of 6 mg/kg (based on AIBW) for the 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. The nonclinical development program for mirvetuximab soravtansine and the cytotoxic payload, DM4, consisted of studies in rats, monkeys, and rabbits to evaluate the primary and safety pharmacology, general toxicity, ocular toxicity, phototoxicity, and genotoxicity. During the nonclinical development, mirvetuximab soravtansine was referred to as IMGN853 or M9346A-sulfo-SPDB-DM4.

Folate receptor alpha (FRα, also known as FOLR1 or FR1) is an N-glycosylated protein anchored to the plasma membrane via glycosyl phosphatidylinositol with a molecular weight of 28 kD (Shen, et al., 1994). FRα is upregulated on the surface of many epithelial-derived tumors, compared to normal tissue. This receptor plays a critical role in cellular uptake of folate, a basic component of cell metabolism and DNA synthesis and repair.

In primary pharmacology studies, mirvetuximab soravtansine bound to FRα expressed on human or Rhesus monkey cells but not endogenous mouse or rat FRα. Binding to surface FRα leads to internalization of the receptor-ADC complex and lysosomal degradation of mirvetuximab soravtansine. This degradation releases the DM4 from the antibody and can result in cell cycle arrest and cell death. In vivo, mirvetuximab soravtansine delayed tumor growth and caused tumor regression in several ovarian cancer xenograft mouse models when mice were administered a single IV dose of mirvetuximab soravtansine containing antibody doses as low as 1.2 mg/kg and DM4 dose of 25 µg/kg. Based on the nonclinical pharmacology studies provided in the BLA submission, the established pharmacological class (EPC) of “folate receptor α-directed antibody and microtubule inhibitor conjugate” is appropriate based on its pharmacological activity, prior EPC for related approved products, and the approved EPC for microtubule inhibitors.

In vitro, DM4 was not stable in rat, human, and monkey plasma but was stable in human, rat, and monkey blood for up to 90 minutes. Metabolite S-methyl-DM4 (DM4-Me) was stable in human plasma either tested alone or in combination with DM4. In addition, S-methyl-DM4 was

stable in human, rat, and monkey blood after incubation for up to 90 minutes. The binding of DM4 and S-methyl-DM4 to human plasma protein in vitro was 99.38% and 99.27%, respectively.

In the 10-week GLP repeat-dose toxicity study in monkey, after a single IV dose of mirvetuximab soravtansine, the plasma exposure (C_{max} and AUC $_{0-24}$) increased in an approximately dose proportional manner with no remarkable gender differences. The $T_{1/2}$ values ranged from 95 to 106 hours on Day 1 and from 102 to 129 hours on Day 64. Upon repeated IV infusion of mirvetuximab soravtansine once every 3 weeks, no accumulation was observed. All monkeys administered mirvetuximab soravtansine at doses up to 8 mg/kg/dose tested negative for the presence of anti-drug antibodies (ADAs). Animal to human exposure margins were calculated using the mean clinical AUC_{last} (15.91 h*mg/mL) for mirvetuximab soravtansine, C_{max} (143900 ng/mL) for mirvetuximab soravtansine, and C_{max} (4080 ng/mL) and AUC_{last} (208.5 h*ng/mL) for DM4 after the first dose in patients receiving the recommended dose. Per the clinical pharmacology team, there was no accumulation with repeated dosing of mirvetuximab soravtansine; therefore, the steady state exposures after repeated dosing were similar to exposures seen after the first dose.

In safety pharmacology studies, inhibition of hERG channels was not evaluated with mirvetuximab soravtansine; however, up to 60 µM DM4 and metabolite S-methyl-DM4 had < 50% inhibition on hERG potassium channels. Additionally, mirvetuximab soravtansine did not have effects on the nervous, cardiovascular, or respiratory systems in monkeys after repeated IV dosing up to 8 mg/kg (4-fold the exposures at the recommended dose based on AUC) based on ECG analysis and clinical observation.

Following a single IV dose of 5 mg/kg radio-labeled mirvetuximab soravtansine to male Sprague Dawley rats, high radioactivity concentrations were observed in liver, bone marrow, lung, kidneys, and spleen. The eye:plasma ratio increased through the duration of the study, suggesting that drug clearance from the eyes was slower than from plasma. Radioactivity was also observed in testes suggesting that drug also penetrated the blood:testes barrier. The brain:plasma ratio was < 3% of the plasma radioactivity of mirvetuximab soravtansine, indicating limited blood:brain barrier penetration. The major route of mirvetuximab soravtansine elimination was via feces in rats.

A 10-week GLP compliant repeat-dose toxicity study with mirvetuximab soravtansine was conducted in cynomolgus monkey using the clinical IV route of administration, and the payload DM4 was assessed in cynomolgus monkey in a non-GLP single IV dose toxicity study. Administration of mirvetuximab soravtansine at 8 mg/kg for 10 weeks resulted in bone marrow toxicity with corresponding decreases in absolute neutrophils, white blood cells, and reticulocytes in both sexes when compared to control group. In addition, administration of mirvetuximab soravtansine at dose ≥ 4 mg/kg resulted in ocular toxicity (minimal to marked degeneration/necrosis and attenuation in the corneal epithelium and minimal to slight epithelial degeneration/necrosis and inflammation of skin on the eyelids). Generally, the

hematopoietic and ocular toxicity fully or partially recovered by the end of the 5-week recovery period. In humans, mirvetuximab soravtansine caused hematological toxicities, including pancytopenia (≥ 10% Grade 2-4 decreased lymphocytes, hemoglobin, and neutrophils) at the recommended dose of 6 mg/kg IV once every 3 weeks. Mirvetuximab soravtansine also caused eye disorders (vision blurred, keratopathy, dry eye, cataract, photophobia, and eye pain) at the recommended dose. Thus, toxicological findings in the hematopoietic system and eyes in cynomolgus monkeys were consistent with the frequent adverse events observed in clinical trials.

Mirvetuximab soravtansine at 5 to 10 mg/kg as a single dose and 8 mg/kg once every 3 weeks for 10 weeks resulted in skin toxicity, including slight to moderate epithelial ulceration/erosion, acanthosis, hyperkeratosis, and edema in both sexes (≥ 1-fold the exposure at the recommended dose based on AUC). Changes in skin were not observed at end of recovery period. In addition, DM4 showed phototoxicity with IC_{50} values of 0.582 µg/mL and 8.712 µg/mL in the presence and absence of UV light, respectively, in an in vitro Balb/c 3T3 mouse fibroblasts study. Mirvetuximab soravtansine showed positive staining of human skin in a tissue cross reactivity study; however, skin toxicity was not observed in clinical trials.

Due to ocular toxicities observed in both animal toxicity studies and in patients, the Applicant also conducted GLP compliant repeated-dose toxicity studies to evaluate ocular toxicity of mirvetuximab soravtansine in male rabbits. Rabbits received up to 12 mg/kg/dose mirvetuximab soravtansine IV once weekly for 4 weeks or up to 10 mg/kg/dose once every 3 weeks for 12 weeks. A dose of 12 mg/kg once weekly resulted in early moribund sacrifice on Day 22 due to weight loss, anorexia, and skin lesions. Doses ≥ 4 mg/kg weekly caused microscopic findings of attenuation and degeneration/necrosis of the corneal epithelium in the eyes of rabbits. These findings were still observed at the end of a 3-week recovery period. Similar microscopic findings in the eyes and skin were also observed in rabbits administered ≥ 4 mg/kg mirvetuximab soravtansine once every 3 weeks; however, these findings were less severe when compared to once weekly dosing. Changes were still present following a 3-week recovery period but trending towards recovery.

In a non-GLP single dose toxicity study of DM4, target organs of toxicity in cynomolgus monkeys included bone marrow (depletion), lung (hemorrhage) and inflammation at the site of injection. Microscopic findings in eye included mild mononuclear cell infiltration in ciliary body and minimal mononuclear cell infiltration in uvea. Similar histopathology findings in bone marrow and injection site were also observed in cynomolgus monkeys administered mirvetuximab soravtansine for 10-weeks.

The Applicant submitted genotoxicity studies that evaluated the payload DM4 and its metabolite S-methyl-DM4. DM4 and S-methyl-DM4 were negative in the vitro bacterial reverse mutation assay but positive in the in vivo rat bone marrow micronucleus assay. The genetic toxicity results with DM4 and S-methyl-DM4 are consistent with the mechanism of action and primary pharmacological activity. Carcinogenicity studies were not conducted with

mirvetuximab soravtansine in accordance with ICH S9 guidance for advanced cancer indications.

Dedicated reproductive toxicity studies were not conducted with mirvetuximab soravtansine in accordance with ICH S9 based on the expected adverse effects of DM4 on actively dividing cells and the intended indication for the treatment of patients with advanced cancer. Since mirvetuximab soravtansine targets actively dividing cells (e.g., adverse effects on the hematopoietic system in nonclinical studies and clinical trials) and is genotoxic, it is expected to cause teratogenicity and/or embryo-fetal death if administered to a pregnant woman. In addition, FRα gene mutations have been associated with human birth defects, such as neural tube defects and neurologic disease (Trembath, et al., 1999; Cario, et al., 2009; and Steinfield, et al., 2009). Effective contraception use is recommended for females of reproductive potential during treatment with mirvetuximab soravtansine and for 7 months following the last dose. Since mirvetuximab soravtansine is clastogenic, a contraception period of 6 months with an additional 5 half-lives (mirvetuximab soravtansine half-life ~5 days) is recommended to minimize the risk for DNA damage in oocytes, in accordance with FDA guidance *Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations*. Additionally, effective contraception use is recommended for male patients with female partners of reproductive potential during treatment and for 4 months after the last dose (3 months with an additional 5 half-lives) based on the FDA guidance. Due to the current ovarian cancer indication, the Applicant and review team agreed not to include a contraception recommendation for males in the prescribing information. In addition, mirvetuximab soravtansine has the potential to cause adverse reactions in a breastfed child. Based on the plasma half-life of ~5 days in patients, the majority of mirvetuximab soravtansine should be cleared after 25 days; thus, women are advised not to breastfeed during treatment and for 1 month after the last dose.

Recommendation

The submitted nonclinical pharmacology and toxicology data with mirvetuximab soravtansine are adequate to support approval of Elahere for the proposed indication.

5.2. Referenced NDAs, BLAs, DMFs

None.

5.3. Pharmacology

Primary pharmacology

Results of primary pharmacology of mirvetuximab soravtansine (IMGN853) were reviewed primarily under IND 111915 and additional relevant pharmacology studies are also reviewed and summarized below.

Mirvetuximab soravtansine bound folate receptor 1 (FR1 or FRα) expressed on human (Kd = 0.05-0.1 nM) or Rhesus monkey cells (Kd = 0.1 nM) but not endogenous mouse or rat folate receptor when determined by flow cytometry analysis (Study no. IMV28-004). When analyzed by an ELISA method, mirvetuximab soravtansine bound to FRα expressed on human and cynomolgus monkey with a similar affinity (Kd = 0.2 nM) (Study no. IMV28-006). Amino acid sequence comparison showed high similarity (98%) between human FRα and Rhesus monkey FRα. Rabbit, dog, mouse, and rat sequences showed 87-90% sequence similarity and 83-88% sequence identity (Study no. IMV28-004).

The binding specificity of unconjugated antibody M9346A was analyzed by flow cytometry in murine cells transfected with human FRα and compared with non-transfected murine cells. The results showed that M9346A bound to human FRα expressing cells but not to non-transfected cells. Similarly, M9346A did not bind to a FRα negative human multiple myeloma cell line (Study no. IMV28-001). When analyzed by flow cytometry , M9346A and mirvetuximab soravtansine also bound to endogenous FRα-positive human SKOV-3 ovarian cancer cells with the same Kd value at 0.1 nM (Study no. IMV28-001). In addition, the binding affinity of M9346A and mirvetuximab soravtansine was assessed by ELISA where recombinant human FRα-Fc protein (human FRα fused to Fc moiety of murine IgG2a) was used as the antigen. The affinity value (Kd) was 0.05 nM for both M9346A and IMGN853 (Study no. IMV28-001). M9346A also showed no competitive binding with natural folate for binding to FRα (Study no. IMV28-001). Using an ELISA assay, M9346A did not bind to human FRβ, FRɣ, or FRδ recombinant protein (Study no. IMV28-010, Study IMV28-012).

To further assess the mechanism of action, the Applicant evaluated catabolism and lysosomal processing of IMGN853 and unconjugated antibody M9346A (Study no. IMV28-008). In vitro, when KB cervical carcinoma cells expressing high levels of FRα were incubated with ^{3}H-IMGN853 (M9346A-sulfo-SPDB-[^{3}H]-DM4) for 22 hours, the major metabolites were lysine-N6-sulfo-SPDB-DM4, DM4, and S-methyl-DM4. The metabolites represented approximately 12% of the initial dose of ^{3}H-DM4. To evaluate whether IMGN853 is activated primarily through lysosomal degradation, the Applicant compared the rate for processing of ^{3}H-IMGN853 to its three catabolites to the catabolism rate of unconjugated ^{3}H-M9346A antibody. M9346A was labeled with the radioactive tracer, *N*-succinimidyl-[2,3, ^{3}H] propionate to allow tracking of the intact antibody and release of the free label after culture with KB cells for 22 hours. The amount of protein-free radioactivity (processed) and protein-associated radioactivity (un-processed) was assessed following acetone extraction and liquid scintillation counting. The percentage of processed ^{3}H-M9346A antibody and ^{3}H-IMGN853 was similar, 28% vs. 23%, respectively. The Applicant concluded that activation of IMGN853 was primarily through lysosomal degradation. Thus, binding to surface FRα on cancer cell lines leads to internalization of the receptor-ADC complex, lysosomal degradation of IMGN853, and intracellular release of maytansinoids.

Anti-tumor activity of IMGN853 was evaluated in several ovarian cancer xenograft mouse models OVCAR-3, Igrov-1, and OV-90 (Study no. IMP28-001, IMP28-002, and IMP28-003). Treatment with a single IV dose of IMGN853 resulted in either delays in tumor growth (21 days

to 120 days compared to control) or partial or complete regression with % tumor growth inhibition ranging from 9%-78% compared to control group. Anti-tumor activity was noted with IMGN853 containing antibody doses as low as 1.2 mg/kg and DM4 dose of 25 µg/kg (Study no. IMP28-001, IMP28-002, IMP28-003).

IMGN853 mediated antibody-dependent cellular cytotoxicity in the presence of natural killer cells (Study no. IMV28-002) but did not mediate complement dependent cytotoxicity (Study no. IMV28-005). Moreover, antibody-dependent cellular phagocytosis (ADCP) activity of IMGN853 was also evaluated by incubating human peripheral blood mononuclear cell (PBMC)-derived macrophages with 2 target tumor cell lines expressing FRα on their cell surface (adenocarcinoma KB cell line and human ovarian carcinoma IGROV1 cell line) in the presence of either IMGN853 or M9346A antibody at various concentrations (6.67×10^{-8} M to 6.67×10^{-13} M) and incubated for 2 hours at 37°C in 5% CO_2. The results demonstrated that IMGN853 and M9346A antibody induced a concentration-dependent ADCP activity against 2 cell lines tested, suggesting that conjugation to DM4 did not impact the ADCP activity of the antibody. The EC_{50} values were only determined for M9346A antibody, which were 1.4×10^{-11} M and 4.2×10^{-11} M ADCP activity for IGROV1 and KB cells, respectively.

IMGN853 bound to both human and cynomolgus monkey tissues by immunohistochemical analysis (Study no. IMH28-003). Significant positive membrane staining was observed in 17 unique structural components isolated from 12 human tissues (lung, kidney, breast, choroid plexus, fallopian tube, pancreas, parathyroid, pituitary, salivary gland, skin, spinal cord, and stomach). Nine monkey tissues also showed significant positive staining in the choroid plexus, fallopian tube, kidney, pancreas, salivary gland, parathyroid, pituitary, spinal cord but weak staining in the skin, lung, breast, and stomach. The similarity of binding in human and cynomolgus monkey tissues confirmed that the cynomolgus monkey was an appropriate model for toxicological evaluation (Study no. IMH28-003).

Safety Pharmacology

Study Title/Number: Effects of DM4 and DM4-Me on cloned hERG potassium channels expressed in human embryonic kidney cells/ 150328.JNO

Methods: The effect of DM4 (10-60 µM) and S-methyl-DM4 (DM4-Me, 10-60 µM) on in vitro hERG current was evaluated by using stably transfected HEK293 cells and the whole cell patch clamp method.

Results: The IC_{50} for the inhibitory effect of DM4 and S-methyl-DM4 on hERG potassium current was not calculated but was estimated to be greater than 60 µM. Therefore, DM4 and S-methyl-DM4 are considered low potency potassium channel blockers.

5.4. ADME/PK

Type of Study	Major Findings
Absorption	
Study Title/Number: Plasma pharmacokinetics of IMGN853 (M93469A-sulfo-SPDB-DM4) from a single-dose toxicity study in cynomolgus monkeys/IMK28-002 Cynomolgus monkey (n=5/sex/group), single IV dose at 0, 1, 3, 5, and 10 mg/kg of IMGN853 (plasma samples from study no. WRT28-001)	-No pharmacokinetic differences were observed between sex; thus, the data were shown in combined sex. -Exposure to both conjugated and unconjugated antibodies was dose-dependent and dose proportionate. **IMGN853**

Dose (mg/kg)	1	3	5	10
Parameters				
$T_{1/2}$ (hr)	86	94.7	96.5	98.2
C_{max} (µg/mL)	35.6	87.8	135.1	280.6
$AUC_{0\text{-}inf}$ (hr*µg/mL)	2142	7015	12716	25583
$AUC_{0\text{-}tobs}$ (hr*µg/mL)	2104	6956	12606	25313
CL (mL/hr/kg)	0.5	0.4	0.4	0.4
V_{ss} (mL/kg)	45	45.3	44.8	42.2

Total M9346A antibody

Dose (mg/kg)	1	3	5	10
Parameters				
$T_{1/2}$ (hr)	113.1	138.3	167.8	168.9
C_{max} (µg/mL)	31.5	75.4	120.2	249.3
$AUC_{0\text{-}inf}$ (hr*µg/mL)	2724	9225	15208	30287
$AUC_{0\text{-}tobs}$ (hr*µg/mL)	2597	8859	14299	28200
CL (mL/hr/kg)	0.4	0.3	0.3	0.3
V_{ss} (mL/kg)	51.6	57.4	74.3	74.3

Linker stability of IMGN853

<table>
<tr><td></td><td>
<table>
<tr><th colspan="3">LINKER</th></tr>
<tr><th>Dose (mg/kg)</th><th>$t_{1/2}$ (h)</th><th>$t_{1/2}$ (d)</th></tr>
<tr><td>1</td><td>328.9</td><td>13.7</td></tr>
<tr><td>3</td><td>278.1</td><td>11.6</td></tr>
<tr><td>5</td><td>242.3</td><td>10.1</td></tr>
<tr><td>10</td><td>248.9</td><td>10.4</td></tr>
</table>
(Excerpted from Applicant's submission)
</td></tr>
<tr><td>Study Title/Number: Plasma concentrations of free DM4 in samples of IMGN853 (M9346A-sulfo-SPDB-DM4) from a single dose toxicity study in cynomolgus monkeys/ IMI28-001

Male cynomolgus monkey (n=5/sex/group), single IV dose at 0, 1, 3, 5, and 10 mg/kg of IMGN853</td><td>-Total free DM4 generally increased with increasing dose with a maximal detectable level less than 5% of the maximal conjugated maytansinoid at each dose level.
-Free DM4 was detectable in the serum for only up to 2 days.</td></tr>
</table>

		Free DM4 Species		IMGN853		%Cobs	%Cmax
Dose (mg/kg)	Time (hr)	Cobs (µg/mL)	Cobs (µM)	Cobs (µg/mL)	Cobs (µM)		
1	IFD	0.028	0.04	35.62	0.86	4.4	4.4
	0.5	0.035	0.04	32.58	0.78	5.1	4.7
	24	0.026	0.03	15.05	0.36	8.3	3.5
	48	<LLQ	·	9.94	·	·	·
3	IFD	0.062	0.08	85.59	2.06	3.9	3.8
	0.5	0.058	0.07	87.75	2.11	3.3	3.3
	24	0.027	0.03	50.21	1.21	2.5	1.4
	48	<LLQ	·	33.44	·	·	·
5	IFD	0.095	0.12	135.07	3.25	3.7	3.7
	0.5	0.080	0.10	122.04	2.93	3.4	3.1
	24	0.025	0.03	89.52	2.15	1.4	0.9
	48	<LLQ	·	63.77	·		
10	IFD	0.129	0.17	280.61	6.74	2.5	2.5
	0.5	0.112	0.14	271.17	6.52	2.1	2.1
	24	0.051	0.07	195.15	4.69	1.5	1.0
	48	0.041	0.05	135.57	3.26	1.5	0.7
	168	<LLQ	·	31.44	·	·	·

%Cobs (mean concentration observed at time point) and %Cmax (mean maximal concentration): µM free DM4 species/µM IMGN853 using molecular weight for free DM4 species as 780.37 g/mole and IMGN853 as 145,676 g/mole and assuming µM of conjugated DM4 equals µM IMGN853 x 3.5 DM4 per IMGN853.

Concentration values for IMGN853 are reported in ImmunoGen, Inc. Report IMK28-002.

· plasma level of free DM4 species was below the limit of quantitation and values are not calculated.

(Excerpted from Applicant's submission)

Distribution	
Study Title/Number: A non-GLP disposition study of IMGN853 (M-sulfo-SPFB-^{3}H-DM4) following intravenous bolus injection in male Sprague Dawley rats/ CVK28-002 Assess the distribution, pharmacokinetics, metabolism, and excretion following a single IV administration of 5 mg/kg IMGN853 (M9346A -sulfo-SPDB-^{3}H-DM4) to male Sprague Dawley rats (n =3-15/group).	-$T_{1/2}$ = 138-214 hr -Mean blood to plasma concentration ratios ranged from 0.657 to 0.846. -The tissues with the highest maximum observed radioactivity concentration (C_{max} > 9000 ng equivalent M9346A-sulfo-SPDB-^{3}H-DM4/g) included liver, bone marrow, lung, kidneys, and spleen. -The eye:plasma ratio increased through the duration of the study from 0.0312 to 0.603, suggesting the clearance of radioactivity from the eyes was slower than from plasma. -Radioactivity concentrations observed in testes suggested that drug also penetrated the blood:testes barrier. The testes:plasma ratio increased through the duration of the study from 0.0375 to 0.241.

<table>
<tr><td></td><td>-The brain:plasma ratio indicated less than 3% of the plasma radioactivity was in the brain.
-Fecal excretion was the observed predominant route of elimination, accounting for a mean of 62.3% of the administered dose through 336 hours post-dose. Urinary excretion accounted for a mean of 2.27% of elimination.</td></tr>
<tr><td>Study Title/Number: In vitro plasma protein binding and blood-to-plasma partitioning of DM4 and DM4-Me in rat, monkey, and human/CVG28-001

Plasma protein binding in rat, monkey, and human</td><td>-DM4 was not stable in human, rat, and monkey plasma. However, S-methyl-DM4 (DM4-Me) was stable in human plasma either tested alone or in combination with DM4 for up to 8 hours.
-DM4 and S-methyl-DM4 were stable in human, rat, and monkey blood following incubation for up to 90 minutes.
-The plasma protein binding of DM4 was 96-99% across species.

-The blood-to-plasma partitioning of DM4 and S-methyl-DM4 was determined for human, rat, and monkey following incubation for 60 minutes. Overall, the blood-to-plasma concentration ratio and percent associated with blood cells decreased with increased DM4 concentrations.
-For S-methyl-DM4, partitioning to blood cells decreased with increased S-methyl-DM4 concentrations in rat and monkey blood, but not in human blood.

Summary of DM4 and DM4-Me Blood-to-Plasma Partitioning
<table>
<tr><th></th><th colspan="2">Rat</th><th colspan="2">Monkey</th><th colspan="2">Human</th></tr>
<tr><th>Test article</th><th>Blood-to-plasma ratio</th><th>% associated with blood cells</th><th>Blood-to-plasma ratio</th><th>% associated with blood cells</th><th>Blood-to-plasma ratio</th><th>% associated with blood cells</th></tr>
<tr><td>DM4</td><td>0.907-1.62</td><td>35.5-63.8</td><td>0.925-4.33</td><td>34.2-86.2</td><td>0.488-1.85</td><td>0-67.5[a]</td></tr>
<tr><td>DM4-Me</td><td>0.809-1.10</td><td>28.0-47.1</td><td>0.635-4.04</td><td>6.31-85.3</td><td>0.551-0.583</td><td>0-4.72[a]</td></tr>
</table>
[a] Negative values for % associated with blood cells was considered as 0.

(Excerpted from Applicant’s submission)</td></tr>
<tr><td>Excretion</td><td></td></tr>
<tr><td>Study Title/Number: Evaluation of the clearance of the maytansinoid DM4 in cynomolgus monkeys/ IMK14-001</td><td>-$T_{1/2}$ = 2 hr
-The plasma concentration of maytansinoid DM4 in monkeys was only detectable at 0.5 hours post-administration (~ 0.56 µg/mL).
-Following 7 hours post-administration, levels of DM4 were below the limit of quantitation (3.6 ng/mL).</td></tr>
</table>

<table>
<tr><td>The in vivo pharmacokinetics of the maytansinoid DM4 was evaluated in cynomolgus monkeys given a single IV dose of free DM4 at 0.1 mg/kg (n=4).</td><td></td></tr>
<tr><td>Metabolism</td><td></td></tr>
<tr><td>Study Title/Number: In vivo metabolism of IMGN853 (M-sulfo-SPDB-^{3}H-DM4) in male Sprague Dawley rats following intravenous bolus injection/ IMG28-001

The in vivo metabolism of IMGN853 was assessed to characterize free payload (DM4) and related metabolites in acid treated plasma, urine, and bile after a single IV injection of 5 mg/kg [^{3}H]-IMGN853 (i.e., M-sulfo-SPDB-^{3}H-DM4) in male Sprague Dawley rats (n = 3).</td><td>-Total radioactivity excreted in bile and urine within 0-72 hr was 18.4% and 0.7%, respectively.
-In plasma, radioactivity in organic extract (i.e., non-protein fraction that contained free payload and other small-molecule metabolites) represented 1% of total radioactivity through 336 hours post-dose.

<table>
<tr><th colspan="3">(% present in medium from the total administered dose)</th></tr>
<tr><th>Bile</th><th>Urine</th><th>Plasma</th></tr>
<tr><td>M6
(4.0%)</td><td>M1
(< 0.3%)</td><td>M1
(0.3%)</td></tr>
<tr><td>M7
(3.8%)</td><td>M2
(< 0.3%)</td><td>M2
(0.2%)</td></tr>
<tr><td>M8
(4.1%)</td><td>M6
(< 0.3%)</td><td></td></tr>
<tr><td>M10
(3.1%)</td><td>M8
(< 0.3%)</td><td></td></tr>
</table>

M1 = S-methyl DM4
M2 = DM4
M6 = S-methyl-DM4 sulfoxide
M7 = DM4-sulfo-TBA
M8 = DM4-sulfo-SPDB-lysine
M10 =DM4-sulfonic acid</td></tr>
<tr><td>TK data from toxicology studies</td><td></td></tr>
<tr><td>Study title/ no.: 10-Week intravenous (slow push) toxicity and toxicokinetic study in cynomolgus monkeys with a 5-week recovery period/ CVT28-001.

Cynomolgus monkey (n = 6/sex/group), IV once every 3</td><td>This study was previously reviewed under IND 111915.

Dose proportionality: exposure to IMGN853, M9346A antibody, and DM4 generally increased proportionally at IMGN853 dose levels from 2 to 8 mg/kg.
Sex differences: less than 2-fold
Accumulation: No</td></tr>
</table>

weeks at 0, 2, 4, and 8 mg/kg of IMGN853	*Half-life:* IMGN853 and total antibody $T_{1/2}$ was dose- and time-independent, but mean $T_{1/2}$ values of DM4 were dose-dependent Due to limited data above the lower limit of quantitation, toxicokinetic analysis was not performed on S-methyl-DM4 concentration data.

IMGN853

Interval	Dose Group	Dose Level (mg/kg/dose)	Sex	C_{max} (ng/mL)	AUC_{0-24} (ng·hr/mL)	$t_{1/2}$ (hr)
Day 1	2	2	M	51800	867000	94.5
			F	61300	1040000	100
			MF	56500	952000	97.4
	3	4	M	112000	1940000	96.7
			F	110000	1860000	99.4
			MF	111000	1900000	98.1
	4	8	M	229000	3850000	99.7
			F	214000	3490000	106
			MF	221000	3670000	103
Day 64	2	2	M	56500	959000	102
			F	52000	917000	108
			MF	54200	938000	105
	3	4	M	119000	1950000	129
			F	106000	1970000	112
			MF	113000	1960000	121
	4	8	M	226000	3830000	123
			F	216000	3880000	118
			MF	221000	3850000	121

Note: The Day 22 predose values were used as the 504 hour timepoint in order to calculate $t_{1/2}$.

(Excerpted from Applicant's submission)

M9346A antibody

Interval	Dose Group	IMGN853 Dose Level (mg/kg/dose)	Sex	C_{max} (ng/mL)	AUC_{0-24} (ng·hr/mL)	$t_{1/2}$ (hr)
Day 1	2	2	M	49300	811000	134
			F	53400	924000	148
			MF	51300	867000	141
	3	4	M	101000	1620000	162
			F	93700	1550000	172
			MF	97400	1590000	167
	4	8	M	193000	3160000	177
			F	191000	2960000	210
			MF	192000	3060000	195
Day 64	2	2	M	52600	903000	142
			F	52100	917000	156
			MF	52300	910000	149
	3	4	M	101000	1760000	175
			F	102000	1730000	148
			MF	102000	1740000	161
	4	8	M	202000	3610000	225
			F	204000	3650000	187
			MF	203000	3630000	206

Note: The Day 22 predose values were used as the 504 hour timepoint in order to calculate $t_{1/2}$.

(Excerpted from Applicant's submission)

DM4

Interval	Dose Group	IMGN853 Dose Level (mg/kg/dose)	Sex	C_{max} (ng/mL)	AUC_{0-24} (ng·hr/mL)	$t_{1/2}$ (hr)
Day 1	2	2	M	0.229	3.63	NA
			F	0.226	3.83	NA
			MF	0.227	3.73	NA
	3	4	M	0.362	6.45	36.9
			F	0.390	6.38	11.2
			MF	0.376	6.42	19.8
	4	8	M	0.752	12.8	42.2
			F	0.709	12.2	32.7
			MF	0.730	12.5	39.0
Day 64	2	2	M	0.151	3.96	NA
			F	0.188	NA	NA
			MF	0.185	3.96	NA
	3	4	M	0.414	6.56	NA
			F	0.362	6.78	NA
			MF	0.388	6.65	NA
	4	8	M	0.784	12.3	NA
			F	0.742	12.9	NA
			MF	0.763	12.6	NA

(Excerpted from Applicant's submission)

Study title/ no.: 4-Week intravenous infusion ocular toxicity and toxicokinetic study with IMGN853 (M9346A-sulfo-SPDB-DM4) and M9346A-SPDB-DM4 administered once weekly to male Dutch belted rabbits with a 3-week recovery phase/CVT28-002 Male rabbits (n = 5/group), IV once weekly of 0, 4, 8, or 12 mg/kg/dose of either IMGN853 or M9346A-SPDB-DM4 (ADC with different linker)*. Blood was collected on Days 1, 8, 15, and 22 at pre-dose, 0.5, 2, 8, 24, 72, and 168 hours post-dose. *Data not included in review	**IMGN853** *Accumulation*: slight accumulation (< 2-fold) of IMGN853 *Dose proportionality*: mean exposure (C_{max} and AUC) for IMGN853, its total antibody and DM4 increased proportionally as dose increased from 4 to 12 mg/kg. However, mean exposure was less than dose proportional for S-methyl DM group.

Parameters	IMGN853					
	Day 1			Day 22		
	4 mg/kg N=5	8 mg/kg N=4	12 mg/kg N=5	4 mg/kg N=5	8 mg/kg N=5	12 mg/kg N=4
t_{max} (hr)	0.5 (0)	0.9 (0.75)	0.5 (0)	0.5 (0)	1.4 (0.82)	0.5 (0)
C_{max} (µg/mL)	105.12 (25.80)	259.29 (17.18)	359.05 (99.27)	132.10 (28.10)	247.46 (34.52)	323.38 (154.71)
AUC_{last} (hr•µg/mL)	4979.63 (1365.75)	11024.83 (1706.95)	15143.35 (4256.14)	6943.36 (1859.05)	13140.29 (2809.22)	17528.00 (8528.95)
$AUC_{0\text{-}INF}$ (hr•µg/mL)	6140.71 (1719.87)	12822.46 (1960.84)	17359.06 (4333.03)	8618.62 (2457.17)	15416.67 (3316.34)	20067.00 (9354.93)
V_{ss} (mL/kg)	65.61 (24.76)	49.04 (5.48)	56.06 (16.25)	46.29 (15.84)	42.67 (10.25)	61.19 (44.55)
CL (mL/hr/kg)	0.70 (0.22)	0.63 (0.08)	0.73 (0.18)	0.50 (0.15)	0.54 (0.13)	0.77 (0.51)
$t_{1/2\beta}$ (hr)	69.96 (11.81)	60.06 (6.00)	56.67 (7.16)	69.91 (15.45)	59.79 (10.11)	58.01 (3.33)

SD Standard deviation, N Number of animals

(Excerpted from Applicant's submission)

Parameters	Total M9346A Antibody (IMGN853)					
	Day 1			Day 22		
	4 mg/kg N=5	8 mg/kg N=4	12 mg/kg N=5	4 mg/kg N=5	8 mg/kg N=5	12 mg/kg N=4
t_{max} (hr)	0.5 (0)	0.5 (0)	0.5 (0)	0.8 (0.671)	0.5 (0)	1.25 (0.8)
C_{max} (µg/mL)	108.73 (19.65)	194.10 (27.54)	327.88 (47.74)	133.88 (19.96)	230.55 (26.56)	307.38 (68.77)
AUC_{last} hr•µg/mL)	4999.76 (889.50)	9287.71 (1062.68)	16559.07 (3237.85)	9787.86 (2596.95)	15179.31 (3041.56)	21233.42 (6000.61)
$AUC_{0\text{-}INF}$ (hr•µg/mL)	8017.17 (1867.56)	14667.36 (2253.50)	23677.73 (4953.72)	18439.02 (9700.33)	24695.63 (7794.47)	33520.23 (12052.46)
V_{ss} (mL/kg)	85.48 (17.23)	89.10 (26.57)	70.14 (12.18)	46.34 (7.60)	53.31 (8.36)	59.49 (16.91)
CL (mL/hr/kg)	0.52 (0.14)	0.56 (0.09)	0.53 (0.11)	0.26 (0.11)	0.36 (0.14)	0.41 (0.20)
$t_{1/2\beta}$ (hr)	126.48 (45.77)	122.57 (55.36)	101.89 (15.38)	146.49 (58.88)	114.86 (36.42)	107.97 (21.55)

SD Standard deviation, N Number of animals

(Excerpted from Applicant's submission)

Parameters	DM4 (IMGN853)					
	Day 1			Day 22		
	4 N=5	8 N=4*	12 N=5	4 N=5	8 N=5	12 N=4
t_{max} (hr)	0.5 (0)	0.5 (0)	0.5 (0)	0.5 (0)	0.8 (0.67)	0.5 (0)
C_{max} (ng/mL)	0.642 (0.135)	1.105 (0.194)	1.986 (0.320)	0.701 (0.098)	1.482 (0.202)	1.610 (0.405)
AUC_{last} (hr•ng/mL)	5.962 (0.654) [a]	16.122 (6.925)	31.761 (1.794)	6.956 (0.926)	26.812 (9.146)	30.482 (8.029)
AUC_{0-INF} (hr•ng/mL)	8.973 (2.129) [a]	29.187 (13.224)	39.870 (3.304)	10.340 (1.050)	38.717 (21.803)	38.864 (9.548)

[a]N=4, SD Standard deviation, N Number of animals
*One animal was removed as an outlier (F35974)

(Excerpted from Applicant's submission)

Parameters	S-methyl DM4 (IMGN853)					
	Day 1			Day 22		
	4 mg/kg N=2	8 mg/kg N=3	12 mg/kg N=5	4 mg/kg N=0	8 mg/kg N=3	12 mg/kg N=3
t_{max} (hr)	24; 8	13.333 (9.238)	24 (0)	NA	59.333 (94.156)	13.193 (9.361)
C_{max} (ng/mL)	0.118; 0.104	0.166 (0.107)	0.182 (0.014)	NA	0.170 (0.086)	0.169 (0.018)
AUC_{last} (hr•ng/mL)	1.416; 0.416	1.535 (1.681)	8.235 (4.602)	NA	12.237 (17.157)	2.469 (1.307)

SD Standard deviation, N Number of animals

(Excerpted from Applicant's submission)

Study title/ no.: 12-Week study of IMGN853 and M9346A-SPDB-DM4 conjugate following intravenous infusion administration in Dutch Belted rabbits with a 3-week recovery/CVT28-003 Male rabbits (n = 5/group), IV once every 3 weeks of 0, 4, 8, or 12 mg/kg/dose of either IMGN853 or M9346A-SPDB-DM4 (ADC with different linker)*. Blood was collected on Days 2, 4, 6, 13, 20, and 22 at pre-dose, 5, 10, and 24 hours post-dose. *Data was not included in review	**IMGN853** *Accumulation*: slight accumulation (≤ 2-fold) of IMGN853 *Dose proportionality*: mean exposure (C_{max} and AUC) for IMGN853, its total antibody, and DM4 concentrations increased dose proportionally as dose increased from 4 to 8 mg/kg, but less than dose proportional from 8 to 12 mg/kg. In addition, mean exposure for S-methyl DM4 was less than dose proportional from 8 to 12 mg/kg. The exposure level for S-methyl DM4 at 4 mg/kg was not determined.

Parameters	IMGN853					
	Day 1			Day 64		
	4 mg/kg n=5	8 mg/kg n=4	12 mg/kg n=5	4 mg/kg n=5	8 mg/kg n=5	12 mg/kg n=5
t_{max} (hr)	0.083 (0)	0.083 (0)	0.083 (0)	0.083 (0)	0.083 (0)	0.083 (0)
C_{max} (ug/mL)	106 (22)	220 (24)	311 (37)	112 (26)	241 (66)	340 (41)
AUC_{last} (hr•ug/mL)	6088 (818)	14111 (1361)	13274 (5534)	7733 (8374)	10114 (14590)	20742 (23376)
$AUC_{0\text{-}INF}$ (hr•ug/mL)	6167 (865)	14136 (1402)	15942 (3838)[a]	16916 (427)[b]	36168[c]	44475 (17638)[b]
V_{ss} (mL/kg)	60.1 (5.1)	46.1 (5.1)	75.2 (32.2)	9.6 (2.6)[b]	7.4[c]	8.0 (0.5)[b]
CL (mL/hr/kg)	0.66 (0.09)	0.57 (0.05)	0.88 (0.27)	0.24 (0.01)[b]	0.22[c]	0.29 (0.12)[b]
$t_{1/2}$ (hr)	81.0 (11.9)	49.6 (14.0)	68.6 (14.2)	102.9 (16.7)[b]	93.6[c]	74.3 (35.3)[b]

[a]n=4, [b]n=2, [c]n=1, SD Standard deviation, n = Number of animals

(Excerpted from Applicant's submission)

Parameters	Total M9346A Antibody (IMGN853)					
	Day 1			Day 64		
	4 mg/kg n=5	8 mg/kg n=4	12 mg/kg n=5	4 mg/kg n=5	8 mg/kg n=5	12 mg/kg n=5
t_{max} (hr)	0.083 (0)	0.083 (0)	1.266 (2.646)	0.083 (0)	0.083 (0)	0.083 (0)
C_{max} (ug/mL)	114 (14)	212 (17)	290 (29)	127 (3)	245 (77)	364 (24)
AUC_{last} (hr•ug/mL)	7942 (1718)	10458 (2778)	18163 (7889)	11202 (12556)	10095 (14887)	24723 (29558)
$AUC_{0\text{-}INF}$ (hr•ug/mL)	10715 (2386)	15172[a]	26637 (4251)[b]	25615 (2714)[c]	37328[a]	54149 (27721)[c]
V_{ss} (mL/kg)	63.3 (14.3)	75.8 (12.8)	80.0 (18.4)	25.4 (9.4)[c]	29.7[a]	15.9 (10.9)[c]
CL (mL/hr/kg)	0.39 (0.09)	0.55 (0.08)	0.57 (0.23)	0.16 (0.02)[c]	0.21[a]	0.26 (0.13)[c]
$t_{1/2}$ (hr)	141.9 (44.0)	106.4 (22.5)	117.1 (37.9)	191.8 (52.1)[c]	174.7[a]	141.8 (58.6)[c]

[a]n=1, [b]n=3, [c]n=2, SD = Standard deviation, n = Number of animals

(Excerpted from Applicant's submission)

Parameters	DM4 (IMGN853)					
	Day 1			Day 64		
	4 mg/kg n=5	8 mg/kg n=4	12 mg/kg n=5	4 mg/kg n=5	8 mg/kg n=5	12 mg/kg n=5
t_{max} (hr)	0.083 (0)	0.083 (0)	0.083 (0)	0.083 (0)	0.083 (0)	0.083 (0)
C_{max} (ng/mL)	1.38 (0.24)	2.30 (0.30)	3.30 (0.37)	1.45 (0.34)	2.32 (0.86)	3.62 (0.43)
AUC_{last} (hr•ng/mL)	19.4 (4.4)	36.5 (4.7)	62.4 (21.7)	15.2 (3.4)	24.6 (7.8)	39.3 (3.4)

SD = Standard deviation, n = Number of animals

(Excerpted from Applicant's submission)

Parameters	S-methyl DM4 (IMGN853)					
	Day 1			Day 64		
	4 mg/kg n=0	8 mg/kg n=1	12 mg/kg n=5	4 mg/kg n=2	8 mg/kg n=4	12 mg/kg n=5
t_{max} (hr)	N/A	10	23.6 (28.0)	17.0 (9.9)	20.5 (7.0)	18.4 (7.7)
C_{max} (ng/mL)	N/A	0.13	0.19 (0.05)	0.11 (0.01)	0.16 (0.03)	0.25 (0.03)
AUC_{last} (hr•ng/mL)	N/A	2.37	9.77 (4.67)	0.88 (0.46)	2.51 (0.90)	3.63 (1.51)

SD = Standard deviation, n = Number of animals, NA = Not applicable

(Excerpted from Applicant's submission)

5.5. Toxicology

5.5.1. General Toxicology

GLP compliant single and repeated dose toxicity studies of IMGN853 and a non-GLP single dose toxicity study of DM4 in cynomolgus monkeys were reviewed previously under IND 111915 and summarized below.

Study title/ number: 10-week intravenous (slow push) toxicity and toxicokinetic study in cynomolgus monkeys with a 5-week recovery period/ CVT28-001

IMGN853 at doses of 0, 2, 4, and 8 mg/kg/dose was administered intravenously (slow push) to cynomolgus monkeys once every 3 weeks for up to 10 weeks (a total of 4 doses) with a 5-week recovery period (n=6/sex/group). No early mortalities occurred. Drug-related clinical signs of toxicity included broken skin, dry skin, discolored skin, scaly skin, sores, scabs, and/or scars noted mostly in monkeys given ≥ 4 mg/kg/dose.

IMGN853-related ophthalmoscopic findings included keratopathy (faint perilimbal corneal pigment migration into cornea, especially superiorly) of both eyes in 3/6 males and 3/6 females at 8 mg/kg/dose in Week 9. Corneal pigmentation was likely secondary to other corneal changes. At the end of recovery period, similar corneal lesions developed in the superior perilimbal cornea in one previously unaffected female at 8 mg/kg/dose. In addition, the lesions (corneal pigmentation) were unchanged in a second female and more advanced in both eyes in a male at 8 mg/kg/dose. Target organs of toxicity associated with IMGN853 in monkeys were hematopoietic system (decreases ≥ 30% in absolute neutrophils, white blood cell, and reticulocytes when compared to control in both sexes at 8 mg/kg dose), injection sites (at 8 mg/kg/dose showed slight to moderate epithelial ulceration/erosion); skin/subcutis (areas other than injection sites in males at 8 mg/kg/dose showed slight to moderate epithelial ulceration/erosion, acanthosis, hyperkeratosis, and edema); cornea (at ≥ 4 mg/kg/dose showed minimal to marked degeneration/necrosis, pigmentation, and attenuation in the corneal epithelium); and skin of the eyelids (at ≥ 4

mg/kg/dose showed minimal to slight epithelial degeneration/necrosis and inflammation). Hematology and histopathology findings were trending towards recovery at end of 5-week recovery period. Histopathology findings of major target organs of toxicity for male and female rats are presented in Table 4 and Table 5, respectively.

However, there were histopathology findings observed during the recovery period only, including minimal axon degeneration in the sciatic nerve in 1/2 females at 8 mg/kg/dose and minimal to slight fibrosis observed in testis in males at ≥ 2 mg/kg/dose IMGN853 in 1/2 males in each dose group.

Table 4 IMGN853-related microcopic findings in male rats

Dose (mg/kg/dose)	0		2		4		8	
Day	71	Rec 36	71	Rec 36	71	Rec 36	71	Rec 36
n	6	2	6	2	6	2	6	2
Eye, Left								
Attenuation, epithelium, cornea								
Marked							1	
Degeneration/necrosis, individual cell, epithelium, cornea								
Minimal					2		2	
Slight							1	
Marked							1	
Infiltrate, lymphocytes/macrophages, choroid								
Minimal		1					1	
Infiltrate, lymphocytes/macrophages, ciliary body								
Minimal	2		3	1	1		1	1
Slight			1				1	
Infiltrate, lymphocytes/macrophages, iris								
Minimal					1		2	
Pigmentation, epithelium, cornea								
Minimal							2	
Eye, Right								
Degeneration/necrosis, individual cell, epithelium, cornea								
Minimal					3		2	
Slight							2	
Infiltrate, lymphocytes/macrophages, choroid								
Minimal			2					

Infiltrate, lymphocytes/macrophages	1	1	2		2	1	2	
Minimal			1				2	1
Slight								
Skin/Subcutis								
Acanthosis/hyperkeratosis								
Moderate							2	
Edema								
Slight							1	
Moderate							1	
Exudate								
Slight							2	
Hemorrhage								
Slight							1	
Inflammation, chronic-active								
Slight							2	
Ulcer/erosion								
Slight							2	

(Table excerpted from 111915 nonclinical review)

Table 5 IMGN853-related microscopic findings in female rats

Dose (mg/kg/dose)	0		2		4		8	
Day	71	Rec 36	71	Rec 36	71	Rec 36	71	Rec 36
n	6	2	6	2	6	2	6	2
Eye, Left								
Degeneration/necrosis, individual cell, epithelium, cornea								
Minimal					3		2	
Slight							2	
Infiltrate, lymphocytes/macrophages, ciliary body								
Minimal			1				1	
Slight	1							
Pigmentation, epithelium, cornea								
Minimal							3	
Eye, Right								
Degeneration/necrosis, individual cell, epithelium, cornea								
Minimal					3		2	
Slight							2	
Infiltrate, lymphocytes/macrophages, ciliary body								
Minimal				1	1			
Slight							1	
Pigmentation, epithelium, cornea								
Minimal							1	
Slight							1	
Eyelid, Lower Left								
Degeneration/necrosis, individual cell, epithelium								
Minimal							2	
Infiltrate, lymphocytes/macrophages								
Minimal							1	
Inflammation, chronic-active								
Slight							1	
Eyelid, Lower Right								
Degeneration/necrosis, individual cell, epithelium								

Study title/number: A single-dose intravenous (slow push) toxicity study of IMGN853 (M9346A-sulfo-SPDB-DM4) in cynomolgus monkeys/ WRT28-001

Five cynomolgus monkeys/sex/group were administered a single dose of IMGN853 at 0, 1, 3, 5, or 10 mg/kg. On Day 5, 3 animals/sex/group were sacrificed. The remaining recovery group animals were sacrificed on Day 29. There were no unscheduled mortalities in this study. The skin was a major target organ based on clinical observations of reddened areas and desquamation and histopathology findings of moderate vasculitis and ulceration. These toxicities occurred before Day 14 and with greater frequency in animals in the 10 mg/kg dose group; however, they were also observed at the lowest dose of 1 mg/kg. The other target organs of toxicity included injection site (minimal to moderate inflammation, ulceration, edema, and hemorrhage), bone marrow (minimal to moderate bone marrow depletion), spleen (mild lymphoid depletion), lymph nodes (mild lymphoid depletion), kidney (minimal to mild mononuclear cell infiltration and calculus formation, along with mild changes in clinical chemistry including decreased urea nitrogen and phosphorus at the 10 mg/kg dose), and lung (mild pleural fibrosis in the lung). Histopathology findings in bone marrow, kidney, and lungs were still observed at end of recovery period with less severity. There were no positive findings for anti-IMGN853 or anti-DM4 antibody production in any animals.

Study title/number: Single dose toxicity study of maytansinoid DM4 in cynomolgus monkeys/ CRT14-001

Monkeys were IV administered DM4 (L-DM4) at a dose of 0.1 mg/kg (n = 2/sex/ group) on Day 1 and euthanized on Day 5 (1/sex/group) and Day 29 (1/sex/group). No eye examination was performed/reported. All animals survived to the end of the study. Target organs of DM4 in monkeys include bone marrow (moderate to severe erythroid and myeloid depletion), lung (mild alveolar hemorrhage, erythrophagocytosis, and pigment), and inflammation in several organs (minimal to mild mononuclear cell infiltration in stomach, esophagus, and site of injection). Microscopic findings in eye included minimal and mild mononuclear cell infiltrates in ciliary body and minimal mononuclear cell infiltration in uvea.

5.5.2. Genetic Toxicology

<u>In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)</u>

Study title/ number: DM4: bacterial reverse mutation assay/ CVT14-001

Key Study Findings:

- DM4 was negative with all tester strains in the presence and absence of S9 activation in the bacterial reverse mutation assay

GLP compliance: Yes

Test system: Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and Escherichia coli strain WP2 *uvr*A; +/-S9 up to 5000 µg/plate

Study is valid: Yes

Study title/ number: S-methyl-DM4: bacterial reverse mutation assay/ CVT14-002
Key Study Findings:

- S-methyl-DM4 (metabolite of DM4) was negative with all tester strains in the presence and absence of S9 activation in the bacterial reverse mutation assay

GLP compliance: Yes
Test system: Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and Escherichia coli strain WP2 *uvr*A; +/-S9 up to 5000 µg/plate.
Study is valid: Yes

<u>In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)</u>
Study title/ number: DM4: in vivo rat bone marrow micronucleus assay/ CVT14-003
Key Study Findings:

- DM4 was clastogenic in male rats at 0.04 mg/kg.

GLP compliance: Yes
Test system: Rat bone marrow from animals administered DM4 intravenously twice (approximately 24 hours apart) at 0.01, 0.02, and 0.04 mg/kg. The positive control was cyclophosphamide and administered by oral gavage at 60 mg/kg/day.
Study is valid: Yes

Results

- DM4 induced statistically significant increases in the mean percent of micronucleated polychromatic erythrocytes (PCE) in the high dose group when compared to the vehicle control. The increases in micronucleated PCEs were outside of both the historical vehicle control range and the 95% confidence interval.

Micronucleus Assay – 24-Hour Summary Table (Males)

Study No.: 8323435
Test Article: DM4 Species/Strain: Rat: Sprague-Dawley (SD)
Initiation of Dosing: 28 March 2016

Treatment group (mg/kg/day)	Harvest Time (hours)	Sex	% PCE	Group mean % micronucleated PCE per treatment group (±sd)
Vehicle, 0	24	M	46.36	0.03 ± 0.03
0.010	24	M	44.60	0.06 ± 0.03
0.020	24	M	44.68	0.05 ± 0.04
0.040	24	M	35.20	0.71 ± 0.14***
CP, 60.0 [a]	24	M	38.67	0.98 ± 0.14***

*** = $P \leq 0.001$
[a] = The positive control was dosed once 24 hours prior to bone marrow harvest.
CP = Cyclophosphamide
PCE = Polychromatic erythrocyte
Vehicle = 0.9% NaCl:Tween 20:Ethanol (84:8:8)

(Excerpted from Applicant's submission)

Study title/ number: S-methyl-DM4: in vivo rat bone marrow micronucleus assay/ CVT14-004
Key Study Findings:

- S-methyl-DM4 was clastogenic in male rats at 0.02 and 0.04 mg/kg.

GLP compliance: Yes
Test system: Rat bone marrow from animals administered S-methyl-DM4 intravenously twice (approximately 24 hours apart) at 0.01, 0.02, and 0.04 mg/kg. The positive control was cyclophosphamide and administered by oral gavage at 60 mg/kg/day.
Study is valid: Yes

Results

- S-methyl-DM4 induced a dose-dependent and statistically significant increase in the mean percent of micronucleated PCEs in the mid and high dose groups, compared to the vehicle control. The increase in micronucleated PCEs in the high dose group were outside the historical vehicle control range and the 95% confidence interval. In addition, S-methyl-DM4 was cytotoxic to the bone marrow at 0.04 mg/kg/day.

Micronucleus Assay – 24-Hour Summary Table (Males)

Study No.: 8323437
Test Article: s-methyl-DM4 Species/Strain: Rat: Sprague-Dawley (SD)
Initiation of Dosing: 30 March 2016

Treatment group (mg/kg/day)	Harvest Time (hours)	Sex	% PCE	Group mean % micronucleated PCE per treatment group (±sd)	
Vehicle, 0	24	M	47.30	0.04 ±	0.03
0.010	24	M	45.27	0.06 ±	0.03
0.020	24	M	44.53	0.13 ±	0.04***
0.040	24	M	39.60	0.44 ±	0.23***
CP, 60.0 [a]	24	M	42.20	1.60 ±	0.75***

*** $P \leq 0.001$
[a] = The positive control was dosed once 24 hours prior to bone marrow harvest.
CP = Cyclophosphamide
PCE = Polychromatic erythrocyte
Vehicle = 0.9% NaCl:Tween 20:Ethanol (84:8:8)

(Excerpted from Applicant's submission)

5.5.3. Carcinogenicity

Carcinogenicity studies were not needed to support the advanced cancer indication, consistent with ICH S9 guidance.

5.5.4. Reproductive and Developmental Toxicology

No reproductive or developmental animal toxicity studies were conducted with mirvetuximab soravtansine. The cytotoxic component of ELAHERE, DM4, disrupts microtubule function, is genotoxic, and can be toxic to actively dividing cells, suggesting it has the potential to cause embryotoxicity and teratogenicity.

5.5.5. Other Toxicology Studies

Ocular toxicity:

Study title/ Study number : 4 week intravenous infusion ocular toxicity and toxicokinetic study with IMGN853 (M9346A-sulfo-SPDB-DM4) and M9346A-SPDB-DM4 administered once weekly to male Dutch belted rabbits with a 3-week recovery phase /CVT28-002

Key Study Findings

- Administration of 12 mg/kg/dose IMGN853 in 1 out of 5 males was associated with early moribund sacrifice due to body weight loss, anorexia, and skin lesions on Day 22.
- IMGN853-related microscopic findings of minimal to moderate attenuation and degeneration/necrosis (individual cell) of the corneal epithelium were noted in the eyes of animals administered IMGN853 at ≥ 4 mg/kg/dose. Slight to moderate corneal pigmentation was present in animals given 12 mg/kg/dose of IMGN853. These findings were still observed at end of recovery period.

GLP compliance: Yes

Methods

Dose and frequency of dosing:	4, 8, 12 mg/kg/dose of IMGN853 (M9346A-sulfo-SPDB-DM4) or 4, 8, 12 mg/kg/dose of M9346A-SPDB-DM4* administer once weekly *M9346A-SPDB-DM4 contains a different drug linker, and data were not included in this review.
Route of administration:	Intravenous infusion over 15 or 30 minutes
Formulation/Vehicle:	(b) (4) mM acetate, 9% (w/v) sucrose, (b) (4)% (w/v) (b) (4) (polysorbate 20), pH 5.02
Species/Strain:	Dutch Belted rabbits
Number/Sex/Group:	N = 5 males/group
Age:	17 to 19 weeks old
Satellite groups/ unique design:	No
Deviation from study protocol affecting interpretation of results:	No

Study design

Group[a,b]	Test Article	No. of Animals[c] Male	Dose Level (mg/kg/dose)	Dose Concentration (mg/mL)[d]	Dose Volume (mL/kg)
1 (Control)	Vehicle Control Article	5	0	0	2.35
2 (Low)	IMGN853	5	4	5.1	0.78
3 (Mid)	IMGN853	5	8	5.1	1.57
4 (High)	IMGN8531	5	12	5.1	2.35
5 (Low)	M9346A-SPDB-DM4	5	4	5.3	0.75
6 (Mid)	M9346A-SPDB-DM4	5	8	5.3	1.51
7 (High)	M9346A-SPDB-DM42	5	12	5.3	2.26

a Group 1 received vehicle control article only.
b Subgroup 1 consisted of the first two animals/group and Subgroup 2 consisted of the second three animals/group. Day 1 of the dosing phase was defined as the first day of dose administration for each subgroup. The subgroup- initiation was staggered by 1 day.
c Animals designated for terminal sacrifice (up to three animals/group) were sacrificed on Day 29 of the dosing phase. Animals designated for recovery sacrifice (two animals/group) underwent 3 weeks of recovery following completion of the dosing phase (Day 29 of the dosing phase) and were sacrificed on Day 22 of the recovery phase.
d Dose concentrations were based on the actual concentration of each test article (mg antibody) as supplied by the sponsor.

(Excerpted from Applicant's submission)

Observations and Results: changes from control

<table>
<tr><th>Parameters</th><th>Major findings</th></tr>
<tr><td>Mortality</td><td>
<table>
<tr><th>Dose level</th><th>No. of animals</th><th>Findings</th></tr>
<tr><td>12 mg/kg IMGN853</td><td>1/5</td><td>This animal was moribund sacrificed on Day 22 because of weight loss and macroscopic findings on skin at the front limbs (bilateral dark red areas up to 5 mm squared in size). Microscopically, there were areas of ulceration and associated inflammation, acanthosis/hyperkeratosis, and exudation of the skin.</td></tr>
</table>
</td></tr>
<tr><td>Clinical Signs</td><td>Dosing Phase
<table>
<tr><th>Observation</th><th>Dose level (mg/kg)</th><th>No. of animals</th><th>Day of observation</th></tr>
<tr><td>Skin and pelage</td><td></td><td></td><td></td></tr>
<tr><td>-Scab at front legs, left ear, midline cervical, right ear, scrotum</td><td>8</td><td>2/5</td><td>15-16, 22</td></tr>
<tr><td>-Alopecia, front legs</td><td>12</td><td>2/5</td><td>15-16</td></tr>
<tr><td>-Discolored hair coated</td><td></td><td>1/5</td><td>8-16, 19-23, 26-27, 28-29</td></tr>
<tr><td>-Discolored skin at ears, midline cervical, ventral cervical, and scrotum</td><td>12</td><td>2/5</td><td>8-29</td></tr>
<tr><td>-Dry skin, ear</td><td>12</td><td>2/5</td><td>22, 23, 28-29</td></tr>
<tr><td>-Scab at ear, legs, scrotum, and ventral cervical</td><td>12</td><td></td><td>8-11, 14-16, 19-21, 26, 27</td></tr>
<tr><td>-Thinning hair coat, both axilla</td><td>12</td><td>1/5</td><td>8, 12, 15-18, 22</td></tr>
<tr><td>-Thinning hair coat, ventral thorax</td><td>12</td><td>2/5</td><td>15, 16, 22</td></tr>
</table>
</td></tr>
</table>

-Thinning hair coat at ventral cervical	12	2/5	8, 12, 22

Recovery Phase
-Abnormal appearances (i.e., irregular ambulation, knuckling on ambulation and short stride of forefeet, and thin appearance) were observed in 1/2 M administered 12 mg/kg IMGN853.
-Reduction in food consumption was still observed at 8-12 mg/kg of IMGN853 in 2/2 M.
-Red color skin at the hind foot and ventral cervical was observed in 1/2 M at 12 mg/kg IMGN853.
-Dry skin at the ears was observed in 2/4 M at 8 mg/kg IMGN853.

Body Weights

Terminal sacrifices (compared to VH control)

- A 12% decrease in body weight was observed on Day 29 in animals administered 12 mg/kg.

Recovery
Changes in body weight normalized to control means at end of recovery period.

Ophthalmoscopy

Terminal sacrifices (compared to VH control)

Dose level (mg/kg)	Day of observation	No. of animals	Findings
8	22	1/5	Multifocal subepithelial punctate microcystic lesions were observed in the immediate perilimbal cornea in both eyes.
	29	2/5	A slight multifocal punctate staining was observed in the perilimbal region of four eyes of two animals.
12	15	4/5	Multifocal subepithelial punctate microcystic lesions were present in the immediate perilimbal cornea of both eyes of these animals.
	22	4/5	
	29	3/4	

Recovery

Dose level (mg/kg)	Day of observation	No. of animals	Findings
4	8	1/2	A slight multifocal punctate fluorescein stain retention affecting 1-25% of the perilimbal cornea in both eyes.
	15	2/2	Subtle multifocal subepithelial punctate microcystic lesions in the immediate perilimbal cornea were observed in both eyes with a slight multifocal punctate fluorescein stain retention (1-25% of the perilimbal cornea). These findings were resolved on Day 22.
8	15	2/2	A slight multifocal punctate fluorescein stain retention, affecting 1 to 25% of the

				perilimbal cornea, was observed in both eyes.
		22	1/2	A slight multifocal punctate fluorescein stain retention, affecting 1 to 25% of the perilimbal cornea, was observed in both eyes. In addition, a faint pigment was present in the perilimbal clear cornea in both eyes.
	12	8	2/2	Faint perilimbal pigment was present in both eyes with slight multifocal perilimbal corneal fluorescein stain retention observed in both eyes of these animals.
		15	1/2	
		22	2/2	

Gross Pathology: Unremarkable

Histopathology Adequate battery: Yes
Peer review: No

Terminal sacrifices (excluded unscheduled sacrifices)

	Males			
Dose levels (mg/kg)	**0**	**4**	**8**	**12**
Total number of animals	**3**	**3**	**3**	**2**
Eye, left				
Attenuation, epithelium, cornea				
Minimal		2	3	
Slight				1
Moderate				1
Degeneration/necrosis, individual cell, epithelium, cornea				
Minimal		1	2	
Slight				2
Pigmentation, epithelium, cornea				
Slight				1
Eye, right				
Attenuation, epithelium, cornea				
Minimal		3	2	2
Slight			1	
Degeneration/necrosis, individual cell, epithelium, cornea				
Minimal		1	3	1
Marked				1
Pigmentation, epithelium, cornea				
Moderate				1
Foreign material, adherent, cornea				
Slight				1

Recovery

- A minimal to slight attenuation of corneal epithelium in both left and right eyes was still observed in 1-2/2 M at 4-12 mg/kg.
- A minimal to slight pigmentation in the corneal epithelium in the left eye was observed in 1M at 8-12 mg/kg.
- A minimal chronic-active inflammation was observed in the lower right eye lid in 1M in all treated groups.

LD: low dose; MD: mid dose; HD: high dose.
-: indicates reduction in parameters compared to control.

Study title/ Study number: 12-week study of IMGN853 and M9346A-SPDB-DM4 conjugate following intravenous infusion administration in Dutch Belted rabbits with a 3-week recovery/ CVT28-003

Key Study Findings

- IMGN853-related microscopic findings of minimal to slight attenuation and degeneration/necrosis (individual cell) of the corneal epithelium were noted in the eyes of animals administered IMGN853 at 12 mg/kg/dose. Slight atrophy of harderian gland was present in the cornea of animals given 12 mg/kg/dose of IMGN853. Changes were trending towards recovery at end of recovery period.

GLP compliance: Yes

Methods

Dose and frequency of dosing:	4, 8, and 12 mg/kg/dose of IMGN853 (M9346A-sulfo-SPDB-DM4) or M9346A-SPDB-DM4 conjugate* once every 3 weeks for 12 weeks *M9346A-SPDB-DM4 contains a different drug linker, and data were not included in this review.
Route of administration:	Intravenous infusion over 15-30 minutes
Formulation/Vehicle:	(b) (4) mM acetate, 9% [w/v] sucrose, (b) (4) % [w/v] (b) (4) [polysorbate 20], pH 5.02
Species/Strain:	Dutch Belted rabbits
Number/Sex/Group:	5 males/ group
Age:	18 to 19 weeks old
Satellite groups/ unique design:	No
Deviation from study protocol affecting interpretation of results:	No

Study Design

Group[a]	Treatment	No. of Animals[b] Male	Dose Level (mg/kg/dose)	Dose Concentration[c] (mg/mL)	Dose Volume (mL/kg)
1	Vehicle	5	0	0	2.50
2	IMGN853	5	4	5.1	0.78
3	IMGN853	5	8	5.1	1.57
4	IMGN853	5	12	5.1	2.35
5	M9346A-SPDB-DM4 conjugate	5	4	4.8	0.83
6	M9346A-SPDB-DM4 conjugate	5	8	4.8	1.67
7	M9346A-SPDB-DM4 conjugate	5	12	4.8	2.50

Vehicle = Vehicle Control Article.
a Group 1 was administered vehicle control article only.
b Animals designated for terminal sacrifice (up to three animals/group) were sacrificed on Day 85 of the dosing phase. Animals designated for recovery sacrifice (two animals/group; dependent on survival and one animal from Group 7) underwent 3 weeks of recovery following completion of the dosing phase (Day 85 of the dosing phase) and were sacrificed on Day 22 of the recovery phase.
c Dose concentrations were based on the actual concentration of each test article (mg antibody) as supplied by the sponsor.

(Excerpted from Applicant's submission)

Observations and Results: changes from control

<table>
<tr><th>Parameters</th><th>Major findings</th></tr>
<tr><td>Mortality</td><td>-There was no mortality for IMGN853.</td></tr>
<tr><td>Clinical Signs</td><td>
<u>Dosing Phase</u>
<table>
<tr><th>Observation</th><th>Dose level (mg/kg)</th><th>No. of animals</th><th>Day of observation</th></tr>
<tr><td>Appearance</td><td></td><td></td><td></td></tr>
<tr><td>Raised, left third eyelid</td><td>12</td><td>1/5</td><td>64-85</td></tr>
<tr><td>Swollen, right ear</td><td>8</td><td>1/5</td><td>9-17, 20-21</td></tr>
<tr><td>Swollen, ventral cervical</td><td>8</td><td>2/5</td><td>21-22</td></tr>
<tr><td>Behavior</td><td></td><td></td><td></td></tr>
<tr><td>Hypoactive</td><td>12</td><td>1/5</td><td>1-2</td></tr>
<tr><td>Respiration</td><td></td><td></td><td></td></tr>
<tr><td>Decreased respiration</td><td>12</td><td>1/5</td><td>1</td></tr>
<tr><td>Skin and pelage</td><td></td><td></td><td></td></tr>
<tr><td>Blister-like lesion, left ear</td><td>12</td><td>1/5</td><td>28-30</td></tr>
<tr><td>Blister-like lesion, right ear</td><td>8</td><td>1/5</td><td>48-51</td></tr>
<tr><td></td><td>12</td><td>1/5</td><td>7-10, 15-16</td></tr>
<tr><td>Scab, left ear</td><td>8</td><td>1/5</td><td>22</td></tr>
<tr><td></td><td>12</td><td>1/5</td><td>6-7</td></tr>
<tr><td>Scab, right ear</td><td>8</td><td>2/5</td><td>52-53</td></tr>
<tr><td></td><td>12</td><td>1/5</td><td>31-36</td></tr>
<tr><td>Scaly skin, ears</td><td>12</td><td>1/5</td><td>11</td></tr>
<tr><td>Scaly skin, left ear</td><td></td><td>1/5</td><td>34-43, 78-83</td></tr>
<tr><td>Scaly skin, right ear</td><td>4</td><td>1/5</td><td>4-5</td></tr>
<tr><td></td><td>8</td><td>1/5</td><td>24-38</td></tr>
<tr><td></td><td>12</td><td>1/5</td><td>65</td></tr>
</table>
<u>Recovery</u>
-All changes in clinical signs were not observed at end of recovery period.
</td></tr>
<tr><td>Body Weights</td><td>Unremarkable</td></tr>
<tr><td>Ophthalmoscopy</td><td>
<u>Terminal sacrifices (compared to VH control)</u>
<table>
<tr><th>Dose level (mg/kg)</th><th>Day of observation</th><th>No. of animals</th><th>Findings</th></tr>
<tr><td>4</td><td>15</td><td>1/5</td><td>Faint bilateral multifocal punctate corneal microcyst affecting the superior quadrant of the cornea and slight multifocal punctate fluorescein stain retention over the</td></tr>
</table>
</td></tr>
</table>

			microcystic lesion. Findings resolved by Day 22.
12	8-71	5/5	Multifocal punctate perilimbal corneal microcysts in the superior quadrant were observed in one animal on Day 8 of the dosing phase. By Day 71 of the dosing phase, all five animals had test-article corneal changes. The changes consisted of multifocal punctate fluorescein stain retention in the superior perilimbal area and the microcyst. However, on Day 85 of the dosing phase, these changes were trending towards less severity compared to Day 71.

Recovery

- In the 12 mg/kg dose group, one animal had no visible lesions whereas the other animal had only perilimbal corneal pigmentation, suggesting changes were trending towards recovery.

Gross Pathology

Unremarkable

Histopathology

Terminal sacrifices (excluded unscheduled sacrifices)

	Males			
Dose levels (mg/kg)	**0**	**4**	**8**	**12**
Total number of animals	**3**	**3**	**3**	**3**
Conjunctiva bulbar, left				
Infiltrate, mixed cell				
Slight				1
Infiltrate, mononuclear cell				
Minimal				1
Conjunctiva, palpebral, lower left				
Infiltrate, neutrophils/ heterophils				
Minimal				1
Conjunctiva, neutrophils/heterophils				
Infiltrate, neutrophils/ heterophils				
Minimal				1
Eye, left				
Attenuation, epithelium, cornea				
Minimal				2
Slight				1
Degeneration/necrosis/individual cell, epithelium, cornea				
Minimal				2
Eye, right				
Attenuation, epithelium, cornea				
Minimal			2	1
Slight				1

	Degeneration/necrosis, individual cell, epithelium, cornea Minimal				1
	Eyelid, lower left Infiltrate, mixed cell Slight				1
	Eyelid, upper left Infiltrate, mononuclear cell Minimal				1
	Eyelid, upper right Infiltrate, mononuclear cell Minimal				1
	Harderian gland, left Atrophy Slight				1
	Lacrimal gland, left Atrophy Moderate Infiltrate, mononuclear cell Minimal Moderate				 1 1 1
	Nictitating, membrane, left Infiltrate, neutrophils/ heterophils Minimal				1
	Recovery • Minimal neutrophil infiltrates in the lower left of conjunctiva palpebral and eyelid of lower right eye were still observed in 1/2 M at 12 mg/kg. • A minimal attenuation of corneal epithelium in the right eye was still observed in 1/2 M at 12 mg/kg.				

LD: low dose; MD: mid dose; HD: high dose.
-: indicates reduction in parameters compared to control.

Phototoxicity:

Study Title/Number: DM4: in vitro Balb/c 3T3 neutral red uptake phototoxicity assay/CVT14-005

Methods: The objective of this GLP-compliant study was to evaluate the phototoxicity potential of DM4 (0.0316-100 µg/mL) as measured by the relative reduction in viability of Balb/c 3T3 mouse fibroblasts exposed to DM4 and ultraviolet radiation (+UVR), as compared with the viability of fibroblasts exposed to DM4 in the absence of ultraviolet radiation (-UVR). Chlorpromazine (0.01-100 µg/mL) was used as the positive control. Chlorpromazine cytotoxicity and phototoxicity criteria were met, indicating that the assay was valid.

Results: Per OECD guideline, DM4 has phototoxicity potential under the conditions tested.

Test Article	IC_{50} Absence of UV-A (µg/mL)	IC_{50} Presence of UV-A (µg/mL)	PIF Value
DM4	8.712	0.582	15.17
Chlorpromazine	62.21	1.084	57.63*

* PIF >6, therefore positive control response was acceptable.

(Excerpted from Applicant's submission)

Immunohistochemistry:

Study Title/Number: Evaluation of FRα in normal human eye FFPE samples by immunohistochemistry/IMH28-018

Methods: Grade 1-2 eye adverse reactions (blurred vision, keratopathy, and dry eye) have been observed in some of the patients treated with mirvetuximab soravtansine in the Phase 1 clinical trial. To help understand whether these adverse reactions are target related, the Applicant evaluated FRα expression in a panel of nine normal human eye fixed paraffin embedded (FFPE) samples. Multiple eye compartments present across all these samples including cornea, limbus, conjunctiva, iris, retina, sclera, choroid, optic nerve, and ciliary body were evaluated.

Results:
The results showed that FRα was not present in eight of the eye structures studied, including cornea epithelia, limbal cells, conjunctiva, iris, retina epithelia, sclera, choroid, and optic nerve. However, FRα positivity was found in the epithelial cells of ciliary body.

X X

Primary Reviewer
Wimolnut Manheng

Supervisor
Tiffany K. Ricks

6 Clinical Pharmacology

6.1. Executive Summary

Mirvetuximab soravtansine (ELAHERE) is an ADC consisting of a anti-FRα monoclonal antibody (immunoglobulin G1 [IgG1]) attached via a cleavable linker to the cytotoxic maytansinoid payload, DM4. Upon release from the antibody, DM4 inhibits tubulin polymerization and microtubule assembly, resulting in cell cycle arrest and apoptosis. The proposed indication for mirvetuximab soravtansine is the 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.

In the pivotal phase 3 trial, the ORR INV per RECIST v1.1 was 31.7% (95% CI: 22.9, 41.6). Median DOR was 6.9 months (95% CI: 5.6, 9.7). Results for ORR and DOR as assessed by BICR were generally consistent with results as assessed by INV, with an overall concordance of 86% for ORR assessment between INV and BICR.

A major focus of this review was the appropriateness of the proposed dosage of 6 mg/kg adjusted ideal body weight (AIBW) administered every 3 weeks (Q3W). Dosages ranging from 0.15-7 mg/kg total body weight and 5 to 6 mg/kg AIBW Q3W were investigated in the dose escalation study. The recommended dose (i.e., 6 mg/kg AIBW Q3W) was identified as the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) in the dose finding trial. The major safety concern for this drug is ocular toxicity. The rate of ocular AEs in patients treated with mirvetuximab soravtansine was 59%, including blurred vision (46%) and keratopathy (37%). In addition, 35% of patients did not have resolution of their ocular AEs at the last follow-up.

Exposure-response relationship for efficacy (ORR) and safety (ocular AEs of Grade 2+ and peripheral neuropathy Grade 2+) were observed at the proposed 6 mg/kg AIBW Q3W dosage. Exposure-efficacy analysis at the 6 mg/kg AIBW Q3W dose level indicated that over the range of exposures achieved at this dose level, lower exposure (AUC) was correlated with lower ORR. However, there was no relationship between maximum plasma concentration (C_{max}) of mirvetuximab soravtansine and ORR. Additionally, there was a correlation between C_{max} and incidence of Grade2+ ocular toxicities. There was insufficient evaluation of the alternative dosing schedules (e.g., modified weekly dosing regimen) that maintains the overall exposure (ie., lowering C_{max}, which is correlated with ocular toxicities while maintaining the overall exposure, or AUC, that is associated with efficacy). Therefore, a dose finding PMR will be issued for the following reasons:

- Dose exploration study was not robust and did not provide sufficient evidence that the optimal dosage has been identified to maximize the risk-benefit profile.
- Mirvetuximab soravtansine caused very high rate of ocular toxicity

The review team also evaluated the dosing recommendations for patients with hepatic impairment (HI). The clinical data contained limited to no information on patients with moderate or severe HI. Population PK analysis indicated that patients with mild HI had similar exposures of DM4 and its metabolite, s-methyl DM4 compared to patients with normal hepatic function. Further, based on the available safety data, there was no apparent impact of hepatic impairment on the safety including ocular AEs at the recommended dose of mirvetuximab soravtansine. Therefore, no dose-modification may be necessary for patients with mild HI. With regards to moderate or severe HI, unconjugated DM4 and s-methyl DM4 exposures are expected to increase in these patients. Additionally, liver metastasis is commonly reported in patients with ovarian cancer. Therefore, avoiding use of mirvetuximab soravtansine in patients with moderate or severe HI would deprive patients with poor baseline liver function (e.g., moderate HI). Therefore, a PMR will be issued to evaluate an appropriate starting dose of mirvetuximab soravtansine in patients with moderate hepatic impairment.

6.1.1. Recommendations

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

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Primary evidence of the effectiveness of mirvetuximab soravtansine in the proposed indication is derived from Study 0417. The observed ORR by IRC (primary endpoint) was 32.4% (95% CI: 23.6- 42.2%). BORs included 5 patients (4.8%) with CR and 29 patients (27.6%) with PR. The median DOR was 5.9 months (95% CI: 5.6, 7.7 months) by IRC. The exposure-response analysis identified a correlation between exposure and probability of achieving ORR. The analysis was conducted with data primarily from one dose level and thus needs to be interpreted with caution.
General dosing instructions	The proposed recommended dosage of mirvetuximab soravtansine is 6 mg/kg AIBW Q3W administered as an IV infusion.
Dosing in patient Subgroups (intrinsic and extrinsic factors)	• No dosage modification is recommended for patients with mild HI (NCI-ODWG criteria). Mirvetuximab soravtansine should be avoided in patients with moderate or severe HI. • No dosage modification is recommended for patients with mild to moderate renal impairment (CLcr ≥ 30 mL/min). There are no data in patients with severe renal impairment (CLcr < 30 mL/min).

	• No mirvetuximab soravtansine dosage modification is recommended when used concomitantly with CYP3A inhibitors. Patients will be closely monitored for adverse reactions (including ocular AEs) when used concomitantly with strong CYP3A4 inhibitors.
Labeling	The clinical pharmacology review team has specific content and formatting change recommendations for the product labeling. Key modifications to the label made by the FDA include the recommendations to add dosing instructions in Section 8.6, Section 8.7 and the format and content in Section 12.3 and 12.6.
Bridge between the to-bemarketed and clinical trial formulations	During development, there were no changes to the formulation.

PMR or PMC	Key Issues to be Addressed	Rationale	Key Considerations for Design Features
PMR	Dose Selection	The Applicant's recommended dosing regimen of mirvetuximab soravtansine is 6 mg/kg based on adjusted ideal body weight (AIBW), every three weeks (Q3W) for the 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. Among 106 patients who received treatment ELAHERE 6 mg/kg Q3W in the pivotal Study (IMGN853-0417), ocular AEs of all grades occurred in 59% of patients. The limited data obtained from the dose escalation study suggest that alternative dosing schedules; specifically, a fractionated dosing regimen where smaller doses are administered more frequently, could possibly lower the incidence of ocular adverse events. Given the high rates of ocular toxicity observed with the 6 mg/kg Q3W dose, and limited data available at alternative dosing	Conduct a randomized clinical trial of at least 2 dose schedules of mirvetuximab soravtansine to characterize the safety and efficacy of the recommended dosage of 6 mg/kg AIBW Q3W and alternative dosing schedule(s) (i.e., modified weekly dosing regimen, where lower doses are administered at a weekly frequency, instead of every 3 weeks) for the 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. The study should evaluate safety parameters including ocular AEs (all grade, Grade ≥ 2), peripheral neuropathy (all grade, Grade ≥ 2), and other

		regimens, additional clinical safety and efficacy information for mirvetuximab soravtansine is needed to determine the appropriate dosing regimen that will minimize the serious risk of ocular toxicity without a clinically significant impact on efficacy.	adverse events of interest and efficacy. The study should evaluate efficacy parameters of the alternate dosing schedules. The study should also include sufficient clinical pharmacokinetic sampling to analyze the exposure-response relationship for efficacy and safety.
PMR	Hepatic impairment	Based on nonclinical data, DM4 and s-methyl DM4 are CYP3A substrates. Hepatic metabolism and/or excretion is expected to play a major role in the elimination of unconjugated DM4 and s-methyl DM4 given that urinary elimination was negligible. Therefore, hepatic impairment may increase the exposure of unconjugated DM4 and s-methyl DM4 and thereby increase the risk of drug toxicity. There is limited to no data in patients with moderate to severe hepatic impairment. Additional information is required to determine appropriate and safe dosing of mirvetuximab soravtansine in patients with moderate hepatic impairment.	Conduct an open-label, non-randomized, dose-escalation trial, with expansion in a sufficient number of patients, to determine an appropriate starting dose of mirvetuximab soravtansine in patients with moderate hepatic impairment, according to the National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria, in the target patient population. Collect safety and pharmacokinetic information for mirvetuximab soravtansine, unconjugated DM4, and s-methyl DM4 from the trial and utilize this information to determine the appropriate starting dose of mirvetuximab soravtansine for this population.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Mechanism of Action: Mirvetixumab soravtransine-gynx is an antibody-drug conjugate (ADC) containing a chimeric IgG1 monoclonal antibody targeting folate receptor alpha (FRα) and a cytotoxic payload (DM4), which is a microtubule inhibitor, attached to the antibody via a cleavable linker. Upon release from the antibody, DM4 disrupts the microtubule network within the cell, resulting in cell cycle arrest and apoptotic cell death.

Absorption: Mirvetixumab soravtransine-gynx is administered as an IV infusion. Peak mirvetuximab soravtansine-gynx concentrations were observed near the end of intravenous infusion, while peak unconjugated DM4 concentrations were observed on the second day after administration of mirvetuximab soravtansine-gynx, and the peak S-methyl-DM4 concentrations were observed approximately 3 days after administration of mirvetuximab soravtansine-gynx. Accumulation of the mirvetuximab soravtansine-gynx, DM4, and S-methyl-DM4 was minimal following repeat administration of mirvetuximab soravtansine-gynx.

Distribution: The mean (±SD) steady state volume of distribution of mirvetuximab soravtansine-gynx was 2.63 (±2.98) L. Unconjugated DM4 and s-methyl DM4 showed >99% plasma protein binding. The blood:plasma ratio for DM4 in human blood was 0.58 – 1.85 with inversely proportional to the concentration. The blood:plasma ratio for s-methyl DM4 in human blood was 0.55 – 0.58.

Metabolism: Unconjugated DM4 and S-methyl-DM4 undergo metabolism by CYP3A4. In human plasma, DM4 and S-methyl DM4 were identified as the main circulating metabolites, accounting for approximately 0.4% and 1.4% of mirvetuximab soravtansine-gynx AUCs, respectively.

Elimination: Non-clinical studies suggest that biliary excretion is the primary route of elimination for DM4 and renal excretion exhibit minor involvement (0.7 %).

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The recommended dosage for mirvetuximab soravtansine is 6 mg/kg via IV Q3W based on AIBW. This dosing regimen showed reasonable efficacy (ORR of 31.7% [95% CI: 22.9, 41.6]) with a generally acceptable tolerability profile in the intended patient population. However, there are significant concerns regarding the high risk of ocular toxicity at the 6 mg/kg Q3W AIBW dosing regimen.

The FDA notes that among 106 patients who received treatment with ELAHERE at 6 mg/kg AIBW Q3W in the pivotal study IMGN853-0417 with a median follow-up of 11.3 months, vision impairment (any grade) occurred in 54% of patients, including 8% Grade 3 with no Grade 4

events reported. Thirty seven percent of patients had keratopathy (any grade) with 8% of patients had Grade 3 and 1 patient with Grade 4 events reported.

Nearly 24% (25/106) of the patients with ocular AEs required at least one dose interruption/reduction/discontinuation. Nineteen (19%) of patients required at least one dose reduction due to blurred vision and 13% of the patients required at least one dose-reduction due to keratopathy. Additional details about the safety of mirvetuximab soravtansine are provided in 8.2.

Due to lack of robust dose finding data and very high rate of ocular AEs, a PMR will be issued in order to identify an optimal dosage schedule of mirvetuximab soravtansine.

Therapeutic Individualization

No dose adjustments are proposed based on intrinsic or extrinsic factors. Based on population PK analyses, mirvetuximab soravtansine PK was not affected by mild or moderate renal impairment and mild hepatic impairment. Of note, only one patient with moderate hepatic impairment was included in the analysis. There were no patients with either severe renal impairment or severe hepatic impairment. In addition, intrinsic factors such as age and AIBW were identified to be significant covariates in population PK analysis. However, the influence of these covariates on the PK of mirvetuximab soravtansine was < ±20%. Nevertheless, AIBW was found to be a significant covariate on IMGN853 exposure and therefore, the recommended dosage is based on AIBW to lower the inter-subject variability. No dosage modifications for any other covariates was warranted. Dedicated drug-drug interactions (DDI) studies were not conducted with mirvetuximab soravtansine. In vitro studies suggest that mirvetuximab soravtansine may exhibit potential DDIs.

There were insufficient number of non-white patients (91.7% White [n = 498], 2.2% Black [n = 12], 2.8% Asian [n = 15], 0.4% American Indian [n = 2], 2.9% Other or Not reported [n = 18]) in the clinical studies included in the application. The Applicant did not assess the impact of race and ethnicity in the population PK analysis. As outlined in the section below (clinical), a PMC will be issued to conduct an integrated analysis containing data from clinical trials and other data sources such as post-marketing reports, real-world evidence and other sources to further characterize the safety and efficacy of mirvetuximab soravtansine in patients from racial and ethnic minority groups.

Outstanding Issues

FDA will issue two PMRs to address the outstanding issues based on the review of the clinical data submitted by the Applicant.

- There was a limited dose-exploration with mirvetuximab soravtansine in the dose-escalation study (Study IMGN853-0401). The applicant selected the dose of 6 mg/kg

AIBW Q3W for the pivotal efficacy study (IMGN853-0417). A significantly higher rate of ocular AEs was reported among all the patients treated at this dosage. Since the dose escalation study enrolled very few patients at dosage schedules other than 6 mg/kg Q3W, robust dose or exposure-response data were not available to enable optimal dose selection. Based on available data, it is difficult to determine whether 6 mg/kg AIBW Q3W of mirvetuximab soravtansine provides the optimal risk-benefit profile.

The limited clinical data obtained from the dose-escalation study suggest that alternative dosing schedules; specifically, a fractionated dosing regimen where smaller doses are administered more frequently (i.e., 3X QW doses over 4 weeks), could possibly lower the incidence of ocular adverse events. Given the high rates of ocular toxicity observed with the 6 mg/kg AIBW Q3W dose, and limited data available at alternative dosing regimens, additional clinical safety and efficacy information for mirvetuximab soravtansine is needed to determine the optimal dosage that will minimize the serious risk of ocular toxicity without a clinically significant impact on efficacy. Therefore, the applicant will be asked to conduct a postmarketing dose finding study to assess the safety and efficacy of alternative dose schedules of mirvetuximab soravtansine.

- The clinical pharmacology portions of the application contains data from only a limited number of patients with moderate (n = 1) or severe hepatic impairment. Based on nonclinical data, unconjugated DM4 and s-methyl DM4 are CYP3A substrates. Therefore, hepatic metabolism and/or excretion is expected to play a major role in the elimination of unconjugated DM4 and s-methyl DM4. Given that the hepatic impairment may increase the exposure of unconjugated DM4 and s-methyl DM4 and thereby increase the risk of drug toxicity, additional information is required to determine appropriate and safe dosing of mirvetuximab soravtansine in patients with moderate hepatic impairment.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

PHARMACOLOGY	
Structure	Mirvetuximab soravtansine consists of an anti-FRα monoclonal antibody (immunoglobulin G1 [IgG1]) attached via a cleavable linker to the cytotoxic maytansinoid payload, DM4. Maytansinoids are anti-mitotic agents that inhibit tubulin polymerization and microtubule assembly, resulting in cell cycle arrest and apoptosis. Mirvetuximab soravtansine contains an average of 3.4 DM4 molecules bound to the antibody. The payload is known to form the active metabolite, S-methyl-DM4.
Mechanism of Action	The anticancer activity mirvetuximab soravtansine is due to the binding of the ADC to FRα expressing cells, followed by internalization of the ADC. Once

	inside, the cytotoxic small molecule, DM4, is released via proteolytic cleavage. DM4 disrupts the microtubule network within the cell, resulting in cell cycle arrest and apoptotic cell death.
QT Prolongation	In the dose-escalation/expansion phase 1 study (IMGN853-0401), no large changes in mean QTc intervals (>20 msec) were noted at the recommended dosage of mirvetuximab soravtansine. Increases in QTcF of > 500 msec were not observed in the mirvetuximab soravtansine arm. Central tendency analysis of the QTcF interval changes from baseline showed that the highest mean (upper bound of the 2-sided 90% CI) for QTcF was 8.1 (4.1, 13.0) msec, which was observed at cycle 3/Day 1/end of infusion in the Expansion cohort 3 of mirvetuximab soravtansine arm.
GENERAL INFORMATION	
Bioanalysis	<u>All Patients (Studies IMGN853-0401, IMGN853-0403, and IMGN853-0417)</u> Plasma concentrations of mirvetuximab soravtansine and total antibody were measured using a validated ELISA method. A validated high performance liquid chromatography coupled to tandem mass spectrometry (MS/MS) detection was developed for the quantitation of DM4 and S-methyl DM4 analytes. <u>Immunogenicity</u> An ECL-based and a cell-based assay were used to detect ADA and nAb to mirvetuximab soravtansine in human plasma.
Dose Proportionality	Following IV infusion, the exposures (Cmax and $AUC_{0\text{-}INF}$) of ADC and total Ab showed dose-proportional increase at 3.3 to 7 mg/kg total BW. In the lower dose range from 0.15 to 2 mg/kg TBW, the clearance decreased with increasing dose, suggesting a saturable mechanism of elimination such as target-mediated drug disposition.
Accumulation	There was minimal accumulation with repeated administrations. Mean (%CV) Accumulation Ratios: ADC – 1.15 (22.4%); TAb – 1.41 (29.1%), DM4 - 1.1 and s-methyl DM4 - 1.01.
Variability	Pharmacokinetic data obtained from the clinical studies show that Mirvetuximab soravtansine exhibits low to moderate variability. The %CV for AUCss and C_{MAX} predicted with PopPK model were 22.6% and 17.7%, respectively at the recommended dose.

	Mirvetuximab soravtansine-gynx Mean (±SD)	**Unconjugated DM4 Mean (±SD)**	**S-methyl-DM4 Mean (±SD)**
C_{max}	137.3 (±62.3) µg/mL	4.11 (±2.29) ng/mL	6.98 (±6.79) ng/mL
AUC_{tau}	20.65 (±6.84) h*mg/mL	530 (±245) h*ng/mL	1848 (±1585) h*ng/mL

Immunogenicity	With a median duration of treatment of 4.3 months in Studies 0417, 0401, and 0403, a total 55/423 (13%) of mirvetuximab soravtansine-gynx treated at

	6 mg/kg AIBW in EOC patients had at least 1 post-baseline positive sample for anti-mirvetuximab soravtansine-gynx antibodies. Of these, 28/423 patients (7%) had developed treatment-emergent ADA and 3/423 patients (<1%) had treatment-enhanced ADA. Neutralizing antibodies were detected in 24/423 (6%) of patients.
DISTRIBUTION	
Volume of Distribution	Based on population PK analysis, the mean volume of distribution (%CV): Cycle 1: 3.198 L (23.2%); Cycle 3: 3.172 L (32.3%) in Study IMGN853-0401. The steady state Vdss = 2.63 (± 2.98) L. Based on the small Vd, distribution may be primarily limited in plasma or in vascular rich tissues.
Plasma Protein Binding	Unconjugated DM4 and s-methyl DM4 were highly bound to plasma proteins (>99%).
Blood-to-Plasma ratio	In preclinical studies, mirvetuximab soravtansine exhibited limited distribution to red blood cells in rats, monkeys, and humans. The blood-to-plasma ratio in human blood was inversely proportional to concentration and ranged between 0.58 – 1.85 for DM4. The blood-to-plasma ratio for s-methyl DM4 was 0.55 – 0.58 in human blood.
ELIMINATION	
Mean Terminal Half-Life	Following IV infusion at 6 mg/kg AIBW, the terminal elimination half-life was 115 h (4.8 days), indicating the steady state can be reached in approximately 24 days (in Cycle 2).
METABOLISM	
Primary Metabolic Pathways	Nonclinical studies using human biomaterials showed that CYP3A4 is the predominant CYP450 enzyme responsible for the biotransformation of DM4 and S-methyl-DM4.
Transporter Substrate	• DM4 and S-methyl DM4 are substrates of the MDR1 but not inhibitors of MDR1. • DM4 and S-methyl-DM4 were substrates of P-pg, but neither was an inhibitor of this efflux transporter.
DDI Potential	• DM4 and S-methyl-DM4 showed no direct inhibition on CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5. • DM4 showed time-dependent inhibition of CYP3A4, and S-methyl DM4 showed weak time-dependent inhibition of CYP2C8 and CYP2C9. • DM4 and S-methyl-DM4 did not induce CYP1A2, CYP2B6, or CYP3A4. Dedicated DDI studies have not been conducted with mirvetuximab soravtansine.
EXCRETION	
Primary Excretion Pathway	In preclinical species, feces, via biliary elimination, is the main route of excretion following IV doses of mirvetuximab soravtansine. Urinary excretion accounting for approximately 0.7% of the dose. No mass-balance studies were conducted in human subjects.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes, the clinical pharmacology data provide supportive evidence of effectiveness. The applicant submitted results of three key studies to support the proposed BLA Table 6. These included a Phase 1 dose-escalation/expansion trial (Study IMGN853-0401), a Phase 3 randomized study (Study IMGN853-0403), and a pivotal Phase 3 single-arm, open-label study (Study IMGN853-0417). Results of the dose-selection and the pivotal studies are discussed below.

Table 6 Clinical Trials supporting mirvetuximab soravtansine approval

Trial Identifier	Description	FRα Expression	Treatment regimens	PK Population (N)	N for Efficacy
IMGN853-0401	Phase 1, Open-label dose escalation and expansion with different dose regimens	FRα-positive **N = 27 FRα high**	Escalation **Sched A**: 0.15 - 7 mg/kg TBW Q3W IV, 5 and 6 mg/kg AIBW **Sched B**: 1.1 – 2.5 mg/kg AIBW 3xQ4W* Expansion 6 mg/kg Q3W AIBW IV	DEsc: 69 (n = 44 Q3W; n = 25 QW) DEx: 137 (n = 113 EOC; n = 24 EC) **Total**: 206	27/113 Dose Expansion
IMGN853-0403	Phase 3, open-label, randomized Study	Medium or high Frα **N = 147 FRα high**	Arm 1: MIRZV 6 mg/kg AIBW IV Q3W Arm 2: IC chemo	366	N = 147
IMGN853-0417	Phase 3, single-arm, open-label Study	**High FRα**	6 mg/kg AIBW Q3W IV	106	N = 105

Dosing Regimen Selection:
To support the proposed dosing regimen of 6 mg/kg AIBW Q3W, the applicant rationalized based on the risk:benefit assessment.

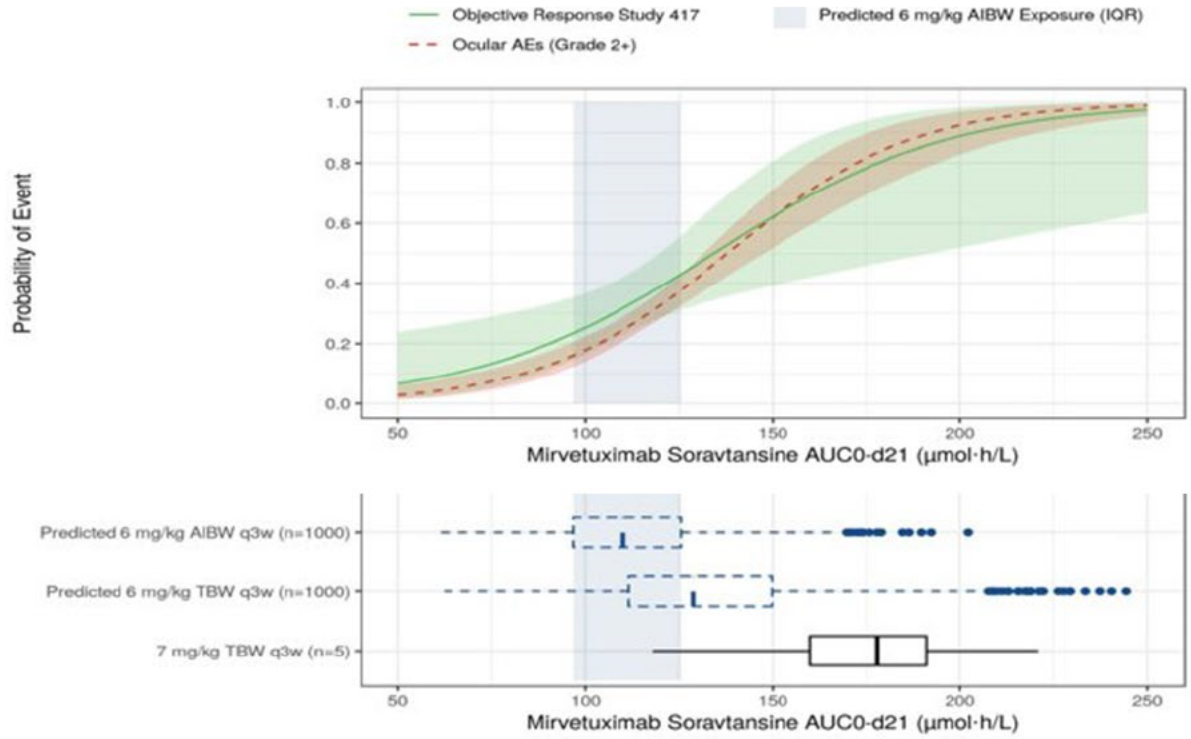
As shown in the Table 6 above, Study IMGN853-0401 evaluated several dose levels administered in a Q3W schedule. In addition, a smaller cohort of the patients were also treated with modified weekly dosing schedule (3 weekly doses over 4 weeks). However, there was limited clinical data collected at dose-levels and/or schedules other than the recommended dosage of 6 mg/kg AIBW Q3W.

Per the Applicant, based upon the totality of the safety, anti-tumor activity data, and PK, 6 mg/kg AIBW IV Q3W was declared the MTD/RP2D for the expansion cohorts. The use of the AIBW dosing at 6 mg/kg ensured maximum dose intensity with a tolerable safety profile. As

shown in Figure 1, the analysis showed that 6 mg/kg AIBW delivered the exposure with balanced efficacy and safety while limiting the variability of exposure.

The observed safety data from different dose-cohorts in study IMGN853-0401 showed a trend for increasing TEAEs and TEAEs of Grade ≥ 3. Similarly, high incidences of Grade ≥ 2 ocular AEs were also observed at dosage ≥ 5 mg/kg Q3W Table 7.

Figure 1 Model-Predicted Relationships between AUC of Mirvetuximab Soravtansine and Response in Efficacy (ORR) and Safety (Ocular Toxicity)



Source: Applicant's E-R analysis Report QPK28-007 – Figure 20

Table 7 Overview of Treatment-emergent Ocular Adverse Events by dose-cohort in patients administered Q3W dosing (Study IMGN853-0401)

	Based on actual BW (TBW)							Based on AIBW		Total	All 6 mg/kg AIBW	
Dose (mg/kg) Q3W	0.15	0.5	1.0	2.0	3.3	5.0	7.0	5.0	6.0		Exp	Total
# of patients (n)	2	1	1	1	9	11	5	7	7	44	113	120
% Patients with any grade ocular AE												
All Grades	**0**	**0**	**0**	**0**	**11**	**45**	**100**	**29**	**57**	**39**	**59**	**59**
Grade 3+	**0**	**0**	**0**	**0**	**0**	**9**	**40**	**0**	**0**	**7**	**5**	**5**
Grade 1	0	0	0	0	11	27	20	29	14	18	26	25

Grade 2	0	0	0	0	0	9	40	0	43	14	28	29
Grade 3	0	0	0	0	0	9	40	0	0	7	5	5
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0	0	0	0	0	0

Source: Applicant's submission of Study 0401 study report; Tables 14.3.1.5 and 14.3.1.6

When compared with the modified weekly dosing regimens, the ocular AEs were generally less frequent Table 8.

Table 8 Summary of Treatment Emergent Ocular Adverse Events by dose-cohort in modified weekly dosing Schedule (Study IMGN853-0401)

	Based on AIBW				**Total**
Dose (mg/kg) Q3W	1.1	1.8	2	2.5	
# of patients (n)	5	4	9	7	25
% patients with any AE					
All Grades	40	75	22	57	44
Grade 3+	0	25	0	0	4
Grade 1	20	50	22	43	32
Grade 2	20	0	0	14	8
Grade 3	0	25	0	0	4
Grade 4	0	0	0	0	0
Grade 5	0	0	0	0	0

Source: Applicant's submission of Study 0401 study report; Table 14.3.1.7

Overall, the safety data from the dose escalation and expansion trials suggest that the modified weekly dosing regimen may improve the safety of ELAHERE. As such, there is limited clinical data collected at dose-levels and/or schedules other than the recommended dosage of 6 mg/kg AIBW Q3W. Therefore, the dose escalation part of the study did not provide complete information regarding the safety and efficacy properties of ELAHERE.

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

The data and information are insufficient to determine whether the proposed dosage of mirvetuximab soravtansine is appropriate. As detailed above, the 6 mg/kg dose was selected for the pivotal study evaluation based on the efficacy and safety data and the exposure-response analysis for efficacy and safety from the phase 1 trial. The pivotal trial IMGN853-0417 was an open-label, single arm study of mirvetuximab soravtansine in adult patients platinum-resistant high-grade serous epithelial ovarian, primary peritoneal, or fallopian tube cancer, whose tumors express a high-level of FRα, and who have received prior bevacizumab

treatment. The primary endpoint was ORR. The observed ORR rate in the pivotal study was 32.4% (95% CI: 23.6, 42.2 %) including 5 CR (4.8%) and 29 PR (27.6%).

Exposure-response relationship

Exposure-response (E-R) analyses for safety and efficacy were conducted using data collected from the pivotal trial (Study IMGN853-0417) at a dose of 6 mg/kg (n = 106) and the supportive phase 1 (Study IMGN853-0401) and phase 3 trial (Study IMGN853-0403) at doses ranging from 0.15 mg/kg to 7 mg/kg.

Due to the differences in study design, the efficacy endpoints were analyzed in two separate data pools, one for the pivotal study (IMGN853-0417, N = 97), and the other for the supporting studies IMGN853-0401 (patients meeting the IMGN853-0403 inclusion criteria, N = 36) and IMGN853-0403 (N = 242) combined. The safety endpoints were analyzed with data from the three studies pooled together (N = 542) and a summary is shown in Table 9.

Table 9: Summary of Dosing Schedule (Cycle 1) included in the E-R analysis

Dosing schedule	IMGN853-0401 (N = 203)	IMGN853-0403 (N = 242)	IMGN853-0417 (N = 98)	All (N = 542)
0.15 mg/kg TBW q3w	2 (1.0%)			2 (0.4%)
0.5 mg/kg TBW q3w	1 (0.5%)			1 (0.2%)
1 mg/kg TBW q3w	1 (0.5%)			1 (0.2%)
1.1 mg/kg AIBW modified weekly	5 (2.5%)			5 (0.9%)
1.8 mg/kg AIBW modified weekly	4 (2.0%)			4 (0.7%)
2 mg/kg AIBW modified weekly	9 (4.4%)			9 (1.7%)
2 mg/kg TBW q3w	1 (0.5%)			1 (0.2%)
2.5 mg/kg AIBW modified weekly	7 (3.4%)			7 (1.3%)
3.3 mg/kg TBW q3w	9 (4.4%)			9 (1.7%)
4 mg/kg AIBW q3w			1 (1.0%)	1 (0.2%)
5 mg/kg AIBW q3w	7 (3.4%)			7 (1.3%)
5 mg/kg TBW q3w	11 (5.4%)			11 (2.0%)
5.37 mg/kg AIBW q3w	1 (0.5%)			1 (0.2%)
6 mg/kg AIBW q3w	140 (69.0%)	240 (99.2%)	96 (99.0%)	476 (87.8%)
6 mg/kg AIBW q4w		2 (0.8%)		2 (0.4%)
7 mg/kg TBW q3w	5 (2.5%)			5 (0.9%)

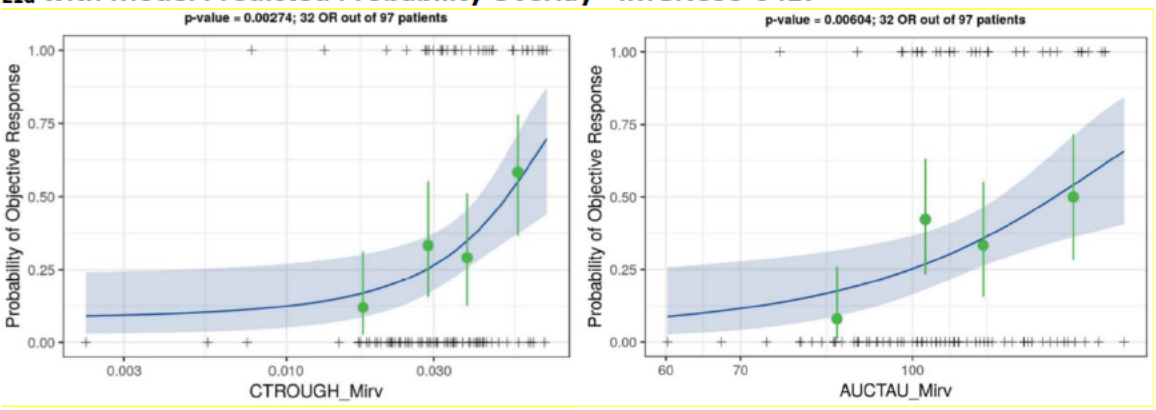
Source: Applicant's E-R analysis Report QPK28-007 – Table 3

As shown in Table 9, the majority of the data used for the E-R analysis are primarily (~88%) obtained from the recommended dose of 6 mg/kg AIBW Q3W. The E-R information presented herein should be interpreted with caution. Detailed exposure-response data sources and analyses are described in section 19.4.

Exposure-efficacy relationship

The E-R analysis for efficacy identified a positive correlation between the AUC of mirvetuximab soravtansine in the first cycle ($AUC_{0\text{-}21d}$) and C_{trough}, and the probability of achieving ORR, shown in Figure 2. *The Applicant stated that there was no relationship between mirvetuximab soravtansine C_{max} and ORR.*

Figure 2: Observed Objective Response Rate vs. Mirvetuximab soravtansine C_{trough} and $AUC_{0\text{-}21d}$ with Model Predicted Probability Overlay - IMGN853-0417



Source: Applicant's E-R analysis Report QPK28-007 – Figures 4 and A.3.4

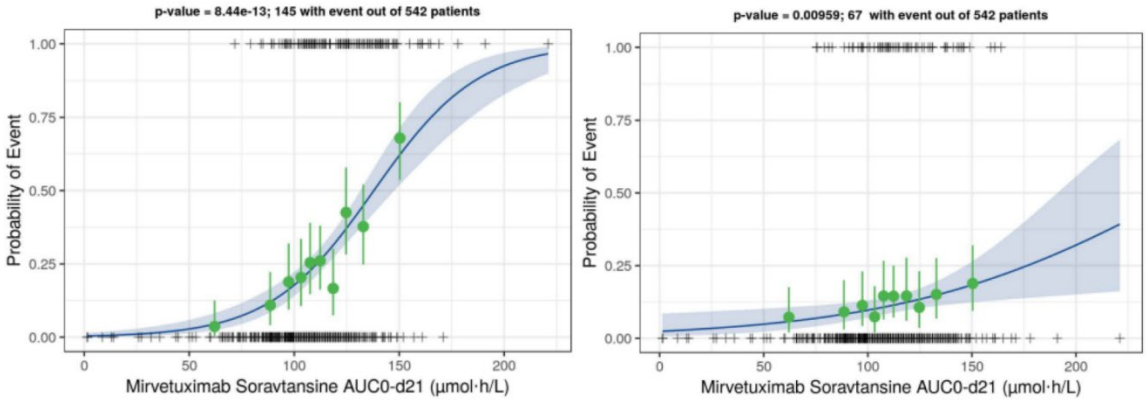
In stepwise model selection procedure, a forward and backward, Akaike information criterion (AIC) based, automatic selection process was used to identify important exposure relationships and covariates. Therefore, the Applicant opined that the C_{trough} and $AUC_{0\text{-}21d}$ are more appropriate exposure parameters for the E-R analysis.

It should be noted that the final E-R analysis for efficacy was conducted with clinical data obtained from Study IMGN853-0417 since the patients from the other studies (i.e., Study IMGN853-0401 and Study IMGN853-0403) were heterogenous with regards to the FRα expression levels.

Exposure-safety relationship

The E-R analysis for safety evaluated a relationship between the ELAHERE exposure and the key safety endpoints including ocular AEs of Grade ≥ 2, peripheral neuropathy (PN), pneumonitis and interstitial lung disease (ILD). The analysis identified a positive correlation between the $AUC_{0\text{-}21d}$ of mirvetuximab soravtansine and probability of ocular AEs of Grade ≥ 2 or PN (Figure 3). As such, the incidence of PN was very low (including Grade ≥ 2) and the E-R for PN showed a shallow relationship.

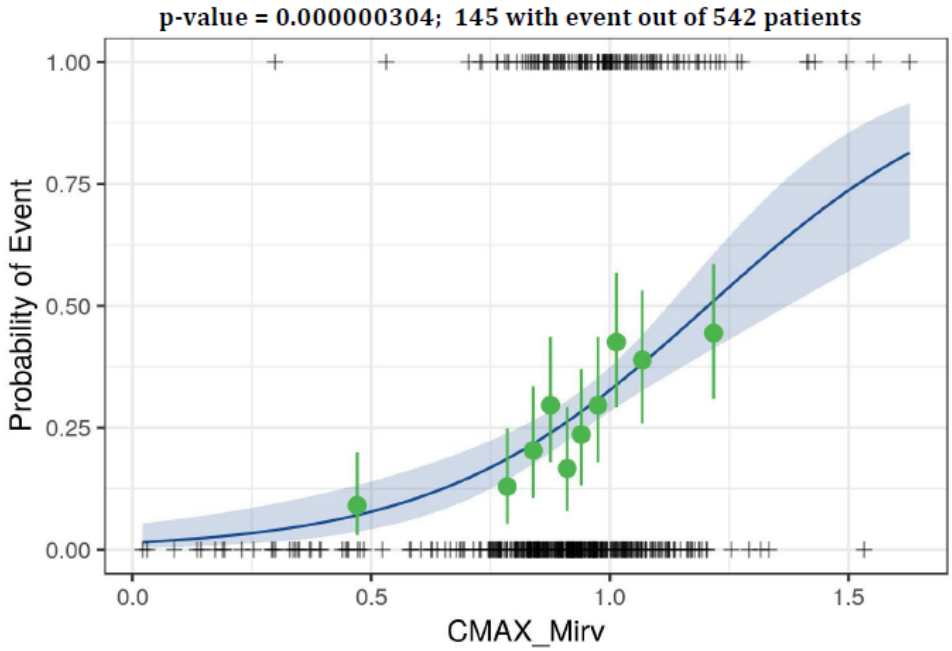
Figure 3: Observed Ocular AEs (Grade ≥ 2) (Left) and Peripheral Neuropathy (Grade ≥ 2) (Right) vs. Mirvetuximab soravtansine $AUC_{0\text{-}21d}$ with Model Predicted Probability Overlay



Source: Applicant's E-R analysis Report QPK28-007 – Figures 16 and 18

In contrast to E-R for efficacy, there was a significant relationship between C_{max} of ELAHERE and ocular AEs of Grade ≥ 2, as shown in Figure 4.

Figure 4: Ocular AEs (Grade ≥ 2) vs. Mirvetuximab Soravtansine C_{max}



Source: Applicant's response to information request – Figure 11

Based on the model predicted exposure parameters for ELAHERE ($AUC_{0\text{-}21d}$, C_{max}, and C_{trough}), the modified weekly dosing regimens generally showed lower C_{max} compared to the Q3W dosing regimens including 6 mg/kg AIBW Q3W (Table 10). Since the clinical data from the modified weekly dosing schedule is available from limited patients (n = 25 across different dose levels), there is inadequate information to determine an ideal exposure parameter that would

explain the relationship between the observed ocular AEs and ELAHERE exposure. It is noteworthy that ~95% of the pooled safety data that was included in the E-R analysis for safety events represent the exposure parameters at Q3W dosing regimens. Therefore, the E-R analysis for efficacy and safety should be interpreted with caution.

Table 10: Summary of Individual Predicted Mirvetuximab Soravtansine Exposure at Cycle 1

Dose group	n	$AUC_{0\text{-}d21}$ (µmol*h/L)	C_{max} (µmol/L)	C_{trough} (µmol/L)
0.15 mg/kg TBW q3w	2	1.45 (11.2)	0.0256 (26.9)	0.000179 (2.13)
0.5 mg/kg TBW q3w	1	8.60 (NA)	0.0877 (NA)	0.00154 (NA)
1 mg/kg TBW q3w	1	13.9 (NA)	0.143 (NA)	0.00176 (NA)
1.1 mg/kg AIBW modified weekly	5	34.0 (59.5)	0.181 (19.4)	0.0249 (227)
1.8 mg/kg AIBW modified weekly	4	79.2 (15.1)	0.331 (13.9)	0.0957 (29.5)
2 mg/kg AIBW modified weekly	9	75.9 (46.2)	0.361 (13.7)	0.0699 (171)
2 mg/kg TBW q3w	1	31.8 (NA)	0.292 (NA)	0.00780 (NA)
2.5 mg/kg AIBW modified weekly	7	116 (11.8)	0.485 (10.1)	0.147 (21.5)
3.3 mg/kg TBW q3w	9	81.0 (26.3)	0.703 (27.3)	0.0225 (43.4)
5 mg/kg AIBW q3w	7	83.7 (53.2)	0.781 (54.6)	0.0235 (87.9)
5 mg/kg TBW q3w	11	123 (22.9)	1.08 (22.6)	0.0359 (51.9)
5.37 mg/kg AIBW q3w	1	106 (NA)	0.841 (NA)	0.0402 (NA)
6 mg/kg AIBW q3w	478	110 (18.4)	0.932 (13.1)	0.0330 (54.5)
6 mg/kg AIBW q4w	2	119 (17.4)	0.972 (7.77)	0.0470 (37.8)
7 mg/kg TBW q3w	5	170 (23.9)	1.45 (12.8)	0.0576 (63.8)

Source: Applicant's PopPK analysis report QPK-006 – Table A.10.2

Collectively, given the limitations noted above regarding the clinical data at alternative dosage schedules, additional clinical safety and efficacy information on mirvetuximab soravtansine is needed to determine a dosing regimen and schedule that may minimize the risk of ocular toxicity without a clinically significant impact on efficacy. The Applicant will be asked to conduct a post-marketing study to evaluate the alternative dosing schedules.

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

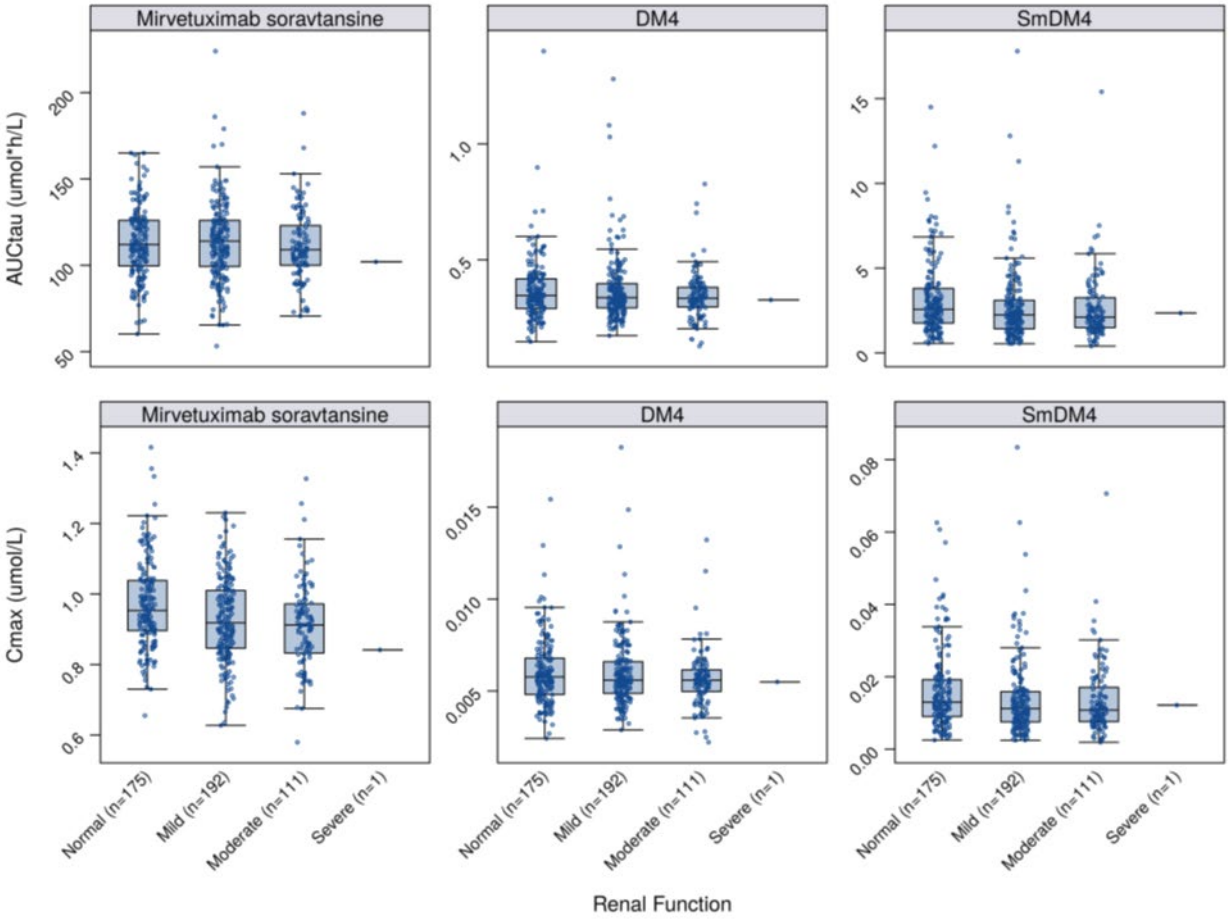
No, an alternative dosing regimen and management strategy is not required based on age and BW. Refer to Section 19.4 for a detailed discussion.

Renal Impairment

No dose modification is recommended in patients with mild or moderate renal impairment. No formal clinical trial has been conducted to assess the effect of renal function on the PK of mirvetuximab soravtansine. The effect of mild and moderate renal impairment on mirvetuximab soravtansine, unconjugated DM4, and s-methyl DM4 exposure was assessed using the population PK model. The population PK analysis included patients with mild (n=192)

and moderate (n=111) renal impairment, in addition to patients with normal (n=175) renal function. There was no marked difference in model-predicted Cycle 1 mirvetuximab soravtansine, unconjugated DM4, and s-methyl DM4 exposures (AUC_τ and C_{max}) between patients with normal renal function and those with mild and moderate renal impairment (Figure 5).

Figure 5: Predicted AUC_τ (upper panel) and C_{max} (lower panel) at Cycle 1, by Renal Function



Source: Applicant's PopPK Report QPK28-006 – Figures 34 and 35

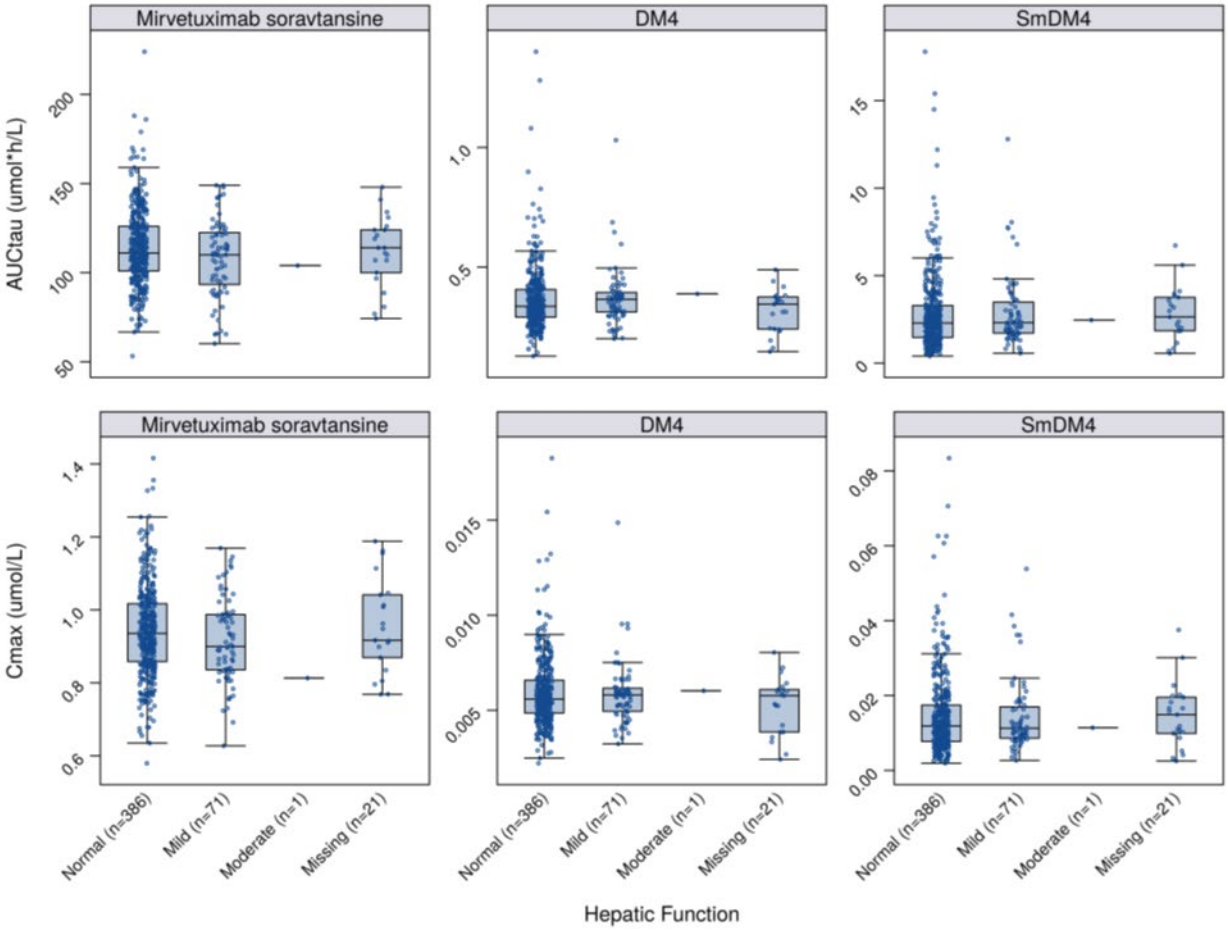
The effect of severe renal impairment on the PK of mirvetuximab soravtansine, unconjugated DM4, and s-methyl DM4 has not been assessed, and this lack of information is conveyed in section 8.6 of product labeling.

Hepatic impairment

No dose modification is recommended in patients with mild hepatic impairment. No formal clinical trial has been conducted to assess the effect of hepatic function on the PK of mirvetuximab soravtansine. The effect of mild hepatic impairment on mirvetuximab soravtansine, free DM4 or s-methyl DM4 exposure was assessed using the population PK model. The population PK analysis included patients with mild (n=71) hepatic impairment, in

addition to patients with normal (n=386) hepatic function. Model-predicted Cycle 1 ADC, DM4 or s-methyl DM4 exposures in patients with mild hepatic impairment were similar to patients with normal hepatic function (Figure 6). There was only 1 patient with moderate HI and 21 patients whose hepatic impairment status was missing. Given the limited number of patients with moderate and severe HI, the exposures in these patients are unknown.

Figure 6: Predicted AUC_{τ} (upper panel) and C_{max} (lower panel) at Cycle 1, by Hepatic Function



Source: Applicant's PopPK Report QPK28-006 – Figures 37 and 38

Comparison of safety by baseline hepatic function (per the NCI-ODWG criteria) across all patients who received mirvetuximab soravtansine at 6 mg/kg Q3W IV in studies IMGN-0401, IMGN-0403, and IMGN-0417 (Table 11) indicated no marked change in overall tolerability in mild hepatic impairment. However, patients with mild hepatic impairment had a numerically higher incidence of Grade ≥ 3 TEAEs and Grade ≥ 3 SAEs.

Table 11: Summary of Safety by Baseline Hepatic Function

	Mild HI (n = 74)	**Normal (n = 407)**

Median no of total treatment cycles	5 (1, 40)	6 (1, 44)
Median duration of treatment (months)	15.1 (3, 124)	19.0 (3, 132)
Any TEAEs	74 (100)	405 (99.5)
Grade ≥ 3 TEAEs	42 (56.8)	199 (48.9)
Any TRAE	68 (91.9)	381 (93.6)
Grade ≥ 3 TRAE	19 (25.7)	108 (26.5)
SAEs	25 (33.8)	131 (32.2)
Grade ≥ 3 TEAEs	24 (32.4)	100 (24.6)
Patients with dose-modification	35 (47.3)	190 (46.7)
Dose-reductions	17 (23)	91 (22.4)
Dose-interruption	3 (4.1)	24 (5.9)
Patients with dose-discontinuation	8 (10.8)	38 (9.3)
Ocular AEs	35 (47.3)	203 (49.9)
Grade ≥ 3	2 (2.7)	22 (5.4)
Treatment related	34 (45.9)	195 (47.9)
Treatment related and Grade ≥ 3	2 (2.7)	20 (4.9)
Peripheral Neuropathy	23 (31.1)	136 (33.4)
Grade ≥ 3	3 (4.1)	9 (2.2)
Treatment related	17 (23)	109 (26.8)
Treatment related and Grade ≥ 3	1 (1.4)	9 (2.2)

Source: Applicant's response in response to FDA IR.

Given that there is no substantial decrease in the tolerability of mirvetuximab soravtansine in patients with mild hepatic impairment, no dose adjustment is recommended for this population.

The effect of moderate or severe hepatic impairment on the PK and safety of mirvetuximab soravtansine has not been assessed. However, based on the known pathology of patients with ovarian cancer, hepatic involvement leading to impaired hepatic function may be commonly anticipated with the target patient population. The current version of the label Section 8.7 suggests avoiding use of mirvetuximab soravtansine use in patients with moderate or severe HI, which would limit the availability of the treatment to these patients. Therefore, a PMR will be issued to collect additional information to determine appropriate and safe dosing of mirvetuximab soravtansine in patients with moderate hepatic impairment.

Folate Receptor alpha (FRα) Expression:
Eligibility for studies IMGN853-0401, IMGN853-0403, and IMGN853-0417 required patients to have specific tumor expression levels of folate receptor alpha (FRα) as detected by the Ventana FOLR1 IHC assay. If a patient did not have archival material available for analysis, a fresh biopsy was obtained for enrollment. The IMGN853-0403 trial required minimum FRα expression levels of ≥50% of tumor cells with any FRα membrane staining visible at ≤10X microscope magnification. Additionally, a stratification cutoff of ≥75% of tumor cells with any FRα membrane staining visible at 10X magnification was also applied. Analyses of the IMGN853-

0403 trial revealed increased objective response rate (ORR) in the population of patients with ≥75% FRα cutoff, as compared to patients in the ITT population with ≥7550% FRα expression, so this cutoff (≥75%) was utilized in the subsequent IMGN853-0417 trial. The IMGN853-0417 trial utilized a PS2+ scoring method based on membrane stain intensity level of 2 or greater. To be considered positive for FRα expression and eligibility for the trial, ≥75% of viable tumor cells must have exhibited level 2 and/or 3 membrane staining intensity. In addition to determining the FRα expression levels for enrollment, the Applicant performed exploratory analyses investigating the effects of FCGR polymorphisms, BRCA mutations status, and soluble FRα levels on the response of mirvetuximab soravtansine.

To assess the appropriateness of the FRα cutoff utilized by the Applicant to determine FRα High (≥75%) in 0403 trial and subsequent 0417 trial, the reviewer conducted exploratory analyses utilizing a more stringent 90% cutoff and assessing the relationship to efficacy within these trials. For trial 0403, the ORR in patients receiving MIRV was similar across FRα expression levels but was numerically higher in patients taking MIRV with ≥ 90% FRα expression (28%) compared to the ITT (22%), FRα High (24%), and FRα ≥50% but <75% (20%) populations. In trial 0417, patients taking MIRV with FRα expression ≥90% had slightly higher ORR (36%) than the FRα High patients (32%). However, it should be noted, that while the ORR was slightly higher utilizing the FRα ≥ 90% threshold, the number of patients that met this criterion was approximately 50% of the patients meeting the FRα ≥ 75% cutoff (Table 12). As such, it appears that the FRα ≥ 75% cutoff utilized by the Applicant for enrollment in the 0417 trial and for stratification into FRα High in trial 0403 identifies a population of patients who are responsive to MIRV without excluding a large number of patients who may benefit.

Table 12: Impact of FRα Expression Cutoffs on ORR

	ITT (FR ≥ 50%)		**FR High (FR ≥ 75%)**		**FR ≥ 90%**	
STUDY 0403						
	MIRV (N=248)	CHEMO (N=118)	MIRV (N=147)	CHEMO (N=71)	MIRV (N=76)	CHEMO (N=29)
Complete Response (CR)	11	4	8	1	7	1
Partial Response (PR)	44	10	27	6	14	2
ORR, N (%)	55 (22%)	14 (12%)	35 (24%)	7 (10%)	21 (28%)	3 (4%)
STUDY 0417						
			MIRV (N=105)		MIRV (N=50	
Complete Response (CR)	---		5		4	
Partial Response (PR)	---		29		14	
ORR, N (%)	---		34 (32%)		18 (36%)	

The Applicant also performed exploratory analyses related to the impact of FCGR genotype, BRCA mutation status, and soluble FRα levels on the ORR of mirvetuximab soravtansine. In trial 0403, the impact on response was assessed for the FCGR3A F158V variant, which has previously been shown to impact ADCC activity. The analyses showed that patients with the F/F genotype

had numerically higher ORR (31%) than patients with the V/V genotype (19%); however, this relationship was not statistically significant. The analyses for patients with mutations in either the BRCA1 or BRCA2 genes as well as analyses correlating soluble FRα levels with response did not show a statistically significant impact on efficacy.

In summary, exploratory analyses by the Applicant investigating the impact of FCGR polymorphisms, mutations in either the BRCA1 or BRCA2 genes, or soluble FRα levels did not reveal statistically significant impacts on response to mirvetuximab soravtansine. In addition, exploratory analyses by the reviewer investigating the impact of a higher FRα expression cutoff (≥ 90% vs ≥ 75%) illustrates the proposed cutoff of ≥ 75% FRα expression is reasonable, and balances increased ORR in FRα positive patients compared to the ITT population and the number of patients that meet the defined cutoff value.

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

As mirvetuximab soravtansine is administered intravenously, no clinical assessment of potential food-drug interactions has been performed.

Dedicated clinical studies to assess potential drug-drug interactions (DDIs) have not been performed. As such, DDIs involving antibodies are not anticipated. Unconjugated DM4 and s-methyl DM4 are substrates of CYP3A4 and therefore, concomitant use of ELAHERE with strong CYP3A4 inhibitors may increase unconjugated DM4 exposure and thereby AEs associated with ELAHERE. The proposed label Section 7.1 recommends close monitoring of patietns for adverse reactions with ELAHERE when used concomitantly with strong CYP3A4 inhibitors. The applicant performed population PK analysis to evaluate the effect of concomitant CYP3A4 inihibitor with ELAHERE on mirvetuximab soravtansine, free DM4 or s-methyl DM4 exposure. There were 22, 64, and 15 patients taking weak, moderate, or strong Cytochrome P450 3A4 (CYP3A4) inhibitors, respectively, at any time during the study. However, based on the start and end times, ciprofloxacin (a moderate CYP3A4 inhibitor; n = 5) and ranitidine (a weak CYP3A4 inhibitor; n = 6) were the only inhibitors that were administered to multiple patients at or near the start of C1D1 dosing of mirvetuximab soravtansine at 6mg/kg AIBW.

The exposures parameters of mirvetuximab soravtansine, free DM4 or s-methyl DM4 were compared for all of these patients (5 on ciprofloxacin and 6 on ranitidine) were compared with all other patients (n = 231), which showed overlapping exposures (Table 13).

Table 13: Comparison of Exposures to DM4, S-Methyl-DM4, and mirvetuximab soravtansine in Individual Patients Who Received Concomitant Ciprofloxacin or Ranitidine with Data from Other Patients in Study-0403

Analyte	PK Parameters	Ciprofloxacin (Moderate) (n = 5)	Ranitidine (Weak) (n = 6)	None (n = 231)
DM4	C_{max} (μmol/L)	0.0042 (24%)	0.0063 (25%)	0.0058 (29%)

	C_{trough} (µmol/L)	0.00006 (21%)	0.00008 (46%)	0.00010 (44%)
	AUC_{tau} (hr*µmol/L)	0.243 (27%)	0.358 (28%)	0.341 (34%)
S-Methyl-DM4	C_{max} (µmol/L)	0.0132 (62%)	0.0319 (70%)	0.0139 (71%)
	C_{trough} (µmol/L)	0.00116 (58%)	0.00208 (77%)	0.00127 (74%)
	AUC_{tau} (hr*µmol/L)	2.624 (58%)	5.568 (69%)	2.692 (74%)
ADC	C_{max} (µmol/L)	0.961 (8.5%)	0.953 (14%)	0.962 (12%)
	C_{trough} (µmol/L)	0.033 (44%)	0.023 (75%)	0.038 (38%)
	AUC_{tau} (hr*µmol/L)	111.3 (15%)	98.7 (33%)	114.5 (16%)

Source: Applicant's response in response to FDA IR

Given the lack of sufficient clinical data with concomitant strong CYP3A4 inhibitor, the use of strong CYP3A4 inhibitor should be avoided with mirvetuximab soravtansine. In addition, due to the expected increase in unconjugated DM4 and s-methyl DM4 exposure with concomitant use of strong CYP3A4 inhibitors, patients receiving concomitant strong CYP3A inhibitors should be closely monitored for signs of toxicity.

X

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7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 14: Listing of Clinical Trials Relevant to this BLA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration / Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
Study 0417 (SORAYA)	NCT04296890	Phase 3, single-arm, open-label	MIRV 6 mg/kg AIBW IV Q3W	ORR, DOR by INV, ORR, DOR by BICR	Until disease progression, unacceptable toxicity, or withdrawal of consent	106	Patients with platinum-resistant high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer, high FRα expression, and 1-3 prior lines of systemic treatment	39 centers in 8 countries
Study 0416 (MIRASOL)	NCT04209855	Phase 3, two-arm, randomized (1:1), open label	MIRV 6 mg/kg AIBW IV Q3W or investigator's choice chemotherapy (paclitaxel, PLD, or topotecan)	PFS per INV, ORR, OS	Until disease progression, unacceptable toxicity, or withdrawal of consent	361 (to date), 430 (planned)	Patients with platinum-resistant high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer, high FRα expression, and 1-3 prior lines of systemic treatment	Opened in 209 centers in 21 countries, enrollment ongoing
		Studies to Support Safety						

Study 0403 (FORWARD 1)	NCT02631876	Phase 3, two-arm, randomized (1:1), open-label	MIRV 6 mg/kg AIBW IV Q3W or investigator's choice chemotherapy (paclitaxel, PLD, or topotecan)	PFS by BICR in entire population, PFS by BICR in high FRα expression subpopulation, ORR, OS	Until disease progression, unacceptable toxicity, or withdrawal of consent	366	Patients with platinum-resistant high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer, medium or high FRα expression, and 1-3 prior lines of systemic treatment	101 centers in 12 countries
Study 0401	NCT01609556	Phase 1, FIH, non-randomized, open-label, dose escalation and dose expansion	Dose Escalation Schedule A: TBW: 0.15 mg/kg, 0.5 mg/kg, 1.0 mg/kg, 2.0 mg/kg, 3.3 mg/kg, 5 mg/kg, and 7 mg/kg IV Q3W; AIBW: 5 mg/kg and 6 mg/kg IV Q3W Dose Escalation Schedule B: AIBW 1.1 mg/kg, 1.8 mg/kg, 2 mg/kg, and 2.5 mg/kg IV on Days 1, 8, and 15, of every 28 day cycle Dose Expansion (RP2D): 6 mg/kg AIBW IVQ3W	MTD, RP2D, ORR, DOR, PFS, TTP	For clinical benefit until unacceptable toxicity or withdrawal of consent. Patients with PD could remain on trial if evidence of clinical benefit.	206	Patients with solid tumors that were relapsed and refractory to standard therapies and either tumor types known to have FRα expression (EOC, endometrial cancer, NSCLC) or a different tumor type with FRα expression confirmed by IHC	12 centers in 2 countries

7.2. Review Strategy

Data Sources:
The clinical and statistical review of mirvetuximab soravtansine is primarily based on the protocol, protocol amendments, clinical study report, patient narratives, Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM datasets, and case report forms from Study 0417 (SORAYA) submitted by the Applicant on March 28, 2022. The review also includes information for the safety update, submitted on July 25, 2022.

Supportive evidence of efficacy comes from Study 0416 (MIRASOL), an ongoing, phase 3, randomized trial. FDA received an update on ORR/DOR from Study 0416 from a third party during the review cycle for this BLA. The Applicant was blinded to these data. Further details are included in Section 8.1.3 below. FDA received and reviewed topline data only. No datasets were included.

Supportive evidence of safety comes from Study 0403 (FORWARD 1) and Study 0401. FDA reviewed the protocol, clinical study report, patient narratives, datasets, and case report forms from these trials as part of the integrated assessment of safety. Further details are included in Section 8.2 below.

Data Quality and Integrity:
Data submitted with this application were in SDTM and ADaM formats. For the most part, data were of adequate quality with adequate coding of preferred terms to allow review. Data were generally consistent with information found in the CRFs. During the review, it was noted that there were issues with the following items in the ocular toxicity data for the safety population: Intraocular pressure measurements were missing, visual acuity measurements were entered in error. For further details, see Ophthalmology General Consult Review by Dr. Wiley Chambers dated 7/8/22. FDA sent the Applicant requests for additional information or clarification of existing information using USUBJID, and for the most part, these were addressed in a timely fashion. In addition, FDA conducted clinical site inspections which are described in Section 4 of this review. There were no significant regulatory violations identified during the inspections and it was concluded that Study IMGN853-0417 was overall properly conducted.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

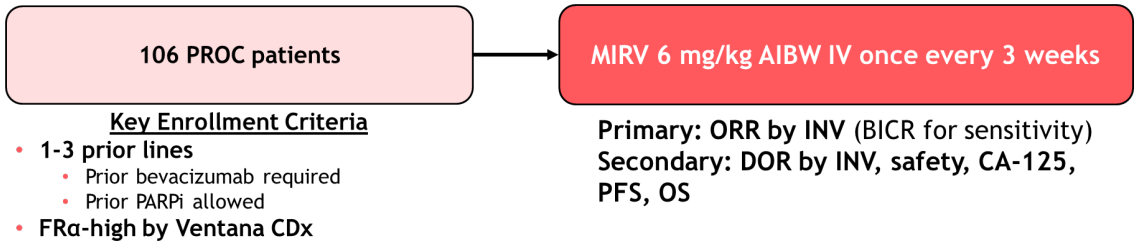
8.1.1. Study 0417 (SORAYA)

Trial Design

Study 0417 was a phase 3, single arm trial evaluating the safety and efficacy of mirvetuximab soravtansine in patients with platinum-resistant high-grade serous epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer with tumors that expressed a high level of FRα. Patients were appropriate for single-agent therapy as the next line of therapy in the opinion of the investigator.

The trial schema is shown in **Figure 7.**

Figure 7: Study 0417 Trial Design



Source: Applicant AOM slides

Study Endpoints

Primary endpoint

- ORR as assessed by investigator(INV) according to RECIST v1.1

Key secondary endpoint

- DOR as assessed by investigator(INV)

Additional secondary endpoints

- TEAEs, laboratory test results, physical exam findings, vital signs
- CA-125 response determined using GCIG criteria defined in Appendix C
- PFS as assessed by investigator according to RECIST v1.1
- OS
- ORR, DOR, and PFS as assessed by blinded independent central review according to RECIST v1.1

Key Eligibility Criteria

Inclusion criteria

- Female patients ≥18 years of age
- Diagnosis of high-grade serous epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer
- Platinum-resistant disease defined as:
    - If patients have received only 1 line of platinum-based therapy, they must have received at least 4 cycles of a platinum agent, must have experienced a CR/PR, and must have progressed >3 months but ≤6 months after the last dose
    - Patients who have received 2-3 lines of platinum-based therapy must have progressed on or within 6 months after the date of the last dose of platinum. Patients with platinum-refractory disease during front-line treatment are excluded.

Reviewer Comment: *Definitions for "platinum-resistant" and "platinum-refractory" disease vary. However, we note that in some definitions, patients who experience PD after completing 1L therapy but <3 months after the last dose may be considered to have platinum-resistant disease. Those patients were excluded from enrolling to Study 0417.*

We also note that patients who experience PD while receiving 2L+ platinum-based therapy may be considered to have platinum-refractory disease in some definitions. These patients were permitted to enroll to Study 0417.

- Radiographic progression on or after most recent line of therapy
- Willing to provide archival tumor tissue or undergo a fresh biopsy with a low-risk, medically routine procedure for immunohistochemistry (IHC) to confirm FRα positivity
- Tumor must be positive for FRα expression as defined by the Ventana FOLR1 assay
- At least 1 lesion that meets the definition of measurable disease by RECIST v1.1 (as determined by the investigator)

- Received at least 1 but no more than 3 prior systemic lines of therapy, including at least 1 line of therapy containing bevacizumab, and must be appropriate for single agent therapy as next line of treatment. Notes:
    - (Neo)adjuvant treatment is considered 1 line of treatment
    - Maintenance therapy is considered part of the preceding line of treatment (not a separate line of treatment)
    - If patients switch therapies due to toxicity without progression of disease (PD), both therapies will be considered as the same line of treatment
    - Hormonal therapy will count as a separate line of therapy unless it was given as maintenance treatment
- Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1
- Completed prior therapies in the following timeframes:
    - Systemic anticancer therapy within 5 half-lives or 4 weeks (whichever is shorter) prior to first dose of mirvetuximab soravtansine
    - Focal radiation at least 2 weeks prior to first dose of mirvetuximab soravtansine
- Completed any major surgery at least 4 weeks prior to first dose
- Recovered all prior treatment-related toxicities to Grade ≤ 1 (except alopecia)
- Adequate organ function defined as:
    - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L without granulocyte colony stimulating factor (G-CSF) in prior 10 days, hemoglobin ≥ 9.9 g/dL without packed RBC transfusion in prior 21 days, platelet count ≥ 100 x 10^9/L without platelet transfusion in past 10 days.
    - Serum creatinine ≤ 1.5 x the upper limit of normal (ULN), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 x ULN, serum total bilirubin ≤ 1.5 x ULN (or ≤ 3 x ULN for patients with diagnosis of Gilbert syndrome), serum albumin ≥ 2 g/dL

- Women of child-bearing potential must have a negative pregnancy test within 4 days prior to first dose and must agree to use highly effective contraceptive methods while receiving mirvetuximab soravtansine and for at least 3 months after the last dose

Exclusion Criteria

- Male patients
- Patients with tumors with endometrioid, clear cell, mucinous, or sarcomatous histology, or mixed tumors containing any of these histologies, or low-grade/borderline ovarian tumor
- Primary platinum-refractory disease defined as disease that did not respond to (CR or PR) or progressed within 3 months of the last dose of first-line platinum-containing chemotherapy
- Prior wide-field radiotherapy affecting at least 20% of bone marrow
- Patients with > Grade 1 peripheral neuropathy per Common Terminology Criteria for Adverse Events (CTCAE) criteria
- Patients with active or chronic corneal disorders, history of corneal transplantation or active ocular conditions requiring ongoing treatment/monitoring (e.g., uncontrolled glaucoma, wet age-related macular degeneration requiring intravitreal injections, active diabetic retinopathy with macular edema, macular degeneration, papilledema, and/or monocular vision)
- Patients with concurrent serious illness or clinically relevant active infection, including but not limited to the following: active hepatitis B or hepatitis C infection, human immunodeficiency virus (HIV), active cytomegalovirus (CMV), or any other concurrent infection requiring IV antibiotics within 2 weeks prior to the first dose of mirvetuximab soravtansine
- History of multiple sclerosis or other demyelinating disease or Lambert-Eaton syndrome
- Clinically significant cardiac disease including, but not limited to any of the following: myocardial infarction ≤ 6 months prior to first dose, unstable angina pectoris, uncontrolled CHF (New York Heart Association (NYHA) > class II), uncontrolled ≥ Grade 3 hypertension, uncontrolled cardiac arrhythmias

- History of a hemorrhagic or ischemic stroke within 6 months
- History of cirrhotic liver disease (Child-Pugh Class B or C)
- History of noninfectious interstitial lung disease including noninfectious pneumonitis
- Currently requiring use of folate-containing supplements (i.e., folate deficiency)
- Prior mirvetuximab soravtansine or another FRα-targeting agent
- Prior hypersensitivity to monoclonal antibodies
- Untreated or symptomatic central nervous system (CNS) metastases
- Women who are pregnant or breastfeeding
- History of another malignancy within 3 years (patients with tumors with negligible risk of metastasis or death may enroll)
- Prior known hypersensitivity to the investigational product or excipients

In Vitro Diagnostic

Assessment of tumor tissue for FRα expression occurred using the Ventana FOLR1 assay. This was an immunohistochemistry (IHC) assay which detects FRα in formalin-fixed, paraffin embedded (FFPE) tissue specimens using the Ventana OptiView DAB IHC Detection Kit. Testing with the assay will occur at a central laboratory. The scoring method for the assay was based on PS2+ which refers to membrane staining intensity of 2 or greater. The pathologist assessed the percentage of tumors cells with moderate (2) or strong (3) membrane staining. FRα positivity was defined as ≥75% of cells with level 2 or level 3 membrane staining intensity. Refer to the CDRH consult for more details regarding the in vitro diagnostic device.

Treatment Regimen

Patients received mirvetuximab soravtansine 6 mg/kg of adjusted ideal body weight (AIBW) administered on Day 1 of every 3-week cycle. Patients continued treatment until PD, unacceptable toxicity, withdrawal of consent, death, or if the trial was terminated.

All patients received premedication with 325-650 mg PO acetaminophen, 10 mg IV dexamethasone, and 25-50 mg PO/IV diphenhydramine approximately 30 minutes prior to each

infusion. An anti-emetic medication was recommended before each dose of mirvetuximab soravtansine.

For repeat cycles, patients must have had an ANC ≥ 1.5 x 10^9/L, platelet count ≥ 100 x 10^9/L, ocular disorders must have been recovered to ≤ Grade 1 or baseline, pneumonitis must have been recovered to ≤ Grade 1, and all other non-hematologic toxicities must have been ≤ Grade 2 or baseline.

Patients could not take folate supplements during the trial.

Ocular Plan

All patients were required to use corticosteroid eye drops as prescribed by the treating physician unless the risk outweighed the benefit in the opinion of the ophthalmologist or treatment physician. Patients self-administered 1% prednisolone drops 6 times daily on Days -1 to 4, and 4 times daily on Days 5 to 8 of each cycle. Alternate corticosteroid eye drops could have been prescribed.

All patients were required to use lubricating artificial tears on a daily basis. Patients were told to wait at least 15 minutes after using corticosteroid eye drops to use artificial tears.

Patients were advised to avoid contact lenses. Patients were told to use baby shampoo and a soft washcloth to clean eyes and could have used warm compresses at bedtime to decrease ocular inflammation. Patients were told to wear UVA/UVB sunglasses during the trial. Also refer to dose modifications and study assessments.

Tumor Assessments

Tumor imaging assessments with computerized tomography (CT) or magnetic resonance imaging (MRI) of chest, abdomen, and pelvis occurred every 6 weeks (±1 week) from cycle 1, day 1 (C1D1) for the first 36 weeks, and then every 12 weeks (±3 weeks) thereafter until progression of disease, death, new anticancer treatment, or withdrawal of consent. Patients who discontinued treatment for reasons other than PD continued to receive tumor imaging assessments until PD or start of new anticancer therapy. All patients who discontinued the study drug were followed every 3 months (±1 month) for survival follow-up until death, lost to follow-up, withdrawal of consent, or the end of the trial, whichever occurred first.

CA-125 assessments were also planned to occur at same intervals as imaging assessments.

Safety Assessments

Safety assessments included the following:

- Vital signs, weight, physical exam, and ECOG PS assessment at baseline, Day 1 of every cycle, end-of-treatment (EOT), and 30-day follow-up
- Pregnancy test at baseline, Day 1 of every cycle, and 30-day follow-up
- Hematology and chemistry labs at baseline, Day 1 of every cycle, EOT, and 30-day follow-up
- 12-lead EKG at baseline, and C1D1
- Ophthalmic exams at baseline, EOT, and 30-day follow-up. If an ocular TEAE occured, exam would occur every other cycle.
- Ocular symptom assessment at baseline, Day 1 of every cycle, EOT, and 30-day follow-up
- Survival phone screen every 3 months following EOT

Dose Modifications

The permitted dose reductions for mirvetuximab soravtansine are shown in Table 15:

Table 15: Permitted Dose Reductions for Mirvetuximab Soravtansine on Study 0417

If the patient was receiving MIRV at:	Dose should be reduced to:
6.0 mg/kg AIBW	5.0 mg/kg AIBW
5.0 mg/kg AIBW	4.0 mg/kg AIBW
4.0 mg/kg AIBW	Permanently discontinue
Reduction of MIRV below 4.0 mg/kg will not be permitted. Dose re-escalation is not permitted.	

Abbreviations: AIBW = adjusted ideal body weight; MIRV = mirvetuximab soravtansine.

Source: Applicant protocol version 2.1

Dose modifications for hematologic toxicities are shown in Table 16.

Table 16: Dosage Modifications for Hematologic Toxicities on Study 0417

Severity Grade (CTCAE v5.0)	**Dose Modifications for MIRV [a]**
Hematological	
Neutropenia	
Grade 2 and Grade 3	Hold drug until ANC is ≥ 1.5 x10^9/L (1500 /μL) and resume at the same dose level
Grade 4	Hold drug until ANC is ≥ 1.5 x10^9/L (1500 /μL) and then resume at one lower dose level
Febrile neutropenia Grade 3 or 4 (with a single temperature reading ≥ 38.3°C or a sustained temperature of > 38°C for > 1 hour	Hold drug until ANC is ≥ 1.5 x10^9/L (1500 /μL) and then resume at one lower dose level
Thrombocytopenia	
Grade 2 and Grade 3	Hold drug until PLT count is ≥ 100 x 10^9/L (100,000/μL) and resume at same dose level
Grade 3 associated with clinically significant bleeding that requires transfusion therapy and Grade 4	Hold drug until PLT count is ≥ 100 x 10^9/L (100,000/μL) and then resume at one lower level

Source: Applicant protocol version 2.1

Dose modifications for non-hematologic toxicities are shown in Table 17, Table 18, Table 19, Table 20, and Table 21.

Table 17: Dosage Modifications for Nausea, Vomiting, and Diarrhea on Study 0417

Non-hematological	
Nausea and Vomiting	
Grade 3 (despite use of optimal antiemetics)	Hold drug until resolved to ≤ Grade 1, then resume at one lower level
Grade 4	Permanently discontinue
Diarrhea	
Grade 3 (despite use of optimal anti-diarrheal treatment)	Hold drug until resolved to ≤ Grade 1, then resume at one lower level
Grade 4	Permanently discontinue

Source: Applicant protocol version 2.1

Table 18: Dosage Modifications and Management for Ocular Toxicity on Study 0417

Severity Grade (CTCAE v5.0)	Management	Guidelines for MIRV Dose Modifications
Grade 1	Complete eye exam as outlined in Schedule of Assessments (Table 2) Monitor for worsening symptoms	Continue MIRV dosing
Grade 2	Complete eye exam as outlined in Schedule of Assessments (Table 2) 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 (Table 2). 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 (Table 2). 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 irreversible by the Investigator	Permanently discontinue MIRV

Abbreviations: AE = adverse event; CTCAE = common terminology criteria for adverse events; MIRV = mirvetuximab soravtansine.

Source: Applicant protocol version 2.1

Table 19: Dosage Modifications and Management for Pneumonitis on Study 0417

CTCAE v5.0 Grade	CTCAE v5.0 Definition	Medical Management of Pneumonitis	Guidelines for Dose Modifications[a]
Grade 1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	• Radiologic assessments (CT scan and/or chest x-ray) should be performed as clinically indicated. • Monitor for pulmonary symptoms.	• Continue dosing in asymptomatic patients and monitor closely.
Grade 2	Symptomatic; medical intervention indicated; limiting instrumental ADL	• Radiologic assessments (CT scan and/or chest x-ray) should be performed as clinically indicated. • Patient must be evaluated by a pulmonary specialist. • Treatment with corticosteroids may be indicated as recommended by a pulmonary specialist and/or institutional guidelines.	• Hold dosing until symptoms resolve to ≤ Grade 1. • MIRV may be resumed at same dose level or one dose level lower after discussion with the Sponsor.
Grade 3	Severe symptoms; limiting self-care ADL; oxygen indicated	• Radiologic assessments (CT scan and/or chest x-ray) should be performed as clinically indicated. • Patient must be evaluated by a pulmonary specialist. • Treatment with corticosteroids until resolution of symptoms may be indicated as recommended by a pulmonary specialist and/or institutional guidelines. • Bronchoscopy with lavage and/or biopsy when clinically feasible should be performed. • The pneumonitis event must be followed until resolution.	• Permanently discontinue MIRV.
Grade 4	Life-threatening respiratory compromise; urgent intervention indicated (eg, tracheotomy or intubation)		

Abbreviations: ADL = activities of daily living; AE = adverse event; CT = computed tomography; MIRV = mirvetuximab soravtansine.

[a] Failure to meet retreatment criteria within 1 cycle (21 days) after the missed dose due to insufficient recovery from a treatment-related toxicity will result in treatment discontinuation unless otherwise specified in the management guidance for a particular toxicity.

Source: Applicant protocol version 2.1

Table 20: Dosage Modifications and Management of Infusion Reactions on Study 0417

Infusion Reaction CTCAE v5.0 Severity Grade	Management
Grade 1: Mild, transient reaction	• Maintain infusion rate unless progression of symptoms to ≥ Grade 2; if symptoms worsen, refer to guidelines below. • Promethazine (or equivalent) 150 mg PO per day (Q4h) PRN for nausea • Diphenhydramine (or equivalent) 25-50 mg PO or IV PRN • Methylprednisolone (or equivalent) 125 mg IV PRN
Grade 2: Moderate	• Interrupt infusion and disconnect infusion tubing from patient • Promethazine (or equivalent) 150 mg PO per day (Q4h) PRN for nausea • Diphenhydramine (or equivalent) 25-50 mg PO or IV PRN • Acetaminophen (or equivalent) 650 mg PO PRN • Methylprednisolone (or equivalent) 125 mg IV PRN • After recovery from symptoms, resume the infusion at 50% of the previous rate and if no further symptoms appear, gradually increase rate until infusion is completed. • For subsequent dosing in future cycles, patients should be pre-medicated with Dex (or equivalent) 8 mg PO BID the day before drug administration and acetaminophen (or equivalent) 650 mg PO and diphenhydramine (or equivalent) 25-50 mg PO 30-60 min before dosing.
Grade 3: Severe, prolonged reaction not rapidly responsive to symptomatic medication and/or brief interruption of infusion; recurrence of symptoms after initial improvement; hospitalization indicated for clinical sequelae OR Grade 4: Life-threatening consequences, urgent intervention indicated	• Immediately stop infusion and disconnect infusion tubing from patient. • Administer diphenhydramine (25-50 mg) IV (or equivalent) • Administer IV steroids (methylprednisolone (or equivalent) up to 0.5mg/kg Q 6h) to treat ongoing reaction and prevent recurrence • Administer bronchodilators (nebulized albuterol/salbutamol, 2.5-5 mg in 3 mL of saline or equivalent) as medically indicated • Administer normal saline as medically indicated • Administer epinephrine (0.2-0.5 mL of a 1:1000 dilution (0.2-0.5 mg) SQ or IM) as medically indicated. Epinephrine should only be used if all other treatment methods fail to manage the IRR. • Advise patient to seek emergency treatment and notify Investigator/clinic if the infusion-related symptoms recur after discharge from clinic. • Report as an SAE (see Section 8.1.1.2). • Permanently discontinue study medication treatment

Abbreviations: BID = twice a day; CTCAE = common terminology criteria for adverse events; Dex = dexamethasone; IM = intramuscular; IRR = infusion-related reaction; IV = intravenously; PO = orally; PRN = as needed; SAE = serious adverse event; SQ = subcutaneous.

Source: Applicant protocol version 2.1

Table 21: Dosage Modifications and Management for other Non-Hematologic Toxicities on Study 0417

All Other Non-hematological Toxicities (except AEs related to underlying disease, Grade 3 fatigue, isolated symptomatic Grade 3 biochemistry laboratory abnormalities that last for < 7 days including electrolyte abnormalities that respond to medical intervention)	
Grade 3	Hold drug until resolved to ≤ Grade 1, then resume at one lower level For any Grade 3 hepatic toxicity that does not resolve to baseline within seven days, an abdominal CT scan must be performed to assess whether it is related to disease progression.
≥ Grade 3 Cardiac events (excluding Grade 3 hypertension)	Permanently discontinue
Grade 4 non-hematological toxicities	Permanently discontinue

Abbreviations: CTCAE = common terminology criteria for adverse events; ANC = absolute neutrophil count; PLT = platelets; CT = computed tomography; AE = adverse event.

[a] Failure to meet retreatment criteria within 1 cycle (21 days) after the missed dose due to insufficient recovery from a treatment-related toxicity will result in treatment discontinuation unless otherwise specified in the management guidance for a particular toxicity.

Source: Applicant protocol version 2.1

Statistical Analysis Plan

The primary endpoint was investigator-assessed confirmed ORR which included a best response of either CR or PR. Along with a point estimate, the 95% exact confidence interval (CI) was estimated by the Clopper-Pearson method. ORR was based on the Efficacy Evaluable population, which included all patients who had measurable lesions at baseline and received at least one dose of mirvetuximab.

The trial was planned to enroll approximately 105 patients, yielding 90% power to detect a difference in ORR of 12% (24% vs. 12%) using a 1-sided binomial test. The target significance level was 0.025 (1-sided). The actual significance level of the test was 0.0242. These targets assumed an ORR of 12% under the null hypothesis and 24% under the alternate hypothesis.

Initial DOR assessment was planned to occur when ORR was determined. A second DOR analysis was also planned to occur 12 months after primary analysis of ORR.

Reviewer comment: *FDA does not conduct formal testing of ORR endpoints. FDA assesses the ORR point estimate and 95% CI in the context of other factors including DOR, safety and tolerability, and other available therapies.*

Protocol Amendments

The key changes in each protocol amendment are listed below:

Protocol Amendment 1 (December 18, 2019)

- Increased the number of enrolled patients from 100 to 110 patients, to have 105 evaluable patients rather than 91 evaluable patients.
- Added that patients who discontinued mirvetuximab soravtansine for reasons other than PD prior to week 36 and who did not initiate other anticancer therapy would continue receiving scans every 6 weeks until week 36 (rather than every 12 weeks until week 36). Patients would continue to receive scans every 12 months thereafter.
- Revised the definition of the efficacy evaluable population as those who received at least one dose of mirvetuximab soravtansine and have measurable lesions at baseline per RECIST v1.1.
- Added an exploratory objective to evaluate tumor-based biomarkers predictive of response to mirvetuximab soravtansine

Protocol Amendment 1.1 (June 18, 2020)

- Added a reference to the Investigator statement to ensure that the investigator had read the Ventana Assay Protocol Plan

Protocol Amendment 1.2 (July 22, 2020)

- Added recommendation to perform monthly pregnancy tests in women of childbearing potential for 3 months following last dose of IP
- Revised list of contraceptive methods to include those considered highly effective according to the Clinical Trials Facilitation and Coordination Group (CTFG) guidelines

Protocol Amendment 2 (August 28, 2020)

- Updated inclusion criterion regarding prior lines of therapy to state that patients who had only received 1 prior line of therapy must have received at least 4 cycles and progressed in >3 months but ≤ 6 months. Patients who had received 2-3 prior lines could have progressed on or within 6 months following last dose of platinum. (Prior to this update, all patients, regardless of prior lines of therapy, must have received at least 4 cycles of treatment.)
- Added an explicit statement that patients who had disease that was platinum-refractory during 1L treatment were excluded.
- Stated that if ocular symptoms last >28 patients, patients may resume mirvetuximab soravtansine with or without dose reduction if they experienced clinical benefit and if agreed upon by Sponsor and Investigator.

- Modified dose modification criteria to add that recurrent G2 ocular toxicity will require 1 level dose reduction and recurrent G3 ocular toxicity will require 1 level dose reduction.
- Added that mirvetuximab soravtansine will be discontinued for G3 pneumonitis and G4 ocular toxicity.
- Added a definition for woman of childbearing potential.
- Added that end of study will occur 12 months after ORR analysis. Either the trial will be amended to allow patients receiving mirvetuximab soravtansine to continue or patients will be given the option to rollover to a long-term extension trial.

Protocol Amendment 2.1 (September 11, 2020)

- Added a reference to the Investigator statement to ensure that the investigator had read the Ventana Assay Protocol Plan.

  Reviewer comment: *These changes appear to be the same changes described in the summary of changes for Protocol Amendment 1.1 but it does not appear that these changes were implemented until Protocol Amendment 2.1. The changes are relatively minor and not expected to affect interpretation of trial results.*

Administrative Letter (May 12, 2021)

- Recommended that the last ophthalmologic exam be performed at the 30 day follow-up visit rather than end-of-treatment

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant conducted Study 0417 in accordance with principles outlined in the International Conference on Harmonization (ICH) Guideline for GCP. Safety monitoring was consistent with the ICH-GCP E6 (R2) guidelines. The Applicant has a GCP audit program to ensure compliance with applicable regulations including ICH E6 R2, and federal, state, and local regulations. The Applicant conducted independent site audits. The Applicant's GCP compliance program determined that Study 0417 was conducted in compliance with GCP and that the trial data are reliable.

Financial Disclosure

Financial disclosure information is summarized in Section 19.2. It is unlikely that the disclosable financial interests affected the conduct of Study 0417.

Patient Disposition

There were n=106 patients enrolled to Study 0417. Of these n=106 patients, n=105 patients were included in the efficacy evaluable by INV population by the Applicant. One patient was excluded due to lacking measurable disease at trial baseline per INV. FDA excluded one additional patient from the efficacy evaluable by INV population because this patient had a platinum-free interval of 18 months, i.e. did not have platinum-resistant disease. FDA's efficacy evaluable by INV population included n=104 patients. Of the n=106 patients, n=95 were included in the efficacy evaluable by BICR population by the Applicant. Eleven patients were excluded due to lacking measurable disease at baseline per BICR.

Among the n=106 patients enrolled to Study 0417, n=85 (80%) are off of therapy, and n=21 patients (20%) remain on therapy. A summary of patient disposition at the data cutoff date of November 16, 2021 is shown in Table 22.

Table 22 Disposition of Patients Enrolled to Study 0417

Disposition	**MIRV N=106 patients N (%)**
Ongoing Treatment	21 (20)
Off of Treatment	85 (80)
Reason for Treatment Discontinuation	
Progressive Disease	71 (67)
Adverse Event	9 (8)
Other	3 (3)
Death	2 (2)
On trial	70 (66)
Off of Trial	36 (34)
Reason for Trial Discontinuation	
Death	33 (31)
Lost to Follow-up	1 (1)
Other	1 (1)
Withdrawal by Patient	1 (1)

The patients who discontinued the investigational treatment due to "other" reasons (n=3) had "worsening of disease" (n=1), "worsening of clinical condition" (n=1), or "clinical deterioration" (n=1). Of patients who discontinued the investigational treatment due to "death" (n=2), one patient had progression of disease and one patient was hospitalized with G3 large intestinal obstruction, started on palliative sedation, and subsequently died.

All patients who came off of the trial for reasons other than death (n=3) had already discontinued the investigational treatment due to progression of disease.

Protocol Violations/Deviations

There were 71 major protocol deviations which occurred in 40/106 patients (38%). The categories for the major deviations are shown in Table 23.

Table 23 Major Protocol Deviations in Study 0417

	MIRV N=106 N (%)
Any Major Protocol Deviation	40 (38)
Categories of Major Protocol Deviations	
Trial Conduct	17 (16)
Safety and Efficacy Endpoint Assessments	15 (14)
Other	9 (8)
Incorrect Dose	6 (6)
Eligibility Criteria	3 (3)
COVID-19 pandemic	1 (1)

All line listings for protocol deviations were reviewed. There were three patients who had protocol violations related to eligibility criteria. Patient (b) (6) had primary platinum-refractory disease, patient (b) (6) had received 4 prior lines of therapy rather than 1-2 prior lines, and patient (b) (6) had platinum sensitive disease (18 months platinum-free interval).

There was an additional patient (patient (b) (6)) who did not have measurable disease assessed by INV per RECISTv1.1 at baseline. This patient was not captured as having a major or minor protocol deviation related to the eligibility criteria in the relevant ADaM dataset. FDA sent a clarifying information request and the Applicant stated that it was discovered that this patient's deviation was not reported to the clinical trial management system until after database lock. The Applicant corrected this error.

There were two additional patients (patient (b) (6) and patient (b) (6)) who had platinum free intervals of 6.01 months. Neither of these patients is captured as having a major or minor protocol deviation related to eligibility criteria in the relevant ADaM dataset.

Reviewer comment: *The overall frequency of deviations was high. However, review of the specific violations did not indicate that they were likely to have impacted overall conclusions regarding efficacy and safety.*

Regarding the patients with major protocol deviations related to eligibility criteria, both the Applicant and FDA excluded patient (b) (6) *from the efficacy evaluable population.*

FDA also excluded patient (b) (6) *from the efficacy evaluable population as this patient did not*

have platinum-resistant disease.

The inclusion of patient (b) (6) *and patient* (b) (6) *in the efficacy evaluable population is thought unlikely to impact overall conclusions regarding efficacy and safety.*

FDA's efficacy evaluable population had a total of 104 patients.

Out of the 95 patients included in the efficacy evaluable by BICR population by the Applicant, FDA included 93 patients in the efficacy evaluable by BICR population after dropping the two patients listed above (b) (6)

Demographic Characteristics

Demographic characteristics for patients in the efficacy evaluable population by INV (N=104) are shown in Table 24.

Table 24 Demographic Characteristics for Patients in the Efficacy Evaluable by INV population in Study 0417

	MIRV **N=104** N (%)
Age, median (range)	62 (35, 85)
Age group	
<65 years	59 (57)
≥65 years	45 (43)
Race	
Asian	2 (2)
White	100 (96)
Not reported	2 (2)
Ethnicity	
Hispanic or Latino	2 (2)
Not Hispanic or Latino	97 (93)
Not reported or unknown	5 (5)
ECOG Performance Status	
0	59 (57)
1	45 (43)
Region	
US	23 (22)
Rest of World	81 (78)
Australia	11 (10)
Belgium	11 (10)
Germany	2 (2)

Ireland	6 (6)
Israel	2 (2)
Italy	23 (22)
Spain	26 (25)

Reviewer comment:

The Surveillance, Epidemiology, and End Results (SEER) database provides data regarding the relative incidence of ovarian cancer cases by race. The relative incidence of ovarian cancer per 100,000 women is 13.1 in White patients, 10.2 in American Indian patients, 9.0 in Black patients, and 8.4 in Asian/Pacific Islander patients. Regarding ethnicity, the relative incidence of ovarian cancer cases per 100,000 women is 9.4 for Hispanic patients and 13.0 for patients who are not Hispanic. Although there is a lower incidence of ovarian cancer among Black patients, they may experience worse outcomes. One study showed that Black patients experienced the lowest 5-year survival compared to White patients, Hispanic patients, and Asian patients at each stage of disease (Goodman 2003).

It is challenging to determine the distribution by race or ethnicity of patients in the U.S. with advanced ovarian cancer. However, the FDA review team does not consider the Study 0417 *trial population to be representative of a U.S. based population with ovarian cancer with respect to race and ethnicity. In terms of race,* Study 0417 *enrolled 96% patients who were White, 2% of patients who were Asian, and 2% of patients who were "Other" (further details unknown). In terms of ethnicity,* Study 0417 *enrolled only 2% of patients who were Hispanic or Latino (Park 2017).*

FDA issued a PMC regarding race and ethnicity. FDA recommended that the Applicant conduct an integrated analysis including data from clinical trials and other data sources to further characterize the safety and efficacy of mirvetuximab soravtansine in patients from racial and ethnic minority groups. See Section 13 for more details.

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

Relevant baseline disease characteristics for patients in the efficacy evaluable by INV population (n=104) are shown in Table 25. Of note, ocular toxicity is a safety signal of concern for the MIRV development program. Information regarding baseline ocular conditions in patients enrolled to Study 0417 can be found in Section 8.2: Review of Safety.

Table 25 Baseline Disease Characteristics for Patients in the Efficacy Evaluable by INV population in Study 0417

	MIRV **N=104** N (%)
Site of primary tumor	
Ovary	83 (80)
Fallopian Tube	8 (8)
Primary Peritoneal	12 (12)
Other	1 (1)
Histology	
High-grade serous	104 (100)
Stage IV at diagnosis	40 (38)
Visceral metastases at baseline per INV	
Yes	53 (51)
No	51 (49)
BRCA mutation	
Yes	20 (19)
No/Unknown	84 (81)
Number of prior therapies	
1	10 (10)
2	41 (39)
3	52 (50)
4	1 (1)
Prior bevacizumab	
Yes	104 (100)
Setting of prior bevacizumab*	
With platinum-based chemotherapy ± maintenance therapy	93 (89)
Alone or in combination with chemotherapy for platinum-resistant disease	17 (16)
Prior PARP inhibitor	
Yes	49 (47)
No	51 (49)

Unknown	4 (4)
Prior chemotherapy Taxane Pegylated liposomal doxorubicin	 101 (97) 74 (71)
Prior platinum-free interval 0 to ≤ 3 months ➢ 3 months to 6 months	 39 (38) 65 (63)
Primary platinum-free interval 0 to ≤ 6 months ➢ 6 months	 31 (30) 73 (70)
Prior treatment in the platinum-resistant setting Yes No	 39 (38) 65 (63)

*6 patients had received prior bevacizumab in both settings: in combination with platinum based chemotherapy ± maintenance treatment and for treatment of platinum-resistant disease

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant monitored drug accountability to ensure that mirvetuximab soravtansine was only given to qualified personnel. Treatment compliance was monitored and captured in the eCRF including data regarding the time of the dose, the actual dose administered, dose modifications, and other details regarding mirvetuximab soravtansine administration. Of note, ocular toxicity and infusion-related reactions (IRRs) are safety signals of concern in the mirvetuximab soravtansine development program. Details regarding concomitant medication administration for prophylaxis and management of these toxicities can be found in 8.2: Review of Safety.

Efficacy Results – Primary Endpoint

The primary efficacy results for INV-assessed ORR are shown in Table 26. Mirvetuximab provided an ORR of 31.7% ([95% CI: 22.9, 41.6] by investigator) in participants with platinum resistant, advanced, high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancers with high folate receptor-alpha expression.

The median DOR in the original BLA submission, based upon a data cutoff (DCO) date of 11/16/21, was 5.9 months (95% CI: 5.6, 7.7 months) with a range of 1.4+ to 9.8 months.

As part of the 120-Day Update, the Applicant included information regarding DOR. The DCO date for the DOR update was 4/29/22 and included an additional 5 months of follow-up. With longer follow-up, among the 33 patients in the INV Efficacy Evaluable population with a

confirmed CR or PR, the updated median DOR per RECIST was 6.9 months (95% CI: 5.6, 9.7). These results are shown in Table 26.

Table 26 INV-Assessment of Efficacy (Efficacy Evaluable Population)*

Endpoint	**MIRV (N=104)**
Objective Response Rate % (95% CI)	31.7 (22.9, 41.6)
Complete Response, n (%) (95% CI)	5 (4.8) (1.6, 10.9)
Partial Response, n (%) (95% CI)	28 (26.9) (18.7, 36.5)
Median Duration of Response (95% CI)	6.9 (5.6, 9.7)

*ORR data cutoff date: 11/16/21, DOR data cutoff date: 4/29/22.

Subgroup analyses of ORR were conducted by age at baseline (<65 vs. ≥65), ECOG (0 vs. 1), region (US vs. non-US), stage at diagnosis (I-III vs. IV), prior PARP inhibitor status (yes vs. no), BRCA mutation (yes vs. no), number of prior therapies (1-2 vs. 3+), most recent platinum-free interval (<3 months vs. 3-6+ months), initial platinum-free interval (<6 months vs. 6+ months), prior systemic treatment in platinum-resistant setting, and setting of prior bevacizumab. These analyses are depicted in Table 27.

Table 27 FDA Analysis of ORR for Subgroups Based on Investigator Assessment

Variables	**ORR (%)**	**95% CI**
Age at Baseline, years		
<65 (N=59)	33.9	(22.1, 47.4)
≥65 (N=45)	28.9	(16.4, 44.3)
ECOG		
0 (N=59)	42.4	(29.6, 55.9)
1 (N=45)	17.8	(8.0, 32.1)
Region		
US (N=23)	30.4	(13.2, 52.9)
Non-US (N=81)	32.1	(22.2, 43.4)
Stage at Diagnosis		
I-III (N=63)	36.5	(24.7, 49.6)
IV (N=40)	25.0	(12.7, 41.2)
Prior PARPi		
Yes (N=49)	36.7	(23.4, 51.7)
No (N=51)	27.5	(15.9, 41.7)

BRCA Mutation		
Yes (N=20)	40.0	(19.1, 63.9)
No (N=84)	29.8	(20.3, 40.7)
Number of Prior Therapies		
1-2 (N=51)	35.3	(22.4, 49.9)
3+ (N=53)	28.3	(16.8, 42.3)
Most Recent Platinum-free Interval (PFI)		
<3 months (N=39)	20.5	(9.3, 36.5)
3-6+ months (N=65)	38.5	(26.7, 51.4)
Initial PFI		
<6 months (N=31)	25.8	(11.9, 44.6)
6+ months (N=73)	34.2	(23.5, 46.3)
Prior Systemic Treatment in Platinum-Resistant Setting		
Yes (N=39)	28.2	(15.0, 44.9)
No (N=65)	33.8	(22.6, 46.6)
Setting of Prior Bevacizumab		
In combination with platinum-based chemotherapy (+/- as maintenance treatment) (N=93)	33.3	(23.9, 43.9)
Alone or in combination with non-platinum-based chemotherapy for treatment of platinum resistant disease (N=17)	17.6	(3.8, 43.4)
Other	-	-

Reviewer comment: *The ORRs were generally consistent across subgroups.*

Data Quality and Integrity

FDA Office of Scientific Integrity (OSI) conducted clinical inspections and did not identify significant issues with data quality or integrity. See Section 4.1 for additional information.

Efficacy Results – Secondary and other relevant endpoints

<u>ORR and DOR by BICR</u>

ORR by BICR was 29.4% (95% CI: 20.8, 39.3). A CR was achieved by 4.9% of participants, and a PR was achieved by 24.5% of participants. The median DOR was 11.7 months (95% CI: 5.0, NR) and ranged from 1.3+ to 11.7 months (data cutoff: 11/16/21). At the 120-Day Update, median

DOR by BICR per RECIST 1.1 was not reached (95% CI: 5.0 months to not reached) and ranged from 2.5 to 12.7+ months (data cutoff: 4/29/22).

Overall concordance between the investigator assessment and assessment by BICR was 86% (Clopper-Pearson exact CI: 77%, 92%). This analysis is depicted in Table 28.

Table 28 Concordance of Best Overall Response between BICR and INV

	INV Responder N (%)	**INV Non-Responder N (%)**
BICR Responder N (%)	24 (23%)	6 (6%)
BICR Non-Responder N (%)	9 (9%)	65 (63%)

CA-125 Response

Of the 106 patients in the Safety population, 86 had a pretreatment sample that was ≥2 times the ULN within 2 weeks prior to the first dose of study drug and had ≥1 postbaseline CA-125 evaluation. The GCIG CA-125 response rate was 46.5% (exact 95% CI: 35.7, 57.6).

Reviewer Comment: *ORR and DOR analyses per BICR were supportive of the INV-assessed analyses. The Applicant reported PFS and OS results in the submission. However, FDA does not consider time-to-event endpoints such as PFS and OS to be interpretable in single arm trials. With a median follow-up of 11.3 months, 33 (32%) of the patients had died.*

Dose/Dose Response

All patients enrolled to Study 0417 received the same starting dosage of mirvetuximab soravtansine. Refer to Section 6: Clinical Pharmacology for more data and discussion regarding dosage.

Durability of Response

Assessment of durability of response, as indicated by the DOR endpoint, are described above.

Persistence of Effect

Not applicable.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

There were no PRO data included in this submission.

Additional Analyses Conducted on the Individual Trial

Not applicable.

Integrated Review of Effectiveness

8.1.3. Assessment of Efficacy Across Trials

The confirmatory, randomized trial, Study 0416 (MIRASOL, NCT04209855), was ongoing during FDA's review of the current application. During a Type B pre-BLA meeting held in January 2022 to discuss the topline results from Study 0417, FDA indicated that they would request ORR and DOR data from the ongoing trial Study 0416 during review of the Study 0417 results, in order to achieve an early indication as to the outcome of trial that would be used to confirm clinical benefit, in the event of an accelerated approval based on Study 0417. During the current review, FDA sent a formal request to the Applicant, requesting blinded ORR and DOR data from both arms of the ongoing, randomized trial, Study 0416. To maintain trial integrity, the Applicant used a third-party vendor to generate the requested results and put in place procedures to prevent anyone from the company from accessing these results, so that the Applicant would remain blinded.

Study 0416 is an ongoing, randomized, phase 3 clinical comparing mirvetuximab soravtansine to investigator's choice chemotherapy in patients with platinum-resistant, high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancer, whose tumors have a high level of FRα expression. Patients should be appropriate for single agent chemotherapy to enroll to this trial, can have received 1-3 prior lines of systemic therapy, and are permitted (but not required) to have received bevacizumab. Patients are also permitted to have received prior PARP inhibitors. Study 0416 is occurring in a similar treatment to Study 0417, except patients were required to have received prior bevacizumab to enroll to SORAYA. Options for investigator's choice chemotherapy included paclitaxel, PLD or topotecan. The primary endpoint is PFS and secondary endpoints include ORR, DOR, and OS.

The data cut-off date for the ORR and DOR data from Study 0416 was May 13, 2022. FDA only reviewed topline results and did not receive datasets. The topline ORR and DOR results from Study 0416 were supportive of the efficacy of mirvetuximab soravtansine in patients with FRα-positive, platinum-resistantant epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received 1-3 prior lines of systemic therapy.

Reviewer Comment: *At the time of the ORR/DOR update,* Study 0416 *had enrolled 361 (84%) patients out of the planned 430 patients.*

8.1.4. Integrated Assessment of Effectiveness

FDA's conclusions regarding efficacy are primarily based on results from Study 0417(SORAYA), a phase 3, single arm trial evaluating the safety and efficacy of mirvetuximab soravtansine in patients with FRα-positive, platinum-resistant, high-grade serous epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer. In Study 0417, the ORR assessed by INV per RECIST v1.1 was 31.7% (95% CI: 22.9, 41.6). Median DOR was 6.9 months (95% CI: 5.6, 9.7). Results for ORR and DOR as assessed by BICR were generally consistent with results as assessed by INV, with an overall concordance of 86% for ORR assessment between INV and BICR. ORR results were also generally consistent across subgroups.

Patients with platinum-resistant ovarian cancer, particularly those who have received prior bevacizumab, represent an area of unmet medical need. Treatment options are limited and generally include single agent chemotherapy, with ORRs ranging from 6-27% in previous trials (**Table 2**). DOR data are scant. An important caveat when interpreting these response rates is that many of the trials with single agent chemotherapies were conducted before establishment of a 1L treatment regimen containing a platinum-based doublet ± bevacizumab followed by maintenance treatment with bevacizumab, niraparib, olaparib , or olaparib + bevacizumab as standard of care for advanced ovarian cancer. The efficacy of the single agent chemotherapies for treatment of platinum-resistant ovarian cancer may be less than seen in historical trials.

A better benchmark for available therapies in the current treatment era may be the chemotherapy control arm from recent trials in platinum-resistant ovarian cancer. These trials are shown in Table 2, and the ORR is 12-13% and median DOR is 4-7.4 months. In addition, not all patients included in these trials had received prior bevacizumab, and many patients had received only 1-2 prior lines of treatment. All patients enrolled to Study 0417 had received prior bevacizumab, and 50% of patients had received 3 prior lines of treatment, representing a more heavily pre-treated population. There are no available therapies specifically for patients with FRα-positive platinum-resistant ovarian cancer.

To support the efficacy results from Study 0417, FDA requested blinded topline ORR/DOR data from Study 0416**,** an ongoing randomized trial in a similar treatment setting to Study 0417. These results were supportive of the efficacy of mirvetuximab soravtansine in patients with FRα- positive platinum-resistant ovarian cancer.

Given the results from Study 0417, supported by additional data from Study 0416, and considering the current therapeutic landscape for patients with platinum-resistant ovarian cancer who have received 1-3 prior lines of therapy, including prior bevacizumab, FDA considers an ORR of 31.7% (95% CI: 22.9, 41.6) and a median DOR of 6.9 months (95% CI: 5.6, 9.7) to represent an improvement over available therapies. The review team determines that these results are reasonably likely to predict clinical benefit for mirvetuximab soravtansine in patients with FRα-positive, platinum-resistant ovarian cancer who have received 1-3 prior systemic treatment regimens. Patients will be selected for treatment using VENTANA FOLR1 (FOLR1-2.1) RxDx Assay. Confirmation of clinical benefit will be based on results from Study 0416, the

ongoing randomized clinical trial comparing mirvetuximab soravtansine to investigator's choice chemotherapy in patients with FRα-positive, platinum-resistant ovarian cancer.

8.2. Review of Safety

8.2.1. Safety Review Approach

Data:

The safety profile summarized in this application consists of data from 3 clinical trials of mirvetuximab soravtansine including 464 patients. All patients received the recommended starting dose of 6mg/kg based on AIBW of mirvetuximab soravtansine. The number of patients in each of the safety analysis groups is described below.

The Study 0417 group includes 106 patients in the safety population, and this was the pivotal trial submitted for this application. All patients had high-grade serous ovarian cancer. All patients had received 1-3 prior lines of systemic treatment and 100% had received bevacizumab. Tumor samples were assessed to have high FRα expression in all patients.

The pooled safety set included all epithelial ovarian cancer (EOC) patients who received mirvetuximab soravtansine 6mg/kg AIBW Q3W on one of 3 studies, including Studies 0401, 0403, 0417. This included EOC patients (expansion cohorts 1, 3, and 5) in Study 0401 (N=113), the Phase 3 portion of Study 0403 (N=245), and all patients in Study 0417 (N=106). Of note, 142 of the total n=464 patients had tumors with FRα high expression according to the criteria used in Study 0417.

The primary evidence of safety is derived from the Study 0417 data, as the subjects represent a more homogeneous patient population than the pooled data. Patients enrolled in Study 0417 had tumors with high FRα expression and received the same protocol-specified mitigation measures and dose modification. Key features of Study 0417 compared to the pooled analysis data sets from Study 0401, 0403 include:

- Study 0417 had implementation of the most up to date recommended dose modifications and mitigation strategies for AEs. In particular, this included changes in the ocular toxicity mitigation strategies from prophylactic corticosteroid eye drops for 10 days (Study 0401) to 8 days per cycle (Studies 0403, 0417).
- Study 0417 had a more homogeneous population based upon FRα High-expression
- The eligibility criteria for Study 0417 included limitations on the number of allowable prior therapies (1 to 3 prior systemic lines of anticancer therapy, including mandatory receipt of prior bevacizumab).

Reviewer comment: *There were no obvious discrepancies identified between the analysis datasets and the information provided in the Clinical Study Reports. The applicant's categorization of data and coding methods were appropriate. The preferred terms (PTs) listed in*

the datasets adequately represented the investigator-recorded term. FDA has noted some minor differences in grouped terms (GTs) noted in sections below. FDA has used their analyses for the data tables in Section 8.2 unless otherwise indicated. The key focus for the safety review was on data majority of the data on was obtained from Study 0417. However, pooled analyses using data from ovarian cancer patients on studies 0401 and 0403 were also reviewed for TEAEs and AEs of Special Interest including peripheral neuropathy, ocular toxicities, and pneumonitis to confirm that safety for the pooled population did not reveal additional safety signals.

The size of the safety population is different from the size of the efficacy population for the single arm trial 0417. The safety population on Study 0417 consisted of all patients who received at least one dose of Mirvetuximab (n=106). The efficacy population included all patients who had efficacy evaluable disease, as per INV assessment, and this led to exclusion of one patient due to lack of measurable disease and one patient due to protocol violation. Therefore, the efficacy population included n=104 patients.

8.2.2. Review of the Safety Database

Overall Exposure

Study 0417 (SORAYA) was the primary trial considered for this review. There were 106 patients in this study who received at least 1 dose of mirvetuximab and comprised the safety population. Information on exposure to mirvetuximab on Study 0417 is shown in **Table 29**. The median duration of therapy was 18 weeks and the median number of doses received was six.

Table 29 Duration of Exposure to Mirvetuximab Soravtansine on Study 0417

	All Patients N=106
Number of doses received	
N	106
Mean (SD)	6.3 (3.9)
Median (min, max)	6 (1, 17)
Duration of dosing (weeks)	
N	106
Mean (SD)	20.2 (12.5)
Median (min, max)	18.2 (3.0, 57.7)
Total cumulative dose (mg)	
N	106
Mean (SD)	2146.7 (1333.0)
Median (min, max)	1807.5 (378.0, 5409.6)

Reviewer's comments: *Patients enrolled in Study 0417 were heavily pretreated, advanced stage and they received an average of 6 doses of therapy and were on treatment 4-5 months on this study.*

Safety Population

The majority of the data on safety was obtained from Study 0417. However, a pooled analysis of safety data from a larger cohort of ovarian cancer patients treated with the recommended dose for mirvetuximab was also conducted. The pooled cohort included 464 patients from studies 0401, 0403, and study 0417. The analyses focused on assessment of common TEAEs and AEs of Special Interest including peripheral neuropathy, ocular toxicities, and pneumonitis. The aim of the assessment was to confirm that safety for the pooled population did not reveal additional safety signals. The pooled safety population is depicted in Table 30.

Table 30 Safety Population, Size and Denominators

Safety Database for the Study Drug[1] **Individuals exposed to the study drug in this development program for the indication under review** **N=464**		
Clinical Trial Groups	New Drug (n=464)	Active Control n/a
All patients in Study 0417 (n=106)[2]	Mirvetuximab soravtansine	N/A
EOC Patients (expansion cohorts 1, 3, and 5) in Study 0401 (n=113)[3] IMGN853-0401	Mirvetuximab soravtansine (IMGN853)	N/A
Study 0403 (n=245) - Phase 3 portion (n=243) and - Stage 1 (n=2)[3] IMGN853-0403	Mirvetuximab soravtansine (IMGN853)	Chemotherapy (paclitaxel, peg-liposomal doxorubicin, topotecan)

[1] *study drug* means the drug being considered for approval.
[2] to be used in product's labeling
[3] if placebo arm patients switch to study drug in open label extension, the n should include their number; do not count twice patients who go into extension from randomized study drug arm
[4] include n in this column only if patients exposed to the study drug for indication(s) other than that in the marketing application have been included in the safety database under review. Consider n=0 in this column if no patients treated for other indication(s) were included in this safety database.

Adequacy of the safety database:

The safety analysis for this BLA is primarily based on data from 106 safety-evaluable patients who received at least 1 dose of study drug and who had at least one post-baseline safety assessment Study 0417. But as noted, the Applicant also provided datasets for the two other clinical studies, the randomized Study 0403 and a dose-escalation phase of the FIH study, Study 0401. The pooled safety cohort including 464 patients from studies 0401, 0403, and study 0417 is considered adequate for an assessment of the safety of mirvetuximab soravtansine.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

FDA review of the ocular toxicity data submitted by the Applicant revealed that there were visual acuity values that appeared to have been entered into the database in error for study 0403. In addition the BCVA and IOP shift tables in the CSR for Study 0417 had missing data. The Applicant resolved these issues through response to information request on July 18, 2022.

Reviewer's Comments: *Visual acuity and intraocular pressure data were originally not considered to be interpretable because of a large number of missing values; additionally there were limited assessments by fundoscopy, dilated slit lamp and evaluations of tear production. This was noted via ophthalmology consultation with Dr. Wiley Chambers and is described in his consult review. The subsequent response and submission of additional information by the Applicant was also reviewed by Dr. Chambers and was considered acceptable to proceed with safety assessment. Though not all of the missing data was obtained, the response was considered adequate to proceed with safety review and did not change the overall safety assessment for the application.*

Categorization of Adverse Events

Safety and tolerability assessment was based on the frequency of deaths, AEs, serious adverse events (SAEs), AEs leading to discontinuation, AEs leading to interruptions, select AEs, clinical laboratory assessments (hematology, serum chemistry, liver, kidney and thyroid function tests), and vital sign measurements. AEs were coded using the MedDRA version 20.0. AEs and laboratory values were graded for severity using the NCI CTCAE version 4.0. Adverse events were categorized by System Organ Class (SOC) and Preferred Term (PT). The Applicant pre-specified adverse events of special interest (AESIs) based on Event of Clinical Interest Guidance. For this application, AESIs comprised of pneumonitis, ocular toxicities, peripheral neuropathy, and infusion-related reactions.

Routine Clinical Tests

The following assessments were planned starting on Cycle 1 Day 1 and continued at regular intervals as pre-specified in the protocol:

- Vital signs including temperature, blood pressure, heart rate, and respiratory rate

were measured before start of each infusion.
• AEs were monitored continuously throughout the study from the time of informed consent until 30 days after the patient's last study treatment.
• A complete physical examination, including assessments of general appearance, skin, head (eyes, ears, nose, and throat), neck, lungs, heart, abdomen, back, lymph nodes, extremities, and neurological system, were completed at Screening and at the 30-Day Follow-up Visit. At all other study visits while on mirvetuximab, patients had symptom-directed PEs.
• Complete blood count (CBCs) with differential, including white blood count (WBC), with 5 part differential, hemoglobin, hematocrit, and platelet count Serum chemistry tests (blood urea nitrogen, calcium, carbon dioxide, chloride, glucose, serum creatinine, sodium, potassium, calcium, magnesium, phosphorus), Liver function tests including AST, ALT, total bilirubin, alkaline phosphatase, albumin(could be performed up to 4 days prior to D1 of each cycle, and as clinically indicated while on treatment, with results reviewed before each mirvetuximab administration)
• PT or INR/aPTT performed at screening
• Urinalysis performed at screening
• Serum CA-125 assessments were performed within 14 days and prior to the first dose of study drug, prior to dosing on Day 1 of every subsequent cycle
• Radiographic tumor evaluation by CT or MRI of chest, abdomen, and pelvis were performed within 28 days before first dose of study drug and every 6 weeks (±1 week) from C1D1 for the first 36 weeks on study and every 12 weeks (±3 week) thereafter
• Pregnancy screening for women of childbearing potential were completed via a serum beta-human chorionic gonadotropin (β-hCG) or urine pregnancy test not more than 14 days before the first dose of study drug and urine or serum pregnancy tests within 4 days of each study drug administration and at the 30-Day Follow-up visit. After the 30-day follow-up visit it was recommended to perform monthly pregnancy tests for 3 months after the last dose of MIRV. Additional testing could be performed in accordance with institutional requirements or local regulation.

• BRCA Mutation status was recorded from prior testing (information was in the source record).

• A standard, single 12-lead ECG will be performed within 28 days prior to first dose

Ocular symptoms assessment: Performed before the start of each cycle by the treating physician or other qualified individual. For patients reporting > CTCAE Grade 1 ocular symptoms, study drug will be held until the patient is evaluated by an ophthalmologist for a complete examination. The ocular symptom assessment was also performed at EOT and the30-Day Follow-up visit. An ophthalmic examination was performed at Screening (within 14 days prior to first dose of study drug) by an ophthalmologist and included the following: distant visual acuity, best corrected visual acuity, slit lamp

examination, intraocular pressure measurement, and indirect fundoscopy. Patients who experienced ocular TEAEs while on study had a complete ophthalmologic exam performed at the emergence of the symptoms and at every other cycle thereafter. All patients who had an ophthalmic exam on study treatment (post-baseline) had a complete ophthalmologic exam performed at the EOT visit or 30-Day Follow-up visit

Patients were assessed for toxicity prior to each dose. All SAEs were collected up until 30 days after the last dose of trial treatment. AEs were documented in the clinical trial database and monitored continuously throughout the study from the time of informed consent until 30 days after the patient's last study treatment. SAEs were followed by ImmunoGen Pharmacovigilance until resolution, stabilization or return to baseline. Beyond this defined reporting period, any unsolicited SAE assessed as related to the study drug by the Investigator and reported to ImmunoGen were collected and processed.

Reviewer comment: *Routine clinical testing of patients enrolled in Study 0417 was generally considered appropriate for evaluating AEs related to Mirvetuximab. However, FDA did not find the assessments of ocular toxicity based on symptoms alone to be adequate for ensuring the proper monitoring. Routine ophthalmologic examination for monitoring was recommended for future studies of Mirvetuximab and in the USPI and further details regarding ocular toxicities are included below.*

8.2.4. Safety Results

Safety Overview

A safety overview for Study 0417 study is included in **Table 31**. Additional discussion will be described in individual adverse event sections.

Table 31 Study 0417 Safety Overview

	MIRVETUXIMAB 6 MG/KG AIBW Q3W N = 106 (%)
All-grade TEAEs	105 (99)
Grade 3-4 TEAEs	53 (50)
Serious TEAEs	32 (31)
Grade 5 TEAEs	2 (2)
TEAEs leading to Dose Delay	41 (39)
TEAEs leading to Infusion Interruption	6 (6)

TEAEs Leading to Dose Reduction	21 (20)
TEAEs Leading to Discontinuation	12 (11)

Deaths

There were 33 (31%) deaths in the overall safety population of 106 patients that received mirvetuximab. The majority (25%) of deaths were due to disease progression. Three patients in Study 0417 experienced AEs that led to death. The AEs leading to death were intestinal obstruction (N=2), and respiratory failure (N=1).

A summary of deaths within 30 days of last study treatment is provided in Table 32. In Study 0417, 7 patients died within 30 days of study drug administration. Four of these deaths were due to disease progression and 2 of these were attributed to adverse events, 1 patient experienced pneumonitis and died of respiratory failure and one patient died of a small bowel obstruction. There was 1 patient who developed a colonic obstruction and was hospitalized and subsequently died, but no imaging was conducted to confirm the cause.

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

Table 32 Study 0417 Summary of Deaths

	MIRVETUXIMAB 6 MG/KG AIBW Q3W N = 106 (%)
Total deaths	**33 (31)**
Deaths within 30 days	7(7)
Progression of disease	4(3.8)
Adverse event	2(1.9)
Other	1(0.9)

Reviewer Comments: *FDA conducted an analysis of all deaths occurring on Study 0417. Of the 33 deaths occurring on Study 0417, the majority were due to progression of disease. Seven patients died within 30 days of study drug. The Applicant attributed 2 deaths to adverse events. One was a patient who was noted to die of respiratory failure which was in the setting of pneumonitis. Another death occurred in a patient who experienced a small bowel obstruction and died, but this event was assessed to constitute an adverse event. FDA reviewed the narratives and case report forms for these 2 patients and agreed with the Applicant's assessment, that these 2 deaths were due to adverse events. There was one additional death, which the Applicant attributed to an "other" cause, but according to the narrative, the patient developed colonic obstruction during cycle 2 of therapy, was hospitalized and died after*

receiving palliative sedation. This was not counted as a death due to adverse event by FDA. Additional information for these 3 deaths is described below.

PATIENT ID# (b) (6) *-Respiratory Failure likely secondary to pneumonitis*
The patient was an 85-year-old white female who received the first infusion of mirvetuximab soravtansine on (b) (6) On (b) (6) 21 (Day 43), a CT scan of the abdomen (including pelvis) showed small bilateral effusions with malignant looking pleural thickening and patchy ground-glass changes noted posteriorly in the lungs and an adverse event (AE) of Grade 1 Pneumonitis was reported. On (b) (6) (Day 54), the subject was admitted for a serious adverse event (SAE) of Grade 3 Esophagitis. The last infusion of mirvetuximab soravtansine prior to onset of this event was the Cycle 3, Day 1 infusion administered on (b) (6) (Day 43).

On (b) (6) (Day 62), the subject experienced increased tiredness and shortness of breath with basal crackles and was subsequently hospitalized for an SAE that also met criteria for an adverse event of interest (AEI) of Grade 3 Respiratory failure. The last infusion of mirvetuximab soravtansine prior to the onset of this event was the Cycle 3, Day 1 infusion administered on (b) (6) (Day 43) and mirvetuximab soravtansine was permanently withdrawn due to this SAE/AEI. On (b) (6) (Day 69), the SAE/AEI of Grade 3 Respiratory failure worsened to Grade 4 Respiratory failure. The following day, the subject returned to oncology/palliative care. A chest x-ray compared to the chest x-ray on (b) (6) (b) (6) (Day 68) revealed persistent diffuse groundglass opacities throughout the mid and lower zones of both lungs, no definite change compared to recent radiographs, compatible with interstitial pneumonia. On (b) (6) (Day 71), 28 days after the last infusion of mirvetuximab soravtansine, the patient died due to respiratory failure. The SAE/AEI of Grade 5 Respiratory failure was assessed by the investigator as possibly related to mirvetuximab soravtansine. The autopsy reported the cause of death as advanced metastatic carcinoma of the ovary complicated by diffuse alveolar damage on a background of idiopathic pulmonary fibrosis with recent clinical bronchopneumonia.

Reviewer comment: *FDA acknowledged that the patient had advanced ovarian cancer, but considered the cause of death to be most likely due to respiratory failure in the setting of pneumonitis caused by mirvetuximab. The Applicant agreed that because pneumonitis was a plausible contributor to the patient's respiratory failure and death, this patient is described in product labeling as having had an adverse event (pneumonitis) leading to death.*

PATIENT ID# (b) (6) *- Small Bowel Obstruction, AE leading to Death*
This patient received the first and only infusion of mirvetuximab soravtansine 6 mg/kg AIBW o (b) (6) An x-ray showed small bowel dilation and the subject was hospitalized due to a serious adverse event (SAE) of Grade 3 Small intestinal obstruction. On (b) (6) (b) (6) (Day 18), 17 days after the last infusion of mirvetuximab soravtansine, the event worsened and the subject died due to an SAE of Grade 5 Small intestinal obstruction. A death certificate was not completed, and an autopsy was not performed. The SAEs of Grade 3 Small

intestinal obstruction and Grade 5 Small intestinal obstruction were assessed by the investigator as not related to mirvetuximab soravtansine. The events were noted to be due to disease progression.

***Reviewer comment**: FDA agrees with the investigator's assessment of attribution of death to disease progression. However, this event of small intestinal obstruction was included in product labeling by the Applicant noted as an AE leading to death, mainly given the timing of the occurrence, within 30 days of the last dose of mirvetuximab.*

PATIENT ID # (b) (6) *- Palliative Sedation*
The subject was a 69-year-old white female who was diagnosed with Stage IV epithelial ovarian cancer in (b) (6) Prior therapies for treatment of epithelial ovarian cancer included carboplatin and paclitaxel ((b) (6) 6 cycles), bevacizumab ((b) (6) 6 cycles), pegylated liposomal doxorubicin hydrochloride and trabectedin ((b) (6) 7 cycles), and carboplatin and gemcitabine ((b) (6) 12 cycles). The subject received the first infusion of mirvetuximab soravtansine at 6 mg/kg AIBW on (b) (6). On (b) (6) (b) (6) (Day 24), the subject presented to an outside hospital with symptoms of worsening colonic obstruction and was hospitalized for a serious adverse event (SAE) of Grade 3 Large intestinal obstruction. On (b) (6) (Day 31), 9 days after the last infusion of mirvetuximab soravtansine, the subject's abdominal pain worsened, and palliative sedation was initiated. The patient was noted to have died due to the palliative sedation. No autopsy was performed, and no further information was provided. This same day, the SAE of Grade 3 Large intestinal obstruction was considered resolved with sequelae and was assessed by the investigator as unlikely related to mirvetuximab soravtansine.

***Reviewer comment:** FDA acknowledged that palliative sedation may have preceded the patient's death but believes the underlying cause of death is more likely to be due to intestinal obstruction related to disease progression. This event was not considered as an adverse event leading to death.*

Serious Adverse Events

Thirty-two (31%) of patients experienced serious adverse events (SAEs). Table 33 includes a breakdown of the types of SAEs that occurred in patients in Study 0417, the most common being gastrointestinal adverse events.

Table 33 Serious Adverse Events (SAEs) Study 0417

	MIRV 6 MG/KG AIBW Q3W **N = 106** **N (%)**
Total Patients with SAEs	**32 (31)**

	MIRV 6 MG/KG AIBW Q3W N = 106 N (%)
Gastrointestinal Disorders	
Ascites	4 (3.8)
Small Intestinal Obstruction	4 (3.8)
Diarrhea (GT)	1 (0.9)
Intestinal Obstruction	2 (1.9)
Large Intestinal Obstruction	2 (1.9)
Abdominal Pain (GT)	1 (0.9)
Constipation	1 (0.9)
Intestinal Haemorrhage	1 (0.9)
Intestinal Perforation	1 (0.9)
Nausea	1 (0.9)
Oesophagitis	1 (0.9)
Respiratory, Thoracic And Mediastinal Disorders	
Pleural Effusion	3 (2.8)
Pneumonitis (GT)	1 (0.9)
Respiratory Failure	1 (0.9)
General Disorders And Administration Site Conditions	
Administration Site Extravasation	1 (0.9)
General Physical Health Deterioration	1 (0.9)
Malaise	1 (0.9)
Pyrexia (GT)	1 (0.9)
Infections And Infestations	
Clostridium Difficile Infection	1 (0.9)
Device Related Infection	1 (0.9)
Peritonitis Bacterial	1 (0.9)

	MIRV 6 MG/KG AIBW Q3W N = 106 N (%)
Respiratory Tract Infection	1 (0.9)
Hepatobiliary Disorders	
Cholecystitis Acute	1 (0.9)
Cholestasis	1 (0.9)
Hepatitis	1 (0.9)
Blood And Lymphatic System Disorders	
Anaemia	1 (0.9)
Cardiac Disorders	
Arrhythmia (GT)	1 (0.9)
Injury, Poisoning And Procedural Complications	
Infusion Related Reaction	1 (0.9)
Metabolism And Nutrition Disorders	
Decreased Appetite	1 (0.9)
Neoplasms Benign, Malignant And Unspecified (incl Cysts And Polyps)	
Basal Cell Carcinoma	1 (0.9)
Nervous System Disorders	
Brain Stem Syndrome	1 (0.9)
Psychiatric Disorders	
Mania	1 (0.9)
Vascular Disorders	
Vasculitis	1 (0.9)

Abdominal Pain (GT) includes PT terms Group Abdominal Pain (GT) includes PT terms Abdominal Pain, Abdominal Pain upper, Abdominal Pain lower, Abdominal discomfort.
Diarrhoea (GT) includes PT terms Diarrhea, Colitis microscopic,
Pyrexia (GT) includes PT terms Pyrexis, Hyperpyrexia
Pneumonitis (GT) includes PT terms Pneumonitis, Interstitial lung disease, Organizing pneumonia
Arrhythmia (GT) includes PT terms Atrial Fibrillation, Electrocardiogram Repolarisation Abnormality, Sinus Tachycardia, Arrhythmia Supraventricular

***Reviewer's Comment*:** *FDA analysis noted that the majority of SAEs in Study 0417 were in the category of gastrointestinal disorders, including intestinal obstruction and ascites, which would not be considered unusual for the advanced ovarian cancer patient population enrolled in the study. Other common SAEs, which are included in product labeling include infections and pleural*

effusions.

Dropouts and/or Discontinuations Due to Adverse Effects

On Study 0417, twelve patients (11%) discontinued treatment with mirvetuximab soravtansine due to adverse events (AEs). Table 34 provides a breakdown of the specific adverse events that lead to treatment discontinuation.

Table 34 Dropouts and/or Discontinuations Due to Adverse Effects Study 0417

	MIRV 6 MG/KG AIBW Q3W **N = 106** **N (%)**
Study treatment - drug discontinued - due to AEs	**12 (11)**
Small Intestinal Obstruction	2 (1.9)
Thrombocytopenia	2 (1.9)
Abdominal Distension/ distention	1 (0.9)
Brain stem syndrome	1 (0.9)
Ascites	1 (0.9)
Fatigue (GT)	1 (0.9)
Infusion Related Reaction	1 (0.9)
Keratopathy (GT)	1 (0.9)
Neuropathy Peripheral (GT)	1 (0.9)
Respiratory Failure	1 (0.9)

Reviewer's Comments: *FDA conducted an analysis of study drug discontinuations due to adverse events. The most common AEs leading to treatment discontinuation were thrombocytopenia (2%) and intestinal obstruction (2%). Other adverse events leading to discontinuation (n= 1 patient each) included ocular toxicity (keratopathy), pneumonitis/respiratory failure, infusion-related reaction, peripheral neuropathy, fatigue, ascites, and brain stem syndrome. These events are mainly consistent with the expected toxicity profile of mirvetuximab or with events that may be expected in an advanced cancer patient population.*

Dose Interruptions/Reductions Due to Adverse Events

The frequency of adverse events leading to dose delays, reductions, and interruptions are described in Table 35.

Table 35 Adverse Events Leading to Dose Interruption / Reduction Study 0417

AEs with Action taken with MIRV	N=106 (%)
TEAEs leading to dose delay	41 (39)
TEAEs leading to dose reduction	21 (20)
TEAEs leading to infusion interruption	6 (6)

The occurrence of dose delays due to adverse events was relatively high, at 39%. The most common adverse events leading to dosage delays included visual impairment (15%), keratopathy (11%), neutropenia (6%), dry eye (6%), cataracts (3%), and GGT elevation (3%). Dose reductions were less common than delays, and the most common reasons for dose reductions were visual impairment (9%) and keratopathy (7%). Infusion interruptions were characterized by events resulting in temporary interruption of an infusion, mainly due to infusion-related adverse reactions. In these events, infusions could be restarted upon improvement/ resolution of symptoms.

Reviewer comment: *Specific guidance to clinicians regarding dose interruption and dose reductions in the management of adverse events is described in Section 2 of product labeling, and these are considered adequate for the safe use of mirvetuximab. Criteria for the management of infusion reactions are also provided in Table 3 of product labeling.*

Significant Adverse Events

For the purposes of this section, grade 3 and higher TEAEs are considered to be significant. TEAEs of grade 3 or higher, regardless of causality, are presented in Table 36.

Table 36 Grade 3-4 Treatment-Emergent Adverse Events (TEAEs) on Study 0417

	MIRV 6 MG/KG AIBW Q3W N = 106 N (%)
Patients with Grade 3-4 TEAEs	**52 (49)**
Eye Disorders	
Keratopathy (GT)	9 (9)
Visual Impairment (GT)	7 (7)
Dry Eye (GT)	2 (2)
Cataract	3 (3)
Gastrointestinal Disorders	

	MIRV 6 MG/KG AIBW Q3W N = 106 N (%)
Abdominal Pain (GT)	7 (7)
Ascites	4 (4)
Small Intestinal Obstruction	3 (3)
Diarrhea (GT)	3 (3)
Investigations	
Gamma-glutamyl transferase Increased	5 (5)
Neutrophil Count Decreased	3 (3)
Blood Alkaline Phosphatase Increased	2 (2)
Aspartate Aminotransferase Increased	2 (2)
General Disorders And Administration Site Conditions	
Fatigue (GT)	3 (3)
Malaise	2 (2)
Blood And Lymphatic System Disorders	
Anaemia	3 (3)
Respiratory, Thoracic And Mediastinal Disorders	
Pleural Effusion	2 (2)
Nervous System Disorders	
Neuropathy Peripheral (GT)	2 (2)
Metabolism And Nutrition Disorders	
Hypokalaemia	2 (2)

Keratopathy (GT) includes PT terms keratopathy, keratitis, punctate keratitis, and corneal toxicities
Visual Impairment (GT) includes PT terms vision blurred, visual impairment, visual acuity reduced, Monocular Diplopia. Presbyopia, Accommodation Disorder, Refraction disorder
Abdominal Pain (GT) includes PT terms Group Abdominal Pain (GT) includes PT terms Abdominal Pain, Abdominal Pain upper, Abdominal Pain lower, Abdominal discomfort.
Diarrhea (GT) includes PT terms diarrhea, colitis microscopic
Dry Eye (GT) includes PT terms dry eye, lacrimation increased
Fatigue (GT) includes PT terms fatigue, asthenia
Neuropathy Peripheral (GT) includes PT terms Peripheral Neuropathy, Paraesthesia, Peripheral Sensory Neuropathy, Peripheral Motor Neuropathy, Hypoaesthesia and Polyneuropathy

***Reviewer comment**: Almost 50% of patients in the Study 0417 study experienced Grade 3-4 TEAEs. Keratopathy, visual impairment, and abdominal pain were the most common severe adverse events. Abdominal pain was significant in 7 patients; however, this AE is not unusual for this patient population with advanced ovarian cancer. Ocular toxicity was a key focus of this*

safety review and this adverse event has been included in a boxed warning in product labeling. Additional details on the ocular adverse events are discussed in Section 8.2.5.1 of this review.

Treatment Emergent Adverse Events and Adverse Reactions

Almost all patients (99%) experienced some treatment-emergent adverse events (TEAEs) and the most common TEAEs are described in Table 37.

Table 37 Adverse Reactions (≥10%) in Patients in Study 0417

Adverse Reaction	All Grades N=106 %	Grades 3-4 N=106 %
Gastrointestinal disorders		
Nausea	40	0
Diarrhea	31	3
Constipation	30	1
Abdominal Pain	36	7
Vomiting	19	0
Abdominal distension	11	0
General disorders		
Fatigue	49	3
Infusion-related reactions/Hypersensitivity	13	1
Eye disorders		
Vision impairment	50	7
Keratopathy	37	8
Dry eye	27	2
Cataract	18	3
Photophobia	17	0
Eye Pain	10	0
Nervous system disorders		
Peripheral neuropathy	33	2
Metabolism and nutrition disorders		
Decreased appetite	18	1
Respiratory, thoracic and mediastinal disorders		
Dyspnea	12	0
Musculoskeletal and connective tissue disorders		
Arthralgia	17	0
Myalgia	10	0

Keratopathy (GT) includes PT terms keratopathy, keratitis, punctate keratitis, and corneal toxicities

Visual Impairment (GT) includes PT terms vision blurred, visual impairment, visual acuity reduced, Monocular Diplopia. Presbyopia, Accommodation Disorder, Refraction disorder
Abdominal Pain (GT) includes PT terms Group Abdominal Pain (GT) includes PT terms Abdominal Pain, Abdominal Pain upper, Abdominal Pain lower, Abdominal discomfort.
Diarrhea (GT) includes PT terms diarrhea, colitis microscopic
Dry Eye (GT) includes PT terms dry eye, lacrimation increased
Fatigue (GT) includes PT terms fatigue, asthenia
Neuropathy Peripheral (GT) includes PT terms Peripheral Neuropathy, Paraesthesia, Peripheral Sensory Neuropathy, Peripheral Motor Neuropathy, Hypoaesthesia and Polyneuropathy

Reviewer comment: *The majority of AEs were Grade 1-2, with gastrointestinal disorders being the most common category of AEs. Ocular AEs were also common, which was consistent with the eye being the key target organ for mirvetuximab-related toxicities. Thirty-four patients (32%) had peripheral neuropathy with the majority being Grade 1-2 in severity (26%). In addition, 28 patients (26%) who experienced peripheral neuropathy did not have resolution of this toxicity. Five patients had infusion-related reactions and 14 patients had hypersensitivity reactions with the distinction being the timing of the symptoms being at the time of the infusion for infusion-related reactions and within 3 days of infusion for hypersensitivity reactions. The 5 patients noted to have hypersensitivity also had infusion reactions and 3 patients with hypersensitivity were noted to have pneumonitis, which the Applicant considered to possibly related to each other.*

Laboratory Findings

The common laboratory abnormalities occurring in ≥ 10% of patients on Study 0417 are shown in Table 38**.**

Table 38 Select Laboratory Abnormalities ≥10% For All Grades, or ≥2% for Grades 3-4 In Patients in Study 0417

Laboratory Abnormality	MIRV 6 MG/KG AIBW Q3W N = 106 %	
	All Grades (%)	Grade 3-4 (%)
Chemistry		
Decreased albumin	31	1
Decreased magnesium	27	2
Increased creatinine	16	0
Decreased potassium	15	4
Hematology		

Laboratory Abnormality	MIRV 6 MG/KG AIBW Q3W N = 106 %	
	All Grades (%)	Grade 3-4 (%)
Decreased lymphocytes	35	7
Decreased leukocytes	26	1
Decreased hemoglobin	25	3
Decreased neutrophils	26	2
Decreased platelets	18	2
Liver Function Tests		
Aspartate aminotransferase	50	2
Alanine aminotransferase	39	2
Alkaline phosphatase	30	1

Reviewer's Comments: *FDA conducted an independent analysis of laboratory abnormalities for patients in Study 0417 noted in the table above. FDA analysis was consistent with the Applicant's assessment in the Clinical Study Report. Grade 1-2 transaminase elevations were the most common laboratory abnormality seen on Study 0417, but it is notable that there were very few grade 3-4 laboratory abnormalities on any kind. The above laboratory abnormalities are described in the USPI for mirvetuximab and incorporated in the overall safety analysis for the drug.*

Vital Signs

Vital signs at last treatment visit were compared to baseline values. The following results were noted by The Applicant in Section 12.5.2 of the Clinical Study Report for Study 0417:

Heart rate: 24 patients (23%) with normal heart rate values at baseline had borderline high (15 patients, 14%) or high (9 patients, 8%) values at the last visit on study drug.
1 (1%) patient with a borderline high value at baseline had a high value at the last visit on study drug.
Systolic blood pressure: 11 patients (10%) with normal values at baseline had borderline high (10 patients, 9%) or high (1 patient, 1%) values at the last visit on study drug. 7 patients (7%) with borderline high values at baseline had high values at the last visit on study drug.
Diastolic blood pressure: 11 patients (10%) with normal values at baseline had

borderline high (9 patients, 8%) or high (2 patients, 2%) values at the last visit on study drug. 3 patients (3%) with borderline high values at baseline had high values at the last visit on study drug.
Respiratory rate: 4 patients (4%) with normal values at baseline had borderline high values at the last visit on study drug.
Body temperature: There were no patients with borderline high or high values at the last on-treatment visit.

Reviewer comment: *FDA did not conduct an independent analysis of vital sign data on Study 0417, but concluded that any clinically significant changes would have been captured as TEAEs.*

Electrocardiograms (ECGs)

All patients enrolled on Study 0417 underwent a 12-lead ECG prior to the first dose of mirvetuximab; subsequent ECGS on study were not scheduled, but could have been obtained by investigators as needed. Five patients experienced TEAEs that were classified as arrythmias (2 with sinus tachycardia, 1 supraventicular arrhythmia, 1 atrial fibrillation and 1 ECG repolarization abnormality). These events were assessed as not likely related to mirvetuximab therapy. It was determined mirvetuximab did not cause meaningful changes in ECG findings over time.

QT

QT/IRT consultation was requested for review of this initial BLA application. The QT team previously reviewed QT data collected during Study IMGN853-0401 (Study 0401), which was conducted under IND 111915. An additional QT study was not performed on Study 0417

The QT data from Study 0401 revealed no large changes in mean QTc intervals (>20 msec) at the recommended dose of mirvetuximab soravtansine (6 mg/kg AIBW every 3 weeks). Likewise, no increases in QTcF of > 500 msec were observed in patients treated with mirvetuximab soravtansine. Central tendency analysis of the QTcF interval changes from baseline showed that the highest mean (upper bound of the 2-sided 90% CI) for QTcF was 8.1 (4.1, 13.0) msec. This level of change was observed at cycle 3/Day 1 in the Expansion cohort 3 on that study. As a result of this assessment, Section 12 of product labeling has included language to convey that, at the approved dose, mirvetuximab does not cause a large mean increase (> 10 msec) in the QTc interval.

Reviewer comment: See also QT consult by Drs. Kitabi, Ruiz, and Stockbridge, dated 6/30/22.

Immunogenicity

Potential for immunogenicity against mirvetuximab was assessed by testing of blood samples for the presence of anti-drug antibodies (ADA) at timepoints including C1D1, C2D1, C4D1, end of therapy and at 30-day follow up. These assessments were performed on 3 separate studies, including 0417, 0401, and 0403. The analysis included data from 423 patients with ovarian cancer treated across the studies. With a median duration of treatment of 4.3 months, 55/423 (13%) of ovarian cancer patients treated at the 6 mg/kg mirvetuximab dose had at least 1 post-baseline positive sample for ADA. Of these, 28/423 (7%) developed treatment-emergent ADA and 3/423 (0.7%) developed treatment enhanced ADA. Neutralizing antibodies were detected in 24/423 (6%) of patients.

Reviewer comment: *The conclusion about the immunogenicity data is that the overall occurrence of anti-mirvetuximab antibodies across the three clinical studies was relatively low. It is not known what effect these antibodies had or may have on the PK, efficacy, or safety of mirvetuximab, therefore, at this time the impact of ADA on the PK, safety, and efficacy of mirvetuximab is not fully characterized. Pertinent information on immunogenicity was included in Section 12 of product labeling.*

8.2.5. Analysis of Submission-Specific Safety Issues

Ocular Adverse Events/Toxicity

Ocular AEs are an adverse event of special interest with mirvetuximab. FDA conducted an independent assessment of the ocular toxicity, focusing mainly on Study 0417, but also considering data from Studies 0401 and 0403 (FORWARD1). See also Ophthalmology Consult from Dr. Wiley Chambers dated 7/8/22.

Terms included in conducting the analysis of ocular toxicities included conjunctival disorders, corneal disorders, lacrimal disorders (dry eye), eye disorders (broad SOC), ocular infections, optic nerve disorders, periorbital and eyelid disorders, scleral disorders, and retinal disorders.

Ocular monitoring on Study 0417 included the use of ocular examinations when symptoms were reported according to CTCAE criteria. Prophylactic use of corticosteroids and lubricating tears were practices that were a part of the study protocol and were implemented for all patients on study.

An overview of the ocular toxicities on Study 0417 is shown in Table 39.

The majority of patients (59%) had ocular TEAEs on Study 0417. The most common ocular adverse events were visual impairment (54%), keratopathy (37%), and dry eye (26%). The majority of ocular adverse events were of grade 1-2 in severity, but 8% of patients on Study 0417 experienced grade 3-4 visual impairment and 9% of patients experienced grade 3-4

keratopathy. In addition, according to FDA analysis, 35% of patients who experienced ocular adverse events on Study 0417 did not have resolution of their ocular AEs at the last follow-up. This was the topic of multiple requests for additional information and datasets from the Applicant, due to difficulties in confirming the Applicant's proposed data on ocular adverse events and the resolution of these events.

Table 39 Study 0417 Ocular Adverse Events

Ocular AEs	**MIRV N=106 (%)**
Grade 1-5	63 (59)
Grade 3	12 (11)
Grade 4	1 (1)
Ocular AEs leading to discontinuation	1 (1)
Ocular AEs leading to dose delay/ interruption	22 (21)
Ocular AEs leading to dose reduction	6 (6)
Patients with ocular AEs NOT recovered/ resolved	37 (35)

Reviewer's comment: *As noted, 59% of patients experienced ocular AEs and 35% of patients had unresolved ocular toxicities. The most common ocular AEs that were not resolved were visual impairment (22%), keratitis (17%), dry eye (12%), and cataracts (10%).*

One patient developed Grade 4 keratopathy on Study 0417, which lead to discontinuation of mirvetuximab therapy. The narrative for this patient is described as follows:

Patient IMGN853-0417- (b) (6) *developed Grade 4 keratopathy in the left eye and Grade 2 in the right eye during Cycle 2. She discontinued treatment the following cycle but continued to have blurry vision. The Applicant provided additional clinical information and ophthalmologic examinations for this patient, which were reviewed by Dr. Chambers. It was confirmed that vision loss was the reason for determining the severity as Grade 4 keratopathy. This adverse event, including the vision loss, subsequently resolved after discontinuation of the drug*.

<u>Ocular analysis in safety database</u>

An analysis of ocular toxicities in the pooled population of 464 patients with ovarian cancer treated on Studies 0417, 0403, and 0401 was also conducted and is shown in Table 40. Overall, the incidence of severe ocular AEs was similar between Study 0417 and in the pooled population, with 61% of patients treated with mirvetuximab experiencing an ocular adverse event. There were slight differences in the frequency of dose interruptions and reductions in the pooled databased, as compared to Study 0417 alone, however the frequency of treatment discontinuations due to ocular AEs was low. According to FDA analysis, 30% of patients in the safety database had ocular AEs that were listed as not recovered by the end of follow-up.

Table 40 Ocular adverse events in pooled ovarian cancer safety database

Ocular AEs	**MIRV N=464 (%)**
Grade 1-4	283 (61)
Grade 3-4	42 (9)
Ocular AEs leading to discontinuation	3 (0.6)
Ocular AEs leading to dose delay/ interruption	61 (13)
Ocular AEs leading to dose reduction	58 (13)
Patients with ocular AEs NOT recovered/ resolved and/or continuing	138 (30)

Reviewer comment:
It is notable that the ocular monitoring, management, and risk mitigation strategy for patients receiving mirvetuximab evolved over the course of the development program. On the dose escalation study, 0401, there was minimal monitoring and patients were only assessed based upon reports of ocular AEs. As it became more apparent that ocular toxicities were a key adverse event in patients receiving mirvetuximab, the Applicant implemented scheduled monitoring and prophylactic measures in an attempt to improve the ocular tolerability.

FDA assessed the use of CTCAE grading of severity of ocular toxicities, as well as the interventions for ocular AEs, based on patient-reported symptoms, rather than routine examinations. One difficulty in conducting the ocular safety review for the mirvetuximab database relates to the use of the CTCAE grading system for ocular adverse events, which relies on symptom-based reporting of AEs. The reason this system is not ideal for ocular adverse events is because there are certain ocular adverse events, such as corneal ulcers, that can be present without symptoms until the event has become severe (Grade 3, which correlates with corneal perforation). In this situation, the adverse event will not be detected until the toxicity has become significant. Additionally, certain ocular adverse events, such as cataracts, do not typically resolve on their own, even after discontinuation of the offending agent.

Discussions took place between the Applicant and FDA, regarding the issue of the reporting of partial and complete resolution of ocular toxicities. It was ultimately agreed upon between FDA and the Applicant that out of the safety database, (n=464 patients), 61% experienced ocular adverse events. Of these patients, 49% subsequently had resolution of their ocular AEs and 39% had partial resolution, which was defined as improvement by one or more grades from worst severity grade. It is notable that although many patients reported having at least partial improvement of ocular toxicities, it could be argued that any ocular toxicity, regardless of grade, may affect quality of life, including that even Grade 2 toxicity may involve some vision loss. Given the severity and prevalence of the ocular toxicities associated with mirvetuximab therapy, the ability of the ocular toxicities to significantly affect patient functioning and quality of life,

and the need for specialized monitoring and mitigation measures, ocular toxicity was included in product labeling as a Boxed Warning for prescribers.

In addition, it was determined by the review team that a post-marketing requirement (PMR) was needed, mandating that the Applicant take steps to identify additional measures which may improve the ocular tolerability for patients receiving mirvetuximab. The PMR mandates that the Applicant conduct or amend an ongoing clinical trial to incorporate a prospectively specified ocular monitoring approach. The monitoring will need to employ scheduled ocular assessments of patients throughout the trial, rather than utilizing symptom-based ocular examinations only. In this trial, the Applicant will also need to investigate additional risk mitigation strategies, such as supportive care prophylaxis. It was advised, and is expected, that the Applicant will meet with FDA in the future to discuss proposed trial designs and mitigation plans as part of an approach to fulfill the post-marketing requirement.

Peripheral neuropathy

Peripheral neuropathy was identified as another adverse event of special interest for mirvetuximab, given that the payload, DM4, is a tubulin-directed compound. Patients with > Grade 1 peripheral neuropathy at baseline were excluded from Study 0417, which is relevant to the study population with ovarian cancer, given that these are patients who have received prior neurotoxic chemotherapies including taxanes and platinum.

On Study 0417 (n=106), 28% of patients reported all-grade adverse events of peripheral neuropathy while on study. The analysis of these events involved pooling of terms including neurotoxicity, peripheral sensory and motor neuropathy, hypoesthesia, polyneuropathy, neuralgia, and oral hypoesthesia. The incidence of severe peripheral neuropathy on Study 0417 was 2%, including two patients experiencing Grade 3 neuropathy, one of whom discontinued treatment with mirvetuximab due to severe peripheral neuropathy.

The narratives for the two patients experiencing Grade 3 neuropathy on Study 0417 are discussed as follows:

Patient 0417- (b) (6) *: Event reported as grade 3 peripheral sensory and motor neuropathy / sciatica; resulted in treatment discontinuation. This patient experienced Grade 2 motor neuropathy and Grade 3 sensory neuropathy on Day 144 of treatment and did have a past medical history of prior platinum chemotherapy and diabetes mellitus. However, the patient did not have baseline neuropathy reported and this AE was thought to be related to the study drug and led to discontinuation of the drug. She subsequently discontinued treatment for progression of disease. The end of treatment visit was on* (b) (6) *and the AEs of Grade 2 Peripheral motor neuropathy and Grade 3 Peripheral sensory neuropathy were not resolved and were assessed by the investigator as probably related to mirvetuximab soravtansine. FDA agrees with the attribution to study drug.*

Patient 0417- (b) (6) *: Event of peripheral motor neuropathy. This patient experienced Grade 3 neuropathy after 7 cycles of mirvetuximab. The patient had received chemotherapy prior to enrollment in Study 0417 but was not noted to have baseline neuropathy. The peripheral neuropathy was not resolved at the time of the patient's last assessment and she discontinued treatment one month later due to progression of disease.*

In the larger safety database of 464 patients with ovarian cancer who received mirvetuximab on clinical trials, peripheral neuropathy was reported in 167 patients (36%). This included 9 patients with G3 peripheral neuropathy (2%) and 2 patients (0.4%) who discontinued mirvetuximab due to peripheral neuropathy. The median time to onset of peripheral neuropathy symptoms was 1.3 months (range 0.03 to 29.1 months). Of patients who experienced peripheral neuropathy during therapy with mirvetuximab, 28% had complete resolution and 13% had partial improvement in neuropathy symptoms. Partial improvement was defined as a decrease in severity by one or more grades from the worst grade experienced. This assessment also indicates that 98 patients (59%) in the mirvetuximab database who experienced peripheral neuropathy while receiving mirvetuximab did not have resolution (partial or complete) of these events, though majority of events were G1-2 in severity.

Reviewer comment: *It is notable that the incidence of peripheral neuropathy in the larger safety base was higher than on the Study 0417 (36% vs. 28%), the reason for this is unclear, however, the majority of events throughout were Grade 1 or Grade 2 in severity. FDA noted that eligibility criteria in Study 0417 permitted enrollment of patients with baseline Grade 1 neuropathy. Review of the data revealed that 15 patients on the Study 0417 had Grade 1 neuropathy at study baseline. Of the patients who had adverse events of peripheral neuropathy, 7 of them had neuropathy at baseline. Neither of the 2 patients who experienced Grade 3 neuropathy on study had neuropathy at baseline, and their events were not completely resolved at data cutoff. While peripheral neuropathy is also a risk with certain chemotherapy agents and was seen at higher rates with paclitaxel in the randomized Study 0403, FDA disagrees with the Applicant's claim that the rates of neuropathy seen with Mirvetuximab are an "improvement over all chemotherapy agents and regimens available to patients in the second-line setting", as this cannot be adequately assessed in the absence of a randomized trial, comparing the agents directly. Both the pooled analysis and the individual analysis of peripheral neuropathy for Study 0417 supported the addition of peripheral neuropathy to the Warnings and Precautions section of the prescribing information for Mirvetuximab.*

Pneumonitis

Pneumonitis affected 8% of patients on Study 0417. Though there were no cases of Grade 3-4 pneumonitis events reported on Study 0417, there were four (n=4) Grade ≥3 events in the overall safety population including 464 patients with ovarian cancer. There was one patient on Study 0417 who died due to respiratory failure in the setting of pneumonitis. The narrative was described previously in this review in Section 8.2.2 (discussion of death narratives).

Reviewer comment: Pneumonitis was included in product labeling as a Warning and Precaution in Section 5 with guidance for investigators to monitor for and manage with potential toxicity.

Hypersensitivity and Infusion-related reactions

Hypersensitivity and infusion-related reactions (IRRs) were designated by the Applicant as AEs of Special Interest. The initial FDA review indicated the incidence of all-grade hypersensitivity reactions to be 13% on Study 0417 and the incidence of all-grade infusion-related reactions to be 5%. However, FDA found overlap with patients experiencing hypersensitivity and IRR AEs and recommending grouping these events into one category. As a result, the reported incidence of the pooled terms for all-grade hypersensitivity / infusion-related reactions was 9% on Study 0417. There was one patient who experienced a Grade 3 infusion-related reaction which was an SAE and resulted in permanent discontinuation of mirvetuximab, and the narrative is described below.

Patient 0417- (b) (6) *- The event was reported to be a Grade 3 infusion-related reaction at Cycle 2 of treatment, which included hypotension and hypoxia. This resolved after 12 hours and was attributed to mirvetuximab soravtansine treatment. The patient discontinued treatment following this event and was discharged from the hospital the same day.*

Reviewer comment: *FDA assessment is that the majority of both toxicity events (hypersensitivity and IRR) were mild and did not lead to treatment discontinuation in most cases. Product labeling provides guidance to prescribers that all patients should receive premedication with acetaminophen, diphenhydramine, and dexamethasone prior to infusion. Likewise, dose modification and management guidelines for infusion-related and hypersensitivity reactions are included in Section 2 of product labeling*.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Clinical outcome assessment analyses were not included in this clinical study.

8.2.7. Safety Analyses by Demographic Subgroups

An analysis of adverse events by demographic subgroups of age and race were assessed for Study 0417. Approximately 44% (n=47) of patients enrolled on Study 0417 were ≥ 65 years of age. An overview of adverse events by age is shown in Table 41. An analysis of exposure to mirvetuximab by age group was also conducted and is shown in Table 42. Overall, there were

no notable differences in the safety of mirvetuximab soravtansine between patients ≥ 65 years of age, as compared to younger patients. Because the majority of patients enrolled on Study 0417 were white (96%), an analysis safety data by race or ethnic group could not be reasonably conducted.

Table 41 Adverse Events By Age Study 0417

Adverse events by age	**18-64 years (%) N=59**	**≥ 65y (%) N=47**
Grade 1-5	59 (100)	47 (100)
Grade 3-5	30 (50)	23 (49)
Serious AEs	22 (37)	14 (30)
Discontinuations	9 (15)	8 (17)
Dose reductions	11 (19)	11 (23)
Dose interruptions	4 (7)	2 (4)

Table 42 Exposure by Age Study 0417

	Patients 18-64 years N=59	**Patients ≥ 65 y N=47**
Duration of exposure in weeks, Median, range (min, max)	18 (3, 58)	20 (6, 48)
Number of cycles, Median, range (min, max)	5 (1, 17)	6 (2, 14)
Absolute dose intensity in mg/kg, median (range)	6 (4.5, 6.4)	6 (4.1, 6.2)
Relative dose intensity in %, median (range)	100 (75, 107)	100 (68, 103)

Reviewer's comments: *FDA did not note any significant safety signals specifically affecting older patients receiving mirvetuximab on Study 0417. A PMC was issued to the Applicant regarding the lack of diversity of patients enrolled in the study to ensure that future evaluations will assess mirvetuximab use in a population with racial and ethnic diversity reflective of the US population of ovarian cancer patients.*

8.2.8. Specific Safety Studies/Clinical Trials

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

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Carcinogenicity studies were not conducted with mirvetuximab soravtansine-gynx or DM4.

Human Reproduction and Pregnancy

Fertility studies have not been conducted with mirvetuximab soravtansine-gynx or DM4. Mirvetuximab soravtansine can cause embryo-fetal harm given that it contains the genotoxic compound DM4 and it affects actively dividing cells. The pregnancy status of females of reproductive potential should be confirmed prior to initiating therapy with mirvetuximab soravtansine. Female patients of reproductive potential should be advised to use effective contraception during treatment with mirvetuximab soravtansine and for 7 months after the last dose. This information is included in Section 8 of product labeling.

Pediatrics and Assessment of Effects on Growth

Safety and effectiveness of mirvetuximab soravtansine have not been established in pediatric patients.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not Applicable.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Not Applicable.

Expectations on Safety in the Postmarket Setting

As noted in section 8.2.5.1, FDA and the Applicant had multiple discussions regarding the implementation of serial ophthalmologic assessments in patients treated with Mirvetuximab.

Reviewer's Comments: *FDA issued a Postmarket Requirement that the Applicant conduct a clinical trial, or amend existing clinical trials, of mirvetuximab soravtansine to incorporate prospectively specified, scheduled ophthalmologic assessments in all patients (symptomatic or asymptomatic) to further characterize the incidence and severity of mirvetuximab soravtansine-related ocular adverse events and evaluate additional risk mitigation strategies for ocular*

adverse events. As noted in Section 8.2.7, a Postmarket Commitment was also issued to conduct analyses in patients from racial and ethnic minority groups as well.

8.2.11. Integrated Assessment of Safety

FDA overall determined that Study 0417 adequately characterized the safety profile of mirvetuximab soravtansine in the indicated population and that the pooled safety population including additional data from Studies 0401 and 0403 were supportive of the findings on Study 0417. There were drug discontinuations due to AEs in 12% of patients in Study 0417. The main toxicities associated with mirvetuximab soravtansine were related to gastrointestinal symptoms, ocular adverse events and peripheral neuropathy. Ocular adverse events occurred in the majority of patients (59%) in 0417 and this resulted in inclusion of this toxicity as a boxed warning in the USPI proposed for the drug. FDA investigated the methods used to grade the severity of this AE by symptoms alone and did not believe that would be adequate to monitor ocular safety. Thus, FDA recommended routine ophthalmology examinations for the first 8 cycles of Mirvetuximab treatment due to the risk of asymptomatic toxicities progressing while on this therapy. In addition, peripheral neuropathy adverse events were overall low grade but affected almost one-third of patients and this toxicity was also added to the Warnings and Precautions for mirvetuximab soravtansine though FDA agrees with the Applicant that this patient population would be considering chemotherapy agents that also have risk for neuropathy. Mirvetuximab soravtansine demonstrated acceptable tolerability for the indicated population with a serious and life-threatening disease. Adverse reactions were common, but overall low-grade and manageable with adequate safety monitoring procedures.

8.3. Statistical Issues

In general, there were no notable statistical issues with the trial design, statistical analysis plan, or efficacy results for the Study 0417. The initial sample size included 106 patients, however, two patients were excluded during review of the data: one for not meeting the definition of having platinum-resistant disease and one for major protocol violation, making the Efficacy Population inclusive of n=104 patients. The confirmed ORR was 31.7% (95% CI: 22.9, 41.6) in the target population (n=104) with an estimated median duration of response of 5.9 months (95% CI: 5.6, 7.7 months), per local investigator assessment (data cutoff: 11/16/21). At the 120-day safety update, the median DOR by investigator assessment per RECIST v1.1 increased to 6.9 months (95% CI: 5.6, 9.7 months) (data cutoff: 4/29/22). The efficacy evaluation was based on the magnitude of response rate and adequate duration of response.

8.4. Conclusions and Recommendations

Mirvetuximab soravtansine demonstrated an ORR of 31.7% (95% CI: 22.9, 41.6) and a median DOR of 6.9 months (95% CI: 5.6, 9.7) in patients with FRα- positive, platinum-resistant ovarian cancer who have received 1-3 prior systemic regimens in Study 0417. Available therapies in this

treatment setting include single agent chemotherapies with ORRs ranging from 6-27%, however, these data were collected prior to establishment of a platinum-based doublet ± bevacizumab followed by maintenance treatment with bevacizumab, niraparib, olaparib, or olaparib + bevacizumab as 1L standard-of-care treatment for advanced ovarian cancer. The FDA review team assessed the chemotherapy control arms from recent trials in platinum-resistant ovarian cancer to determine an ORR of 12-13% and a median DOR of 4-7.4 months as a more contemporary benchmark of efficacy for available therapies. There are no available therapies specifically for treatment of FRα-positive, platinum-resistant ovarian cancer. The review team also examined blinded ORR/DOR data from Study 0416 L, an ongoing randomized trial in a similar treatment setting to support efficacy results from Study 0417. Considering the results from Study 0417, supported by data from Study 0416, within the current therapeutic landscape for platinum-resistant ovarian cancer, the review team considers that mirvetuximab soravtansine demonstrates an improvement compared to available therapies and is reasonably likely to predict clinical benefit in the indicated population.

Mirvetuximab soravtansine demonstrated acceptable safety and tolerability in the indicated population with a serious and life threatening condition and limited therapeutic options. The safety of mirvetuximab soravtansine is manageable through labeling, which includes a boxed warning for ocular toxicity, premedication, dose modification, and supportive care. Because mirvetuximab soravtansine was associated with high rate of ocular toxicities, a PMR will be issued to further characterize the incidence and severity of mirvetuximab soravtansine-related ocular adverse events and evaluate additional risk mitigation strategies for ocular adverse events. Also, there was limited dosage exploration for mirvetuximab soravtansine, and the product was associated with a high frequency of toxicities. It is possible that a different dosing schedule may have a more optimal benefit-risk profile for mirvetuximab soravtansine, therefore, FDA will issue a dose-finding postmarketing requirement for evaluation of alternate dosing schedules.

Based on a favorable benefit-risk assessment, FDA clinical and statistical reviewers recommend accelerated approval for the following indication:

Mirvetuximab soravtansine for the 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 an FDA-approved test.

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

9 Advisory Committee Meeting and Other External Consultations

FDA did not refer this application to an advisory committee as there were no efficacy or safety issues identified during the review which required external input for the proposed indication.

10 Pediatrics

Included in this BLA submission was a request for waiver for study in all pediatric age based on the rationale that mirvetuximab soravtansine requires significant expression of FRα on the cell membrane. The majority of FRα expression in non-epithelial pediatric cancers are cytoplasmic in nature. Therefore, the planned waiver justification across all pediatric age groups is based on the fact that mirvetuximab soravtansine is unlikely to provide meaningful clinical benefit to children and is unlikely to be used.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Summary of Labeling		
Section	**Applicant's Proposed Labeling**	**FDA's Proposed Labeling** ***(As of 11/4/2022)***
Highlights of Labeling		
Product Title	…	Revised [redacted] (b) (4) to "injection" to provide correct dosage form.
Boxed Warning	**None proposed**	Boxed Warning for Ocular Toxicity was added based upon FDA safety review.
Dosage and Administration	…	Revised the dosage and administration statement to specify product should be diluted with 5% dextrose injection prior to intravenous infusion. Revised to add premedicate with an antiemetic, ophthalmic topical steroids, and lubricating eye drops. Added an additional cross reference to for preparation and administration instructions and dose modifications for adverse reactions.
Warnings and Precautions	…	Added Warning and Precaution for Peripheral Neuropathy. Deleted [redacted] (b) (4)
Adverse Reactions	…	Revised to include laboratory abnormalities (≥20%).
Drug Interactions	…	FDA added this to the highlights and the following phrase "Strong CYP3A4 Inhibitors: Closely monitor for ELAHERE adverse reactions"
Use in Specific Populations	…	FDA added: "Moderate or severe hepatic impairment: Avoid use. (8.7)"
Full Prescribing Information		
Boxed Warning	None.	FDA added a Boxed Warning for Ocular Toxicity.

1. Indications and Usage	…	No major changes.
2. Dosage and Administration	**2.1 Patient Selection**	FDA added the following "Information on FDA-approved tests for the measurement of FRα tumor expression is available at http://www.fda.gov/CompanionDiagnostics."
2. Dosage and Administration	**2.3 Premedication Recommended Eye Care** …	Revised existing recommendations to reduce ocular adverse reactions to make these actions requirements; and added the following: - Ophthalmic exam: Conduct an ophthalmic exam including visual acuity and slit lamp exam prior to initiation of ELAHERE, every other cycle for the first 8 cycles, and as clinically indicated. - Ophthalmic Topical Steroids: The use of ophthalmic topical steroids is recommended. The initial prescription and renewals of any corticosteroid medication should be made only after examination with a slit lamp. Administer one drop of ophthalmic topical steroids in each eye 6 times daily starting the day prior to each infusion until day 4; then administer one drop in each eye 4 times daily for days 5-8 of each cycle of ELAHERE [see Warnings and Precautions (5.1)]. - Lubricating Eye Drops: The use of lubricating eye drops at least four times daily and as needed is recommended during treatment with ELAHERE. Instruct patients to use lubricating eye drops and advise to wait at least 10 minutes after ophthalmic topical steroid administration before instilling lubricating eye drops [see Warnings and Precautions (5.1)].

2. Dosage and Administration	**2.4 Dosage Modifications**	Revised the Dosage Modifications for Adverse Reactions (Table 3) to remove (b) (4) to optimize management of specific ocular adverse reactions (ARs). Additional revisions to Table 3 included addition of dosage modifications for keratitis, uveitis, and peripheral neuropathy; and revised dosage modifications for pneumonitis and infusion-related/hypersensitivity reactions. FDA removed (b) (4)
2. Dosage and Administration	**2.5. Instructions for Preparation**	FDA added the following: • "ELAHERE is a hazardous drug. Follow applicable special handling and disposal procedures[1]. • Calculate the dose (mg) (based on the patient's AIBW), total volume (mL) of solution required, and the number of vials of ELAHERE needed [see Recommended Dosage (2.2) and Dose Modifications (2.4)]. More than one vial will be needed for a full dose." These additions clarified the dosing based on AIBW and highlighted the need for special handling procedures.
2. Dosage and Administration	**2.5. Instructions for Dilution**	FDA edited this section to emphasize that ELAHERE must be diluted prior to administration with 5% Dextrose Injection, and that it is incompatible with 0.9% Sodium Chloride Injection.
3 Dosage Forms and Strengths	**…**	Revised to use correct dosage form (injection) for this product.
5. Warnings and Precautions	**5.1 Ocular** (b) (4) (b) (4) …	- Revised the description of ocular disorders to fully characterize this adverse reaction (added visual impairment, corneal disorders, and uveitis adverse reactions) and to provide accurate incidence rates reflecting similar grouped terms for keratopathy ((b) (4) increased to 61%) and other ocular adverse reactions based on FDA safety review.

		- Edited and revised statements regarding time to onset and speculative and potentially misleading resolution of ocular ARs as follows: "The median time to onset for first ocular adverse reaction was 1.2 months (range: 0.03 to 12.9). Of the patients who experienced ocular events, 49% had complete resolution and 39% had partial improvement (defined as a decrease in severity by one or more grades from the worst grade) at last follow up." - Recommendations for ophthalmic examinations were added: "Refer patients to an eye care professional for an ophthalmic exam including visual acuity and slit lamp exam prior to treatment initiation, every other cycle for the first 8 cycles, and as clinically indicated. Promptly refer patients to an eye care professional for any new or worsening ocular signs and symptoms." - Revised the premedication, required eye care, and monitoring consistent with requirements added in Section 2.2.
5. Warnings and Precautions	**5.2 Pneumonitis**	- FDA added language to emphasize the risk of severe or fatal ILD. - FDA removed (b) (4) (b) (4) and revised to the following: "Pneumonitis occurred in 10% of patients treated with ELAHERE, including 0.8% with Grade 3 events, and 1 patient (0.2%) with a Grade 4 event. One patient (0.2%) died due to respiratory failure in the setting of pneumonitis and lung metastases."
5. Warnings and Precautions	**5.3 Peripheral Neuropathy** None proposed.	Added Peripheral Neuropathy to Warnings and Precautions section due to the incidence and severity of this AR in patients treated with ELAHERE.
6. Adverse Reactions	**6.1 Clinical Trials Experience** …	- Revised to add peripheral neuropathy data. - Revised duration of treatment statement to: "The median duration of treatment was 4.3 months (range: 0.7 to 30.4)."

		- Revised serious adverse reactions to group intestinal obstructions and reflect the updated analyses "The most common (≥2%) serious adverse reactions were intestinal obstruction (8%), ascites (4%), infection (3%), and pleural effusion (3%). Fatal adverse reactions occurred in 2% of patients, including small intestinal obstruction (1%) and pneumonitis (1%)." - Revised (b) (4) to "One patient (0.9%) permanently discontinued ELAHERE due to visual impairment (unilateral decrease to BCVA < 20/200 that resolved to baseline after discontinuation)." - Revised Table 4 to include the term visual impairment; provide more accurate incidence rates based on similar grouped terms for abdominal pain, fatigue, and peripheral neuropathy; and to arrange in order of frequency. Added uveitis to clinically relevant adverse reactions occurring in <10% of patients treated with ELAHERE.
6. Adverse Reactions	(b) (4)	
7. Drug Interactions	**7.1** (b) (4) None proposed.	Added this new subsection to identify clinically significant drug interactions between mirvetuximab and strong CYP3A4 inhibitors; and to provide drug interaction management recommendations.
8. Use in Specific Populations	**8.1 Pregnancy** **…**	Revised the Data, *Animal Data* section to include the following "The cytotoxic component of ELAHERE, DM4, disrupts microtubule function, is genotoxic, and can be toxic to actively dividing cells, suggesting it has the potential to cause embryotoxicity and teratogenicity."
8. Use in Specific Populations	**8.6 Renal Impairment**	FDA added this subsection to clarify no dosage adjustments are required for mild to moderate impairment and that the effect of severe renal impairment on ELAHERE is unknown.

8. Use in Specific Populations	**8.7 Hepatic Impairment** …	This section was added by the FDA and includes the statement about moderate to severe hepatic impairment. "Avoid use of ELAHERE in patients with moderate or severe hepatic impairment (total bilirubin >1.5 ULN). No dosage adjustment of ELAHERE is recommended for patients with mild hepatic impairment (total bilirubin ≤ULN and AST >ULN or total bilirubin >1 to 1.5 times ULN and any AST)"
11. Description	…	Revised to include the established names for ingredients and provide the required physical characteristics for this product. "…clear to slightly opalescent, colorless solution containing 100 mg/20 mL of mirvetuximab soravtansine-gynx in single-dose vials. Each mL of solution contains 5 mg of mirvetuximab soravtansine-gynx…"
12. Clinical Pharmacology	**12.1 Mechanism of Action** …	Revised to include the specific antibody-drug conjugate (ADC) mechanism.
12. Clinical Pharmacology	**12.2 Pharmacodynamics**	Minor edits to remove potentially promotional language in this section.
12. Clinical Pharmacology	**12.3 Pharmacokinetics** …	FDA reorganized this section to align with best labeling practices for pharmacokinetic labeling
12. Clinical Pharmacology	**12.6 Immunogenicity**	Additional information included on the antibodies from each of the three studies: "With a median duration of treatment of 4.3 months in Studies 0417, 0401, and 0403, a total of 55/423 (13%) ovarian cancer patients treated with mirvetuximab soravtansine-gynx at 6 mg/kg AIBW had at least 1 post-baseline positive sample for anti-mirvetuximab soravtansine-gynx antibodies…"
13. Nonclinical Toxicology	**13.1 Carcinogenesis, Mutagenesis Impairment of Fertility**	Revised this subsection to provide a concise summary of relevant toxicity data.
14. Clinical Studies	**14.1 Ovarian Cancer**	This section was revised to reflect best labeling practices in reporting race and ethnicity.

		Additional language about exclusion criteria and tumor response assessments were also added.
16. How Supplied/ Storage and Handling	…	Added "to protect from light" in the Storage subsection.
17. Patient Counseling Information	…	Included information for management of ocular disorders "Inform patients about the need for eye exams before and during treatment with ELAHERE." Additional language added to advise females of reproductive potential to use effective contraception.

12 Risk Evaluation and Mitigation Strategies (REMS)

Based on the benefit-risk assessment for mirvetuximab soravtansine, safety issues can be managed through appropriate labeling and routine post-marketing surveillance. A boxed warning for ocular toxicities has also been included in product labeling. The review team determined that a REMS is not required for this application.

13 Postmarketing Requirements and Commitment

The following PMRs and PMCs were agreed upon in association with this accelerated approval:

1. **PMR – Accelerated Approval**

Conduct the clinical trial IMGN853-0416 (MIRASOL) titled "A randomized, open-label, Phase 3 study of Mirvetuximab soravtansine vs. Investigator's choice chemotherapy in platinum-resistant, advanced, high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancers with high folate receptor-alpha expression" and provide the final progression-free survival (PFS), overall response rate (ORR) and overall survival (OS) analyses to obtain data on the clinical efficacy of mirvetuximab soravtansine for patients with platinum-resistant ovarian cancer.

Interim Report Submission:	**09/2023**
Trial Completion:	**06/2024**
Final Report Submission:	**12/2024**

2. PMR- FDAAA

Conduct a randomized clinical trial of at least 2 dose schedules of mirvetuximab soravtansine to characterize the safety of the recommended dosage of 6 mg/kg AIBW Q3W and alternative dosing schedule(s) (i.e., modified weekly dosing regimen, where lower doses are administered at a weekly frequency, instead of every 3 weeks) for the 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. The trial should evaluate safety parameters including ocular AEs (all grade, Grade ≥ 2), peripheral neuropathy (all grade, Grade ≥ 2), and other adverse events of interest. The trial should evaluate efficacy parameters of the alternate dosing schedules. The trial should also include sufficient clinical pharmacokinetic sampling to analyze the exposure-response relationship for efficacy and safety.

Draft Protocol Submission:	**04/2023**
Final Protocol Submission:	**07/2023**
Trial Completion:	**08/2026**
Final Report Submission:	**02/2027**

Submit the datasets with the final report submission.

3. PMR – FDAAA

Conduct an open-label, non-randomized, dose-escalation trial, with expansion in a sufficient

number of patients, to determine an appropriate starting dose of mirvetuximab soravtansine in patients with moderate hepatic impairment, according to the National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria, in the target patient population. Collect safety and pharmacokinetic information for mirvetuximab soravtansine, unconjugated DM4, and s- methyl DM4 from the trial and utilize this information to determine the appropriate starting dose of mirvetuximab soravtansine for this population.

Draft Protocol Submission:	**04/2023**
Final Protocol Submission:	**07/2023**
Trial Completion:	**08/2026**
Final Report Submission:	**02/2027**

Submit the datasets with the final report submission.

4. PMR – FDAAA

Conduct a clinical trial, or amend existing clinical trials, of mirvetuximab soravtansine to incorporate prospectively specified, scheduled ophthalmologic assessments in all patients (symptomatic or asymptomatic) to further characterize the incidence and severity of mirvetuximab soravtansine-related ocular adverse events and evaluate additional risk mitigation strategies for ocular adverse events.

Draft Protocol Submission:	**02/2023**
Final Protocol Submission:	**05/2023**
Study Completion:	**08/2025**
Final Report Submission:	**02/2026**

5. PMC - Clinical

Conduct an integrated analysis containing data from clinical trials and other data sources such as post-marketing reports, real-world evidence and other sources to further characterize the safety and efficacy of mirvetuximab soravtansine in patients from racial and ethnic minority groups. The analyses should support comparative safety and efficacy outcome analyses between the aforementioned populations and White patients.

Draft Protocol Submission (Analysis Plan):	**02/2023**
Final Protocol Submission (Analysis Plan):	**05/2023**
Interim Report Submission:	**12/2024**
Study Completion:	**05/2028**
Final Report Submission:	**11/2028**

6. PMC – CMC #1

To repeat the endotoxin method verification for in-process samples of drug substance (DS) intermediate with one additional batch of product verifying the lysate sensitivity in quadruplicates as per USP <85> and update Section S.2.4 of the DS intermediate.

Final Report Submission: 5/31/2023

7. PMC – CMC #2

To conduct a study to identify where (b) (4) occurs in the DS manufacturing process and to implement an additional (b) (4) specification (b) (4)

Final Report Submission: 6/30/2023

8. PMC – CMC #3

To develop a method capable of reliably detecting endotoxin levels for release testing of DS and DP, to perform method qualification with three batches of product and to implement the new endotoxin detection method.

Final Report Submission: 12/31/2023

9. PMC – CMC #4

To provide the shipping validation report of the drug substance intermediate (b) (4)

Final Report Submission: 12/31/2024

14 Division Director (DHOT) Comments

15 Division Director (OCP) Comments

16 Division Director (OB) Comments

17 Division Director (Clinical) Comments

18 Office Director (or designated signatory authority) Comments

19 Appendices

19.1. References

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19.2. Financial Disclosure

FDA reviewed financial disclosure information provided by the Applicant. There were a total of 252 investigators on Study 0401, 1123 investigators on Study 0403 (FORAWRD 1), and 647 investigators on Study 0417 (SORAYA). Across trials, there were 2 investigators with disclosable financial interests. The first investigator's site enrolled a total of (b) (6) patients onto the (b) (6) trial (b) (6) The second investigator's site enrolled a total of (b) (6) patients onto Study (b) (6) Also refer to Section 8.1.2.

Covered Clinical Study (Name and/or Number): IMGN853-0417 (SORAYA), IMGN853-0401 (Phase 1), IMGN853-0403 (FORWARD 1)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 2022		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455):		

2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 1 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

19.3. Nonclinical Pharmacology/Toxicology

[Insert carci data as needed. Limit to 2 pages]

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Summary of Applicant's Population PK Analyses

Executive Summary of Population PK Analysis

The FDA's Assessment: In general, the applicant's population PK and exposure response analyses on efficacy and safety are considered acceptable for the purpose of supporting analyses objectives. The applicant's analyses were verified by the reviewer, with no significant discordance identified.

The Applicant's Position:

General Information	
Objectives of PPK Analysis	Characterize the pharmacokinetics (PK) of mirvetuximab soravtansine (also known as IMGN853 or the antibody-

		drug conjugate (ADC)) in patients with folate receptor (FRα)-positive ovarian cancer and to explore the impact of patient demographics on the variability in relevant PK Parameters.
Studies Included		IMGN853-0401 and IMGN853-0403 for model development; IMGN853-0417 for model validation.
Dose(s) Included		0.15 mg/kg to 7 mg/kg total body weight
Population Included		Ovarian cancer (female, n=537) and other (male, n=6)
Population Characteristics (Table 43)	General	Age: median 63 yr (range: 34.0-89.0), 238 (43.8%) ≥65 yr, 58 (10.7%) ≥75 yr Weight: median 68.3 kg (range: 36.1-136) Sex: 537 (98.9%) female Race: 498 (91.7%) White, 15 (2.8%) Black, 15 (2.8%) Asian, 18 (2.95%) Other
	Organ Impairment	Hepatic (NCI): 440 (81.0%) normal function, 77 (14.2%) mild impairment, 1 (0.2%) moderate impairment and missing 25 (4.6%). Renal (CrCL): 197(36.3%) normal function, 217(40.0%) mild impairment, 127(23.4%) moderate impairment, and 2(0.4%) severe impairment.
	Pediatrics (if any)	Not applicable
No. of Patients, PK Samples, and below level of quantitation (BLQ)		No. of patients: 543 No. of PK samples: 6819, mirvetuximab soravtansine, 3745 unconjugated DM4, and 3749 S-methyl-DM4 N (%) BLQ: 60 (0.88%) mirvetuximab soravtansine, 139 (37.3%) unconjugated DM4, and 116 (3.09%) S-methyl-DM4
Sampling Schedule	Rich or Sparse Sampling	401: Schedule A (Q3W): For Schedule A patients in Cycles 1 and 3, blood samples for PK measurements were taken at the following nominal time points: Pre-dose, immediately within 10 minutes of completion of infusion, and 2, 4, 6, 8, 24, 48, 72 or 96, 168, 336, and 504 hours post (start of) infusion. In Cycles 2, 4, 5 and 6, blood samples were collected pre-dose, and immediately after the end of infusion. Additional samples were collected at the End of Treatment and 28-Day Follow Up visits. Schedule B (Modied QW): For Schedule B patients in Cycles 1 and 3, Days 1 and 15, blood samples were taken at the following nominal time points: Pre-dose, within 10

		minutes of completion of infusion, and 2, 4, 24, and 168 hours post (start of) infusion. On Day 8 in Cycles 1 and 3, samples were collected pre-dose and post-infusion. In Cycles 2, 4, 5 and 6, blood samples were collected pre-dose, and immediately after the end of infusion. Additional samples were collected at the End of Treatment and 28-Day Follow Up visits. 403: Pre-dose and within 5 minutes following IMGN853 infusion on Day 1 of Cycles 1, 2, 3, and 4; single samples were taken on Days 8 and 15 of Cycles 1 and 3, at the End of Treatment and 30-Day Follow-up. Blood samples for immunogenicity were taken from the PK sample on Day 1 of Cycles 1, 2, and 4. Separate blood samples for assessment of ADA were collected pre-dose on Day 1 of Cycle 6 (if feasible). 417: Sparse samples were collected during the study on Cycle 1 Day 1, Cycle 1 Day 8, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 3 Day 8, and Cycle 4 Day 1. On dosing days, samples were collected at pre-dose and the end of infusion; on other days only one sample was collected.
	In ITT Population	NA
Covariates Evaluated		Covariate relationships that were evaluated using the stepwise covariate modeling (SCM) method. CLmirvetuximab soravtansine: Age, AIBW, ALB, ALP, ALT, AST, CRCL, baseline tumor burden, tumor FR expression (low/medium/high), and FcgR genotype Vmirvetuximab soravtansine: Age, AIBW, ALB, baseline tumor burden, tumor FR expression (low/medium/high) Vmaxmirvetuximab soravtansine: Tumor FR expression (low/medium/high), ALB Kmmirvetuximab soravtansine: Tumor FR expression (low/medium/high), ALB CL_{DM4}: Age, AIBW, CRCL, ALT, ALP, AST, and CYP3A inh/ind conmeds V_{DM4}: AIBW, baseline tumor burden $CL_{S\text{-}methyl\text{-}DM4}$: AIBW, CRCL, ALT, ALP, AST and CYP3A inh/ind conmeds $V_{S\text{-}methyl\text{-}DM4}$: AIBW, baseline tumor burden **AIBW: Adjusted ideal body weight. ALB: Albumin. ALP: Alkaline phosphatase. ALT: Alanine aminotransferase.**

		AST: Aspartate aminotransferase. CRCL: Creatinine clearance. CYP3A: Cytochrome P450 3A4. FcgR: Fc gamma receptors. Baseline tumor burden as determined by the sum of the longest diameter of the target lesions.
	Time-varying	
Final Model	**Summary**	**Acceptability [FDA's comments]**
Software and Version	NONMEM® (version 7.4)	Acceptable
Model Structure	Mirvetuximab soravtansine: a two-compartment model with combined linear (non-specic) and nonlinear (target-mediated) elimination from the central compartment DM4 and metabolite: a central and a target compartment for DM4 and a central compartment for S-methyl-DM4	Acceptable
Model Parameter Estimates	Table 44 and Table 45	Acceptable
Uncertainty and Variability (Relative Standard Error [RSE], IIV, Shrinkage, Bootstrap)	Parameters were generally estimated with good precision (RSE <20%) except for ABW on $V2_{ADC}$, and AST on METDM4. (Table 44 and Table 45)	
BLQ for Parameter Accuracy	PK observations BLQ were retained in the dataset and were flagged as missing. In total, 0.792%, 0.771%, 37.2%, and 2.99% of the mirvetuximab soravtansine, total antibody (TAb), DM4, and S-methyl-DM4 observations were reported as BQL, respectively. Mirvetuximab soravtansine, DM4, and S-methyl-DM4 concentration values that were BQL were omitted from the PopPK analysis. TAb concentrations were not evaluated in the PopPK models.	Acceptable
Goodness of Fit (GOF), Visual Predictive check (VPC)	Figure 8, Figure 9, Figure 10, and Figure 11	Acceptable
Significant Covariates and Clinical Relevance	Figure 12 and Figure 13	Acceptable
Analysis Based on Simulation (optional)		

Labeling Language	Description	Acceptability [FDA's comments]
12.2 PK	In an exposure-response analysis, mirvetuximab soravtansine-xxxx exposure was associated with higher probability of therapeutic response; higher mirvetuximab soravtansine-xxxx exposure was associated with higher incidence of some adverse reactions (e.g., Grade ≥2 ocular adverse reactions, Grade ≥2 peripheral neuropathy).	We recommended as follows: An exposure-response relationship between mirvetuximab soravtansine-xxxx and overall response rates was observed. Higher incidence of Grade ≥2 ocular adverse reactions and Grade ≥2 peripheral neuropathy occurred with increasing mirvetuximab soravtansine-xxxx exposure.
12.3 PK	Based on population pharmacokinetic analysis, no clinically significant differences in the pharmacokinetics of mirvetuximab soravtansine-xxxx were observed for age (34 - 89 years), body weight (36 - 136 kg), mild hepatic impairment (total bilirubin ≤ULN and any AST >ULN or total bilirubin >1 to 1.5 times ULN and any AST, n= 71), or mild or moderate renal impairment (CrCL ≥30 and <90 mL/min, n= 303). The pharmacokinetics of ELAHERE in	No clinically significant differences in the pharmacokinetics of mirvetuximab soravtansine-xxxx at the proposed dosing regimen, 6mg/kg AIBW were observed for age (34 - 89 years), body weight (36 - 136 kg), mild hepatic

	patients with moderate to severe hepatic impairment (total bilirubin >1.5 ULN with any AST) or severe renal impairment (CrCL <30 mL/min) is unknown.	impairment (total bilirubin ≤ULN and any AST >ULN or total bilirubin >1 to 1.5 times ULN and any AST, n= 71), or mild or moderate renal impairment (CrCL ≥30 and <90 mL/min, n= 303). The pharmacokinetics of ELAHERE in patients with moderate to severe hepatic impairment (total bilirubin >1.5 ULN with any AST) or severe renal impairment (CrCL <30 mL/min) is unknown.

Table 43: Summary of Key Baseline Characteristics and Laboratory Values in the Dataset, Stratified by Study

	IMGN853-0401 (N = 203)	IMGN853-0403 (N = 242)	IMGN853-0417 (N = 98)	All (N = 543)
Age (*yr*) Mean (SD)	62.0 (8.8)	62.8 (10)	62.1 (9.6)	62.4 (9.6)
Median (range)	62.0 (37.0 - 86.0)	64.0 (34.0 - 89.0)	62.0 (35.0 - 85.0)	63.0 (34.0 - 89.0)
Elderly Population (65 yr), N (%)				
65 yr or older	83 (40.9%)	112 (46.3%)	43 (43.9%)	238 (43.8%)
Younger than 65 yr	120 (59.1%)	130 (53.7%)	55 (56.1%)	305 (56.2%)
Elderly Population (75 yr), N (%)				
75 yr or older	15 (7.4%)	36 (14.9%)	7 (7.1%)	58 (10.7%)
Younger than 75 yr	188 (92.6%)	206 (85.1%)	91 (92.9%)	485 (89.3%)
Race				
White	185 (91.1%)	219 (90.5%)	94 (95.9%)	498 (91.7%)
Black	5 (2.5%)	7 (2.9%)	0 (0.0%)	12 (2.2%)
Asian	7 (3.4%)	6 (2.5%)	2 (2.0%)	15 (2.8%)
American Indian	2 (1.0%)	0 (0.0%)	0 (0.0%)	2 (0.4%)
Other or Not Reported	4 (2.0%)	10 (4.1%)	2 (2.0%)	16 (2.9%)
Sex				
Female	197 (97.0%)	242 (100.0%)	98 (100.0%)	537 (98.9%)
Male	6 (3.0%)	0 (0.0%)	0 (0.0%)	6 (1.1%)
Height (*cm*)				
Mean (SD)	163 (6.3)	161 (6.6)	162 (6.5)	162 (6.5)
Median (range)	163 (149 - 182)	160 (145 - 180)	161 (146 - 182)	162 (145 - 182)
Weight (*kg*)				
Mean (SD)	72.0 (17)	70.1 (16)	67.6 (14)	70.4 (16)
Median (range)	69.3 (46.4 - 136)	67.0 (36.1 - 125)	66.5 (41.8 - 124)	68.3 (36.1 - 136)
Body surface area (m^2)				
Mean (SD)	1.77 (0.19)	1.73 (0.18)	1.71 (0.18)	1.74 (0.18)
Median (range)	1.74 (1.41 - 2.46)	1.72 (1.28 - 2.32)	1.69 (1.38 - 2.26)	1.72 (1.28 - 2.46)
Body mass index (kg/m^2)				2
Mean (SD)	27.1 (6.0)	27.1 (6.0)	25.8 (5.2)	6.8 (5.9)
Median (range)	25.9 (16.9 - 53.7)	26.0 (15.0 - 50.1)	25.8 (16.5 - 46.0)	25.9 (15.0 - 53.7)
Lean body mass (*kg*)				
Mean (SD)	46.3 (6.4)	44.7 (6.1)	44.4 (5.7)	45.2 (6.2)
Median (range)	45.4 (33.8 - 74.8)	44.3 (31.8 - 65.0)	43.8 (33.4 - 62.3)	44.7 (31.8 - 74.8)
Ideal body weight (*kg*)				
Mean (SD)	54.8 (6.0)	52.8 (5.9)	53.6 (5.9)	53.7 (6.0)
Median (range)	54.3 (41.7 - 75.0)	52.2 (38.5 - 70.3)	52.6 (39.5 - 71.8)	53.8 (38.5 - 75.0)
Adjusted ideal body weight (*kg*)				
Mean (SD)	61.7 (8.4)	59.7 (8.1)	59.2 (7.7)	60.3 (8.2)
Median (range)	60.5 (45.2 - 96.7)	59.1 (42.8 - 87.1)	58.4 (44.8 - 83.4)	59.5 (42.8 - 96.7)
Alkaline phosphatase (*IU/L*)*				
Mean (SD)	113 (1.1e+02)	99.8 (61)	125 (1.2e+02)	109 (95)
Median (range)	90.0 (11.0 - 1.24e+03)	84.8 (30.0 - 573)	95.0 (45.0 - 799)	89.0 (11.0 - 1.24e+03)
Alanine aminotransferase (*IU/L*)*				
Mean (SD)	26.4 (19)	20.9 (16)	21.9 (18)	23.1 (18)
Median (range)	23.0 (4.00 - 154)	17.0 (6.00 - 166)	17.0 (2.00 - 107)	19.0 (2.00 - 166)
Aspartate aminotransferase (*IU/L*)*				
Mean (SD)	27.9 (19)	24.6 (14)	25.8 (16)	26.1 (17)

Median (range)	22.0 (11.0 - 159)	21.0 (8.00 - 124)	21.0 (10.0 - 108)	21.0 (8.00 - 159)
Albumin (*g/dL*)*				
Mean (SD)	3.74 (0.52)	4.08 (0.41)	3.82 (0.48)	3.90 (0.49)
Median (range)	3.80 (2.00 - 5.00)	4.10 (2.60 - 5.30)	3.90 (2.60 - 4.60)	4.00 (2.00 - 5.30)
Creatinine (*µmol/L*)*				
Mean (SD)	78.6 (25)	69.9 (17)	70.2 (20)	73.2 (21)
Median (range)	70.7 (35.4 - 177)	67.0 (40.0 - 141)	66.5 (35.0 - 131)	69.0 (35.0 - 177)
Creatinine clearance (*mL/min*)				
Mean (SD)	81.1 (31)	85.2 (31)	84.0 (31)	83.5 (31)
Median (range)	75.9 (27.5 - 211)	81.5 (31.3 - 217)	77.8 (32.0 - 232)	78.5 (27.5 - 232)
Renal function, N (%)				
Normal	64 (31.5%)	92 (38.0%)	41 (41.8%)	197 (36.3%)
Mild	84 (41.4%)	101 (41.7%)	32 (32.7%)	217 (40.0%)
Moderate	53 (26.1%)	49 (20.2%)	25 (25.5%)	127 (23.4%)
Severe	2 (1.0%)	0 (0.0%)	0 (0.0%)	2 (0.4%)
Liver function, N (%)				
Normal	163 (80.3%)	197 (81.4%)	80 (81.6%)	440 (81.0%)
Mild	30 (14.8%)	33 (13.6%)	14 (14.3%)	77 (14.2%)
Moderate	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Missing	9 (4.4%)	12 (5.0%)	4 (4.1%)	25 (4.6%)
Soluble FOLR1 (pmol/L)*				
Mean (SD)	42.8 (36)	85.5 (1.7e+02)	304 (1.1e+03)	109 (4.8e+02)
Median (range)	40.4 (12.0 - 551)	40.4 (8.39 - 1.47e+03)	40.6 (11.9 - 9.21e+03)	40.4 (8.39 - 9.21e+03)
Target FOLR1 Expression Category, N (%)				
High	81 (39.9%)	142 (58.7%)	98 (100.0%)	321 (59.1%)
Medium	40 (19.7%)	100 (41.3%)	0 (0.0%)	140 (25.8%)
Low	44 (21.7%)	0 (0.0%)	0 (0.0%)	44 (8.1%)
Very Low	29 (14.3%)	0 (0.0%)	0 (0.0%)	29 (5.3%)
Unknown	9 (4.4%)	0 (0.0%)	0 (0.0%)	9 (1.7%)
Investigator Assessed Baseline Tumor Sum of Diameters (mm)*				
Mean (SD)	69.3 (50)	69.4 (51)	60.1 (51)	67.7 (51)
Median (range)	55.0 (10.0 - 294)	56.0 (10.0 - 271)	49.0 (10.0 - 351)	55.0 (10.0 - 351)
FCYRIIA Genotype				
NA	0 (0.0%)	0 (0.0%)	98 (100.0%)	98 (18.0%)
Unknown	73 (36.0%)	34 (14.0%)	0 (0.0%)	107 (19.7%)
H/H	51 (25.1%)	61 (25.2%)	0 (0.0%)	112 (20.6%)
H/R	49 (24.1%)	110 (45.5%)	0 (0.0%)	159 (29.3%)
R/R	30 (14.8%)	37 (15.3%)	0 (0.0%)	67 (12.3%)
FCYRIIB Genotype				
NA	0 (0.0%)	0 (0.0%)	98 (100.0%)	98 (18.0%)
Unknown	73 (36.0%)	34 (14.0%)	0 (0.0%)	107 (19.7%)
A/A	51 (25.1%)	61 (25.2%)	0 (0.0%)	112 (20.6%)
A/G	49 (24.1%)	110 (45.5%)	0 (0.0%)	159 (29.3%)
G/G	30 (14.8%)	37 (15.3%)	0 (0.0%)	67 (12.3%)
FCYRIIIA Genotype				
NA	0 (0.0%)	0 (0.0%)	98 (100.0%)	98 (18.0%)
Unknown	73 (36.0%)	33 (13.6%)	0 (0.0%)	106 (19.5%)
F/F	49 (24.1%)	72 (29.8%)	0 (0.0%)	121 (22.3%)
F/V	59 (29.1%)	106 (43.8%)	0 (0.0%)	165 (30.4%)

V/V	22 (10.8%)	31 (12.8%)	0 (0.0%)	53 (9.8%)
FCYRIIIB Genotype				
NA	0 (0.0%)	0 (0.0%)	98 (100.0%)	98 (18.0%)
Unknown	73 (36.0%)	33 (13.6%)	0 (0.0%)	106 (19.5%)
A/A	49 (24.1%)	72 (29.8%)	0 (0.0%)	121 (22.3%)
A/C	59 (29.1%)	106 (43.8%)	0 (0.0%)	165 (30.4%)
C/C	22 (10.8%)	31 (12.8%)	0 (0.0%)	53 (9.8%)
Strong CYP3A4 Inhibitor				
No	197 (97.0%)	237 (97.9%)	94 (95.9%)	528 (97.2%)
Yes	6 (3.0%)	5 (2.1%)	4 (4.1%)	15 (2.8%)
Moderate CYP3A4 Inhibitor				
No	176 (86.7%)	209 (86.4%)	94 (95.9%)	479 (88.2%)
Yes	27 (13.3%)	33 (13.6%)	4 (4.1%)	64 (11.8%)
Weak CYP3A4 Inhibitor				
No	199 (98.0%)	224 (92.6%)	98 (100.0%)	521 (95.9%)
Yes	4 (2.0%)	18 (7.4%)	0 (0.0%)	22 (4.1%)
Strong CYP3A4 Inducer				
No	203 (100.0%)	242 (100.0%)	98 (100.0%)	543 (100.0%)
Moderate CYP3A4 Inducer				
No	203 (100.0%)	241 (99.6%)	98 (100.0%)	542 (99.8%)
Yes	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.2%)
Weak CYP3A4 Inducer				
No	203 (100.0%)	242 (100.0%)	98 (100.0%)	543 (100.0%)
P-gp Inhibitor				
No	196 (96.6%)	234 (96.7%)	93 (94.9%)	523 (96.3%)
Yes	7 (3.4%)	8 (3.3%)	5 (5.1%)	20 (3.7%)

Source: Applicant's Population PK report QPK28-006 – Table 2.

Table 44: Parameter Estimates and Relative Standard Error from Final Mirvetuximab Soravtansine Population PK Model (run35)

Parameter	Description	Estimate	Units	Relative SE (%)	95% CI
θ_1	CL	0.0153	$L \cdot h^{-1}$		(0.0144 - 0.0162)
θ_2	V1	2.63	L		(2.58 - 2.67)
θ_3	Q	0.0107	$L \cdot h^{-1}$		(0.00956 - 0.0119)
θ_4	V2	1.7	L		(1.53 - 1.88)
θ_5	V_{max}	0.00136	$\mu mol \cdot h^{-1}$		(0.00106 - 0.00173)
θ_6	Km	0.0551	$\mu mol/L$		(0.0395 - 0.0766)
θ_7	CL_{AIWB}	1.07	-	8.9	(0.886 - 1.26)
θ_8	CL_{ALB}	-0.65	-	14.4	(-0.833 - -0.466)
θ_9	$V1_{Age}; V2_{Age}$	0.213	-	18.4	(0.136 - 0.290)
θ_{10}	$V1_{AIBW}$	0.862	-	9.6	(0.700 - 1.02)
θ_{11}	$V2_{AIBW}$	0.296	-	36.7	(0.0830 - 0.510)
$\omega_{1.1}$	ω^2_{CL}	0.0485 (22.3)	var (CV%)	15.2	(0.0340 - 0.0630)
$\omega_{2.1}$	$\omega^2_{V1,CL}$	0.0246	covar	20.5	(0.0147 - 0.0345)
$\omega_{2.2}$	ω^2_{V1}	0.0267 (16.4)	var (CV%)	19	(0.0168 - 0.0367)
$\omega_{4.4}$	ω^2_{V2}	0.0365 (19.3)	var (CV%)	31.3	(0.0141 - 0.0588)
$\omega_{6.6}$	ω^2_{Km}	0.37 (66.9)	var (CV%)	26.5	(0.178 - 0.562)
$\sigma_{1.1}$	Σ_{Prop}	0.034	var	4.9	(0.0307 - 0.0372)

Note: Relative SE was not estimated for parameters that were log transformed in the model. AIBW: Adjusted ideal body weight (kg). ALB: Serum albumin (g/dL). AGE: Age (y). CI: Confidence interval. CL: Systemic clearance. CV: Coefficient of variation. Km: Mechaelis-Menten constant. Q: Intercompartmental clearance. SE: Sstandard error. V1: Volume of distribution of central compartment. V2: Volume of distribution of peripheral compartment. Vmax: Maximum rate. ω^2_X : Variance of the inter-individual variability of parameter X. $\omega^2_{X,Y}$: Covariance of the inter-individual variability of parameters X and Y.

Source: Applicant's Population PK report QPK28-006 – Table 9 .

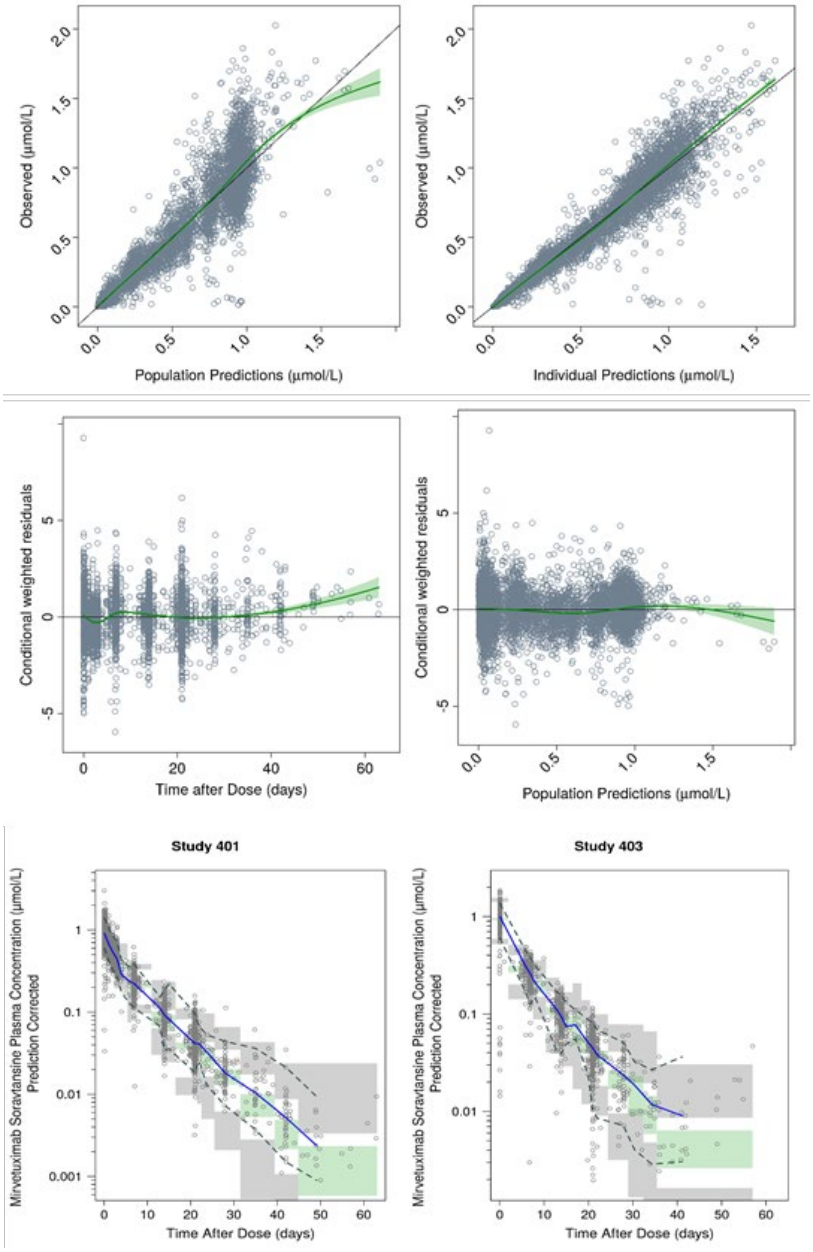
Table 45: Parameter Estimates and Relative Standard Error from Final Combined Population PK Model (run524)

Parameter	Description	Estimate	Units	Relative SE (%)	95% CI
θ_{12}	Alpha	0.664	-		
θ_{13}	Beta	0.0264	h^{-1}		
θ_{14}	VTDM4	228	L		(198 - 261)
θ_{15}	CL34	2.12	$L \cdot h^{-1}$		(1.79 - 2.52)
θ_{16}	VDM4	3.67	L		(3.02 - 4.46)
θ_{17}	CL40	8.83	$L \cdot h^{-1}$		(8.00 - 9.75)
θ_{18}	MetDM4	3.54	$L \cdot h^{-1}$		(3.10 - 4.05)
θ_{19}	VSDM4	6.3	L		(5.12 - 7.77)
θ_{20}	CL50	2.04	$L \cdot h^{-1}$		(1.90 - 2.21)
θ_{21}	$CL40_{AIBW}$	1.05	-	14.9	(0.742 - 1.36)
θ_{22}	$MetDM4_{AST}$	-0.196	-	30.3	(-0.312 - -0.0798)
$\omega_{11.11}$	ω^2_{VDM4}	0.38 (68)	var (CV%)	23.3	(0.206 - 0.554)
$\omega_{12.12}$	ω^2_{CL40}	0.209 (48.2)	var (CV%)	14	(0.152 - 0.267)
$\omega_{13.13}$	ω^2_{MetDM4}	0.0328 (18.3)	var (CV%)	34.7	(0.0105 - 0.0552)
$\omega_{14.14}$	ω^2_{VSDM4}	0.238 (51.8)	var (CV%)	37.7	(0.0623 - 0.414)
$\omega_{15.15}$	ω^2_{CL50}	0.408 (71)	var (CV%)	8.3	(0.342 - 0.475)
$\sigma_{2.2}$	$\sigma_{DM4\ Prop}$	0.0831	var	6.8	(0.0720 - 0.0942)
$\sigma_{3.3}$	$\sigma_{SDM4\ Prop}$	0.199	var	4	(0.184 - 0.214)

Note: Relative SE was not estimated for parameters that were log transformed in the model. AIBW: Baseline adjusted ideal body weight. ALPHA: Constant to constraint DAR(t) to physiologically plausible value. AST: Aspartate aminotransferase. BETA: Macro rate constant. CI: Confidence interval. CL34: Transfer clearance of DM4 from target to central. CL40: Clearance of DM4 from central other than conversion to S-Methyl-DM4. CL50: Clearance of S-methyl-DM4. CV: coefficient of variation. METDM4: Metabolism of DM4 to S-methyl-DM4. SE: standard error. VDM4: Volume of distribution of DM4 in central compartment. VTDM4: Volume of distribution of DM4 in target compartment. VSDM4: Volume of distribution of S-methyl-DM4. ω^2_X : Variance of the inter-individual variability of parameter X. $\omega^2_{X,Y}$: Covariance of the inter-individual variability of parameters X and Y.

Source: Applicant's Population PK report QPK28-006 – Table 11 .

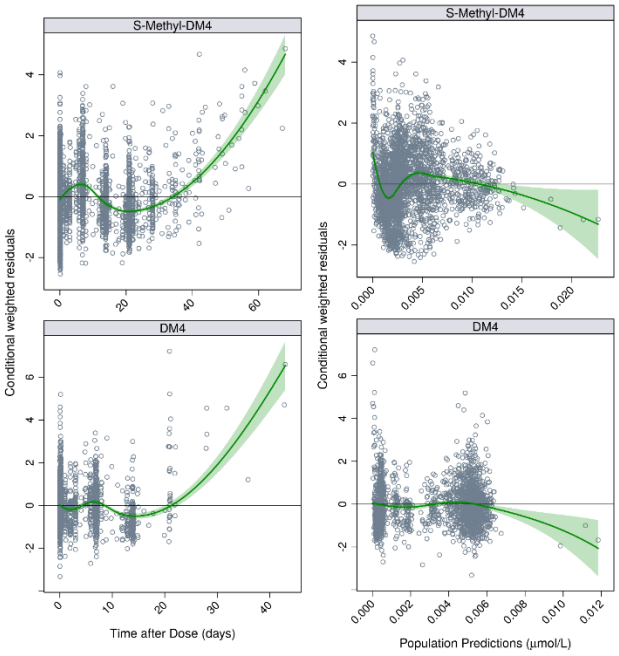
Figure 8: Goodness-of-fit and Visual Predictive Check Plots for the Final Population PK Model (OBS-PRED/IPRED, CWRES-TIME/PRED) Mirvetuximab Soravtansine



Source: Applicant's Population PK report QPK28-006 - Figures 9, 10, 12, 20, 21 and 23

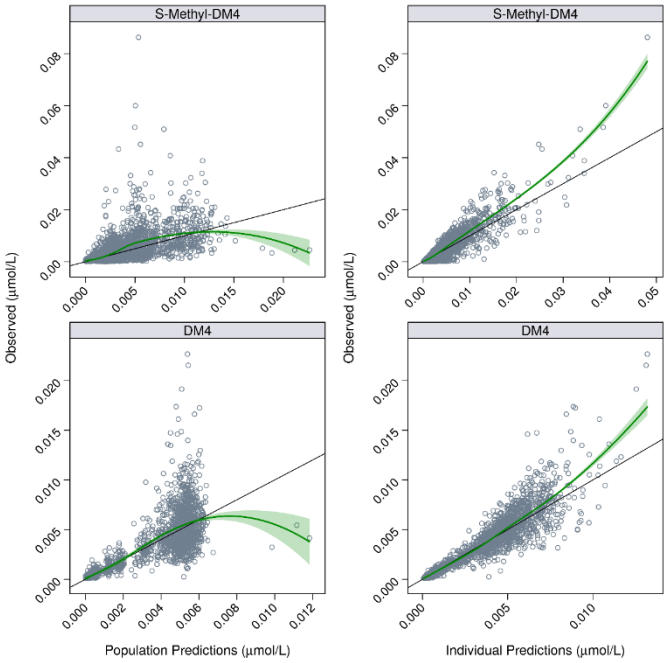
Circles: Observations; Solid Blue Line: Median of the observed mirvetuximab soravtansine concentrations. Dashed Lines: 2.5th and 97.5th percentiles of the observed mirvetuximab soravtansine concentrations. Shaded Area: The shaded areas indicate the 95% CI around the prediction-corrected median (green area), and 2.5th and 97.5th percentiles of the simulated concentrations (grey areas). All observations and predictions are adjusted using prediction correction as described in Bergstrand et al.[2].

Figure 9: Goodness-of-fit for the Final Population PK Model (CWRES-TIME/PRED) for DM4 and s-methyl DM4



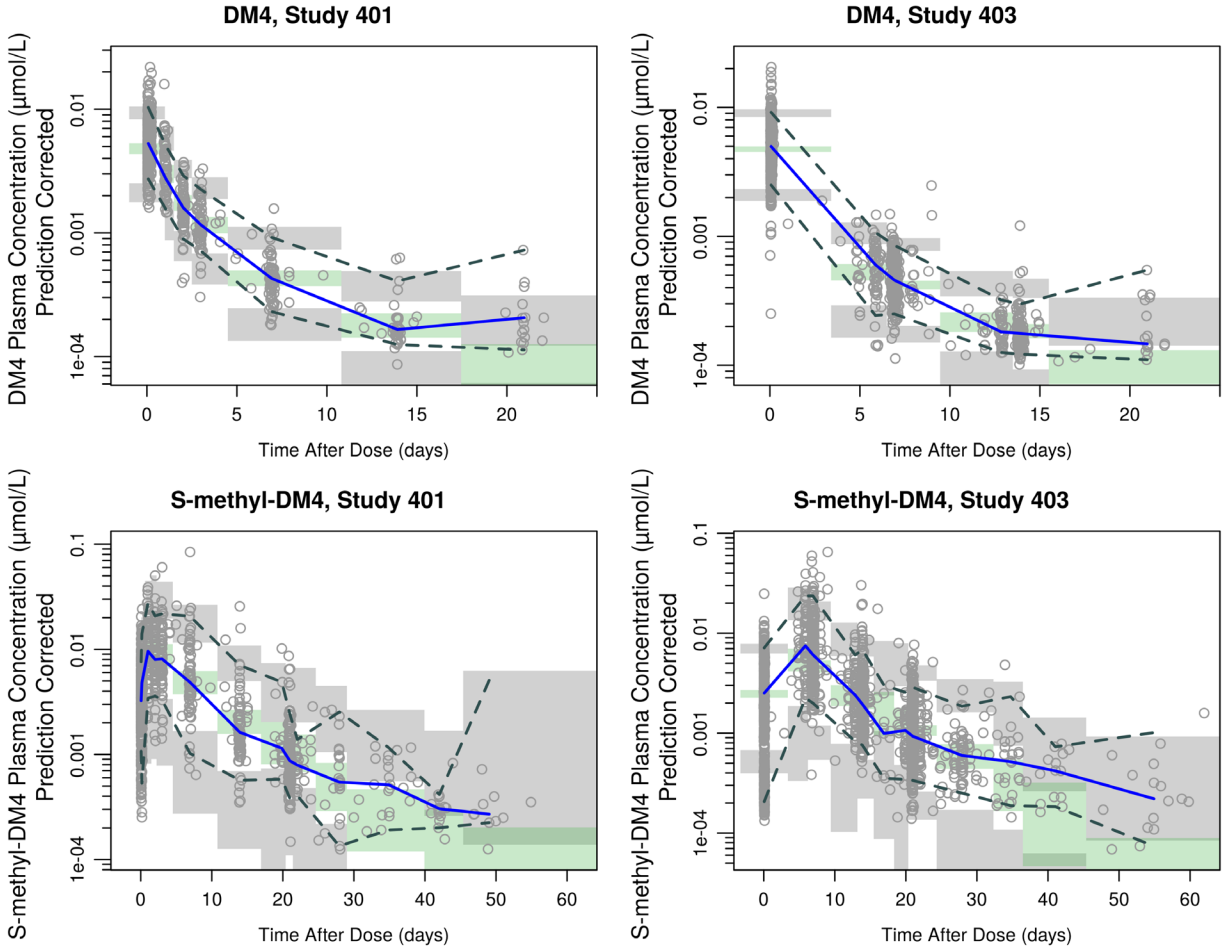
Source: Applicant's Population PK report QPK28-006 – Figure 20

Figure 10: Goodness-of-fit for the Final Population PK Model (OBS-PRED/IPRED) for DM4 and s-methyl DM4



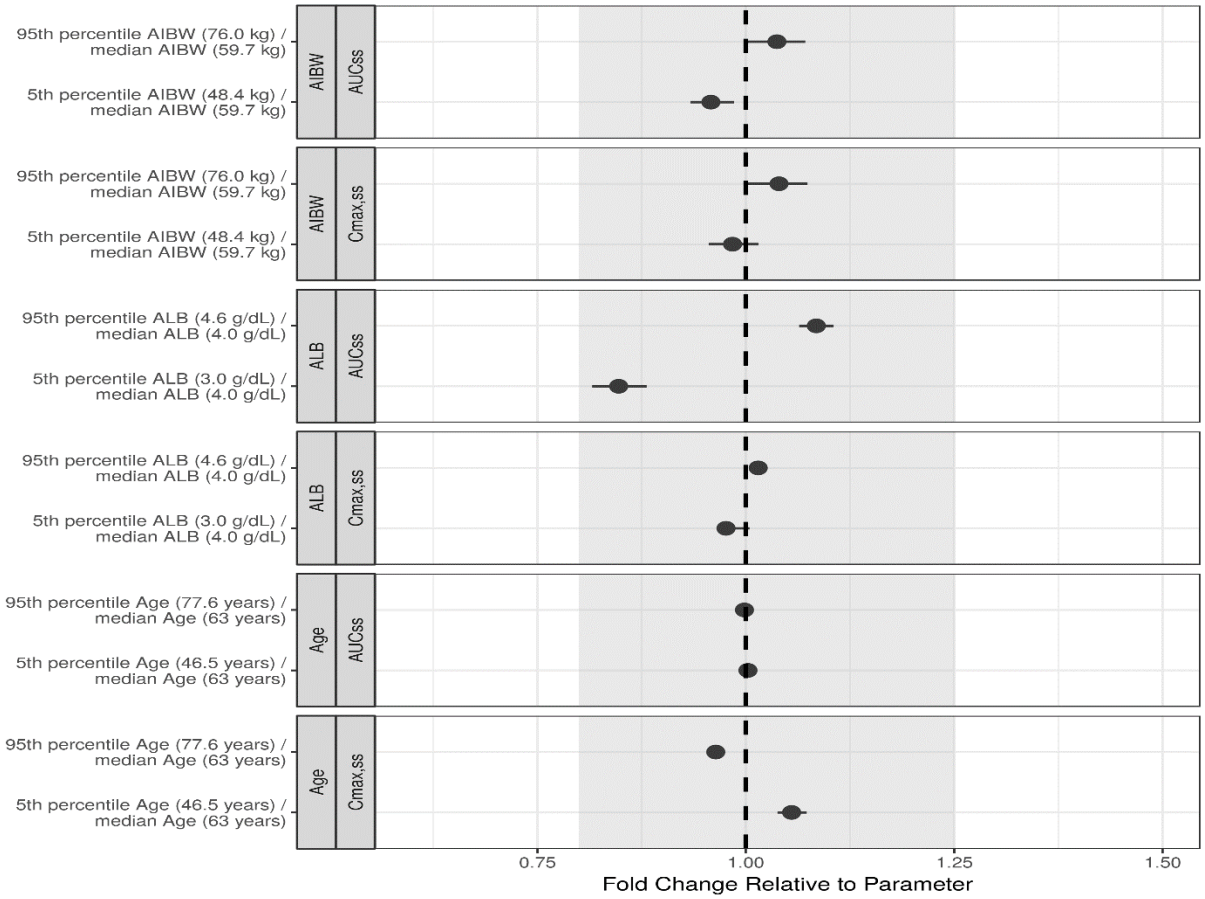
Source: Applicant's Population PK report QPK28-006 – Figure 21

Figure 11: Visual Predictive Check Plots for the Final Population PK Model for DM4 and s-methyl DM4



Source: Applicant's Population PK report QPK28-006 – Figure 23.

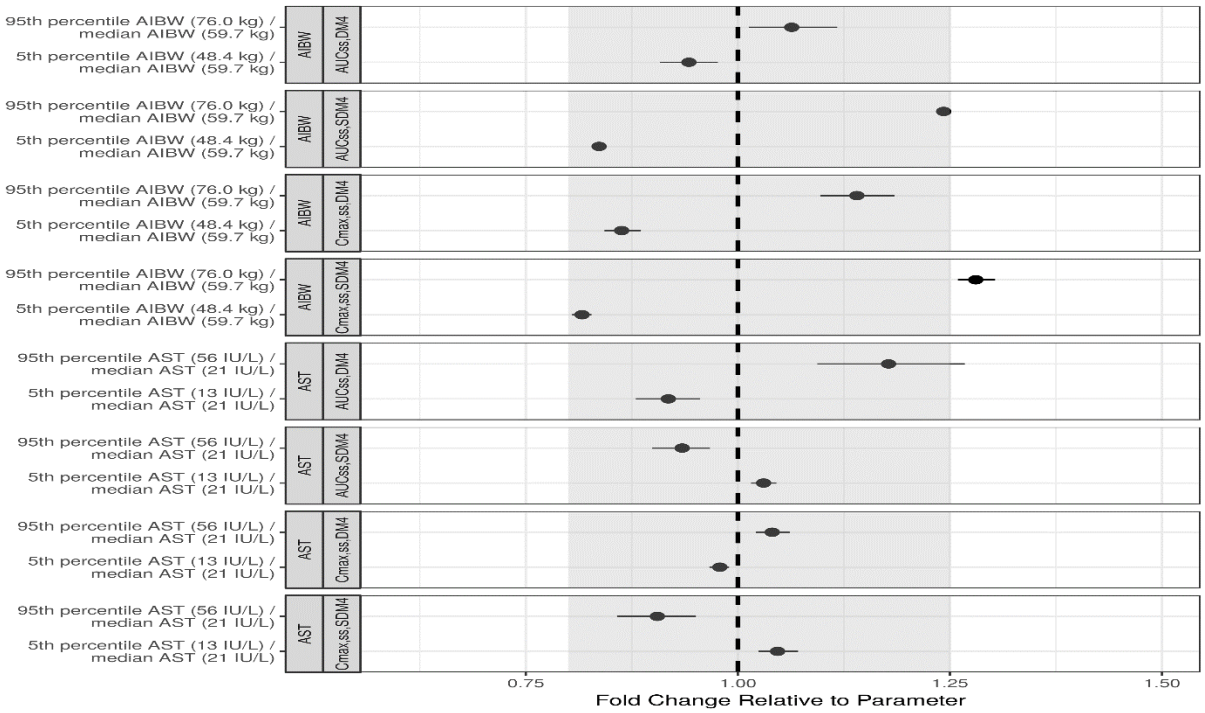
Figure 12: Impact of Significant Covariates on Exposure (AUCss and Cminss) Mirvetuximab Soravtansine



Source: Applicant's Population PK report QPK28-006 – Figure 16.

AIBW: adjusted ideal body weight (kg). ALB: serum albumin (g/dL). AGE: Age (y). AUCss: area under the concentration versus time curve at steady state. Cmaxss: maximum concentration at steady state. Dotted line represent reference (typical value of the parameter given median of each covariate values). Grey area represent 0.8 and 1.25 fold change from the reference value. The points and horizontal lines is the median and 95% CI and represents the ratios based on 1,000 sets of parameter estimates re-sampled from the variance covariance matrix. Covariate effects on mirvetuximab soravtansine exposure at steady state following a 6mg/kg AIBW dose.

Figure 13: Impact of Significant Covariates on Exposure (AUCss and Cminss) on DM4 and s-methyl DM4



Source: Applicant's Population PK report QPK28-006 – Figure 27.

AIBW: adjusted ideal body weight (kg). AST: Aspartate aminotransferase (IU/L). AUCss: area under the concentration versus time curve at steady state. Cmaxss: maximum concentration at steady state. Dotted line represents reference exposure (typical value of the parameter given median of each covariate values). Grey area represent 0.8 and 1.25 fold change from the reference value. The points and horizontal lines is the median and 95% CI and represents the ratios based on 1,000 sets of parameter estimates re-sampled from the variance covariance matrix. Covariate effects on mirvetuximab soravtansine exposure at steady state following a 6mg/kg AIBW dose.

<u>The FDA's Assessment:</u>
The applicant's population PK analysis is considered acceptable for the purpose of supporting analyses objectives.

PPK Review Issues

There are no PPK review issues.

Reviewer's Independent Analysis

The Applicant's analyses were verified by the reviewer, with no significant discordance identified.

19.4.2. Exposure-Response Analysis

ER (efficacy) Executive Summary

The FDA's Assessment:

The Applicant's exposure response analyses on efficacy are considered acceptable for the purpose of supporting analyses objectives. The Applicant's analyses were verified by the reviewer, with no significant discordance identified.

ER (efficacy) Assessment Summary

The Applicant's Position:

General Information		
Goal of ER analysis		Characterize exposure-efficacy relationships for ORR, DOR and PFS. Evaluate covariate relationships to explain potential differences in efficacy or among subgroups of subjects, relative to previous efficacy results in BC
Study Included		401, 403 and 417
Endpoints		Primary: ORR Secondary: PFS
No. of Patients (total, and with individual PK)		Due to differences in study design, the efficacy endpoints were analyzed in two separate data pools, one for the pivotal study (IMGN853-0417, N = 97), and the other for the supporting studies IMGN853-0401 (patients meeting the IMGN853-0403 inclusion criteria, N = 36) and IMGN853-0403 (N = 242) combined.
Population Characteristics (Table 46)	General	Age: median 63.0 yr (min, max: 34.0, 89.0) Weight: median 68.3 kg (min, max: 36.1, 136) Sex: 6 (1.1%) male Race: 497 (91.7%) White, 12 (2.2%) Black, 2 (0.4%) American Indian, 15 (2.8%) Asian, 16 (3.0%) Other
	Pediatrics (if any)	Not applicable
Dose(s) Included		The doses of mirvetuximab soravtansine ranged from 0.15 mg/kg to 7.0 mg/kg intravenous (IV) administration based on total body weight (TBW), which is equivalent to 0.161 mg/kg to 8.71 mg/kg based on AIBW.
Exposure Metrics Explored (range)		Cycle 1 area under the concentration vs. time curve over the first 21-day treatment cycle (AUCo-d21), maximum concentration (Cmax), and trough concentration (Ctrough) for mirvetuximab soravtansine, the payload DM4, and the metabolite, S-methyl-DM4 (safety only) were used as exposure metrics.

Covariates Evaluated	• Continuous Covariates: Age, AIBW, albumin, creatinine clearance (CLcr), baseline tumor burden, and soluble folate receptor α (sFR-α) • Categorical Covariates: Race (white vs. non-white, as the majority was white)	
Final Model Parameters	**Summary**	**Acceptability [FDA's comments]**
Model Structure	Primary endpoints: ORR by logistic regression model Other endpoints: DOR and PFS by Cox regression model	Acceptable
Model Parameter Estimates	Table 47	Acceptable
Model Evaluation	Figure 14, Figure 15, Figure 16, and Figure 17	Acceptable
Covariates and Clinical Relevance	ORR: none for 417 and albumin (ALB) and soluble folate receptor o: (sFR-o:) for pooled 401 and 403 DOR: no correlation and not performed. PFS: Alkaline phosphatase (ALP) given Ctrough for 417 and ALB, sFR-o:, tumor size and age for pooled 401 and 403	Acceptable
Simulation for Specific Population	The ORR model based on mirvetuximab soravtansine AUC0-d21, and the ocular toxicity model based on mirvetuximab soravtansine AUC0-d21 were used to predict the ORR response rate and ocular AE incidence rate over a wide range of exposures. Aligned with the overlaid efficacy and safety ER curves were the AUC0-d21 ranges of mirvetuximab soravtansine for doses from 3.3 mg/kg to 7 mg/kg TBW, including 6 mg/kg AIBW, that were administered in the three clinical studies. In addition, simulated AUC0-d21 range following 6 mg/kg AIBW and 6 mg/kg TBW dosing (n=l000 subjects) is illustrated.	Acceptable

Visualization of E-R relationships	Figure 14, Figure 15, Figure 16, and Figure 17	Acceptable
Overall Clinical Relevance for ER	The joined analysis showed that 6 mg/kg AIBW was a dose with balanced efficacy and safety.	Acceptable
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	In an exposure-response analysis, higher mirvetuximab soravtansine-xxxx exposure was associated with higher probability of therapeutic response; higher mirvetuximab soravtansine-xxxx exposure was associated with higher incidence of some adverse reactions (e.g., Grade ≥2 ocular adverse reactions, Grade ≥2 peripheral neuropathy).	One efficacy exposure-response analyses including multiple dose levels and one including one dose level, consistently support that higher mirvetuximab soravtansine-xxxx exposure was associated with higher probability of therapeutic response; one combined safety exposure-response analysis supports that higher mirvetuximab soravtansine-xxxx exposure was associated with higher incidence of some adverse reactions (e.g., Grade ≥2 ocular adverse reactions, Grade ≥2 peripheral neuropathy).

Table 46: Summary of Baseline Characteristics for exposure-response analysis

	IMGN853-0401 (N = 203)	IMGN853-0403 (N = 242)	IMGN853-0417 (N = 97)	All (N = 542)
Age *(yr)*				
Mean (SD)	62.0 (8.8)	62.8 (10)	61.9 (9.5)	62.4 (9.6)
Median (range)	62.0 (37.0 - 86.0)	64.0 (34.0 - 89.0)	62.0 (35.0 - 85.0)	63.0 (34.0 - 89.0)
Race				
American Indian	2 (1.0%)	0 (0.0%)	0 (0.0%)	2 (0.4%)
Asian	7 (3.4%)	6 (2.5%)	2 (2.1%)	15 (2.8%)
Black	5 (2.5%)	7 (2.9%)	0 (0.0%)	12 (2.2%)
Others or Not Reported	4 (2.0%)	10 (4.1%)	2 (2.1%)	16 (3.0%)
White	185 (91.1%)	219 (90.5%)	93 (95.9%)	497 (91.7%)
Sex				
Female	197 (97.0%)	242 (100.0%)	97 (100.0%)	536 (98.9%)
Male	6 (3.0%)	0 (0.0%)	0 (0.0%)	6 (1.1%)
Weight *(kg)*				
Mean (SD)	72.0 (17)	70.1 (16)	67.8 (14)	70.4 (16)
Median (range)	69.3 (46.4 - 136)	67.0 (36.1 - 125)	67.0 (41.8 - 124)	68.3 (36.1 - 136)
Body surface area (m2)				
Mean (SD)	1.77 (0.19)	1.73 (0.18)	1.72 (0.17)	1.74 (0.18)
Median (range)	1.74 (1.41 - 2.46)	1.72 (1.28 - 2.32)	1.69 (1.38 - 2.26)	1.72 (1.28 - 2.46)
Body mass index *(kg/m2)*				
Mean (SD)	27.1 (6.0)	27.1 (6.0)	25.9 (5.1)	26.9 (5.9)
Median (range)	25.9 (16.9 - 53.7)	26.0 (15.0 - 50.1)	25.8 (16.5 - 46.0)	25.9 (15.0 - 53.7)
Lean body mass *(kg)*				
Mean (SD)	46.3 (6.4)	44.7 (6.1)	44.4 (5.7)	45.2 (6.2)
Median (range)	45.4 (33.8 - 74.8)	44.3 (31.8 - 65.0)	43.8 (33.4 - 62.3)	44.7 (31.8 - 74.8)
Ideal body weight *(kg)*				
Mean (SD)	54.8 (6.0)	52.8 (5.9)	53.7 (5.9)	53.7 (6.0)
Median (range)	54.3 (41.7 - 75.0)	52.2 (38.5 - 70.3)	52.9 (39.5 - 71.8)	53.8 (38.5 - 75.0)
Adjusted ideal body weight *(kg)*				
Mean (SD)	61.7 (8.4)	59.7 (8.1)	59.3 (7.6)	60.4 (8.2)
Median (range)	60.5 (45.2 - 96.7)	59.1 (42.8 - 87.1)	58.5 (44.8 - 83.4)	59.5 (42.8 - 96.7)
Alkaline phosphatase *(JU/ L)*				
Mean (SD)	113 (1.1e+02)	99.8 (61)	126 (1.2e+02)	109 (95)
Median (range)	90.0 (11.0 - 1.24e+03)	84.8 (30.0 - 573)	96.0 (48.0 - 799)	89.0 (11.0 - 1.24e+03)
Alanine aminotransferase *(IU/L)*				
Mean (SD)	26.4 (19)	20.9 (16)	21.9 (18)	23.1 (18)
Median (range)	23.0 (4.00 - 154)	17.0 (6.00 - 166)	17.0 (2.00 - 107)	19.0 (2.00 - 166)
Aspartate aminotransferase *(IU/L)*				
Mean (SD)	27.9 (19)	24.6 (14)	25.8 (16)	26.1 (17)
Median (range)	22.0 (11.0 - 159)	21.0 (8.00 - 124)	21.0 (10.0 - 108)	21.0 (8.00 - 159)
Albumin *(g/dL)*				
Mean (SD)	3.74 (0.52)	4.08 (0.41)	3.81 (0.49)	3.90 (0.49)
Median (range)	3.80 (2.00 - 5.00)	4.10 (2.60 - 5.30)	3.90 (2.60 - 4.60)	4.00 (2.00 - 5.30)

Creatinine *(µmol / L)*				
Mean (SD)	78.6 (25)	69.9 (17)	70.0 (20)	73.2 (21)
Median (range)	70.7 (35.4 - 177)	67.0 (40.0 - 141)	66.0 (35.0 - 131)	69.0 (35.0 - 177)
Creatinine clearance *(mL/min)*				
Mean (SD)	81.1 (31)	85.2 (31)	84.5 **(31)**	83.6 (31)
Median (range)	75.9 (27.5 - 211)	81.5 (31.3 - 217)	78.2 (32.0 - 232)	78.6 (27.5 - 232)
Soluble FOLRl Missing & Imputed				
No	10 (4.9%)	173 (71.5%)	77 (79.4%)	260 (48.0%)
Yes	193 (95.1%)	69 (28.5%)	20 (20.6%)	282 (52.0%)
Soluble FOLRl (pmol/L)				
Mean (SD)	42.8 (36)	85.5 (1.7e+02)	307 (1.le+03)	109 (4.8e+02)
Median (range)	40.4 (12.0 - 551)	40.4 (8.39 - 1.47e+03)	40.7 (11.9 - 9.21e+03)	40.4 (8.39 - 9.21e+03)
Target FOLRl Expression Category				
High	81 (39.9%)	142 (58.7%)	97 (100.0%)	320 (59.0%)
Low	44 (21.7%)	0 (0.0%)	0 (0.0%)	44 (8.1%)
Medium	40 (19.7%)	100 (41.3%)	0 (0.0%)	140 (25.8%)
Unknown	9 (4.4%)	0 (0.0%)	0 (0.0%)	9 (1.7%)
Very Low	29 (14.3%)	0 (0.0%)	0 (0.0%)	29 (5.4%)
Baseline Tumor Sum of Diameters Missing & Imputed				
No	188 (92.6%)	242 (100.0%)	88 (90.7%)	518 (95.6%)
Yes	15 (7.4%)	0 (0.0%)	9 (9.3%)	24 (4.4%)
Investigator Assessed Baseline Tumor Sum of Diameters (mm)				
Mean (SD)	69.3 (50)	69.4 (51)	59.3 (51)	67.6 (51)
Median (range)	55.0 (10.0 - 294)	56.0 (10.0 - 271)	44.0 (10.0 - 351)	55.0 (10.0 - 351)

Source: Applicant's E-R report QPK28-007 – Table 1.

Table 47: Parameter Estimates from Final ER Models of (ORR and PFS) for Mirvetuximab Soravtansine using 417 or pooled 401 and 403

Exposure	Endpoint	Parameter	Estimate	Std Dev	RSE
ORR					
417					
		Coefficient (95% CI)			
		Constant	−2.421*** (−3.660, −1.182)		
		CTROUGH_Mirv	46.790*** (16.178, 77.401)		
		***p<0.01			
Pooled 401 and 403					

	Coefficient (95% CI)
Constant	−10.372*** (−14.332, −6.413)
CTROUGH_Mirv	33.131*** (11.401, 54.861)
logSFOLR1	0.678*** (0.337, 1.019)
ALB	1.387*** (0.562, 2.213)

***p<0.01

PFS

417

Covariate	Hazard Ratio	Coefficient	SE	p-value
CTROUGH_{Mirv}	9.99e-09	-18.4	8.47	0.0297
ALP	1	0.00237	0.000948	0.0123

CTROUGH_{Mirv} = mirvetuximab soravtansine C_{trough} (μmol/L), ALP = Alkaline phosphatase (IU/L), SE = Standard Error.

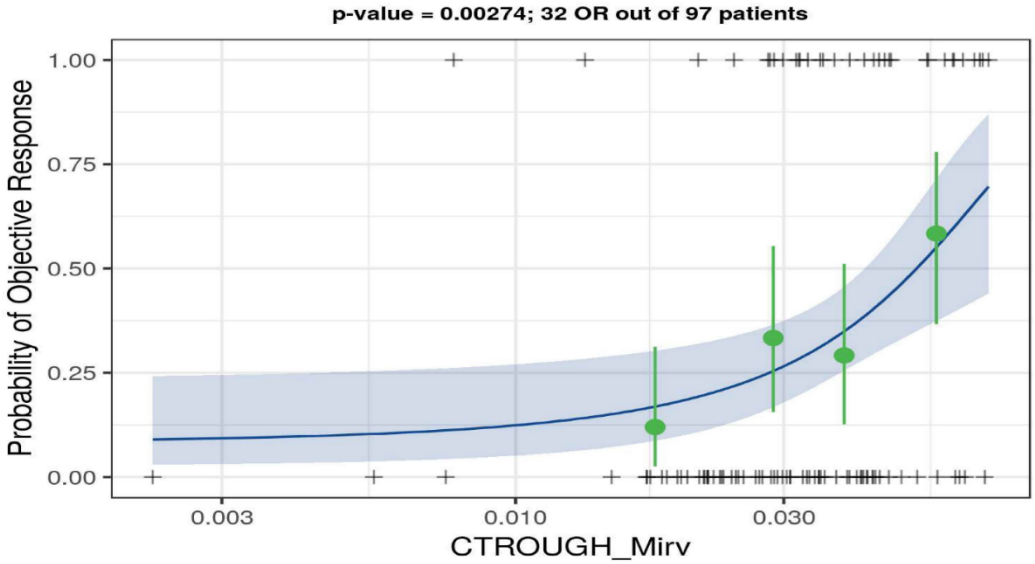
Pooled 401 and 403

Covariate	Hazard Ratio	Coefficient	SE	p-value
CTROUGH_{Mirv}	7.8e-08	-16.4	5.89	0.00546
logSFOLR1	0.689	-0.373	0.085	< 0.0001
ALB	0.452	-0.794	0.202	< 0.0001
TUMORSDB	1	0.00423	0.00138	0.00209
AGE	0.982	-0.0178	0.00749	0.0173

AGE=age (years), ALB=albumin (g/dL), CTROUGH_{Mirv})=mirvetuximab soravtansine C_{trough} (μmol/L), FOLR1=FR-α, logSFOLR1=log of sFR-α, TUMORSDB=baseline tumor sum of diameter (mm), SE = Standard Error.

Source: Applicant's ER report QPK28-007.

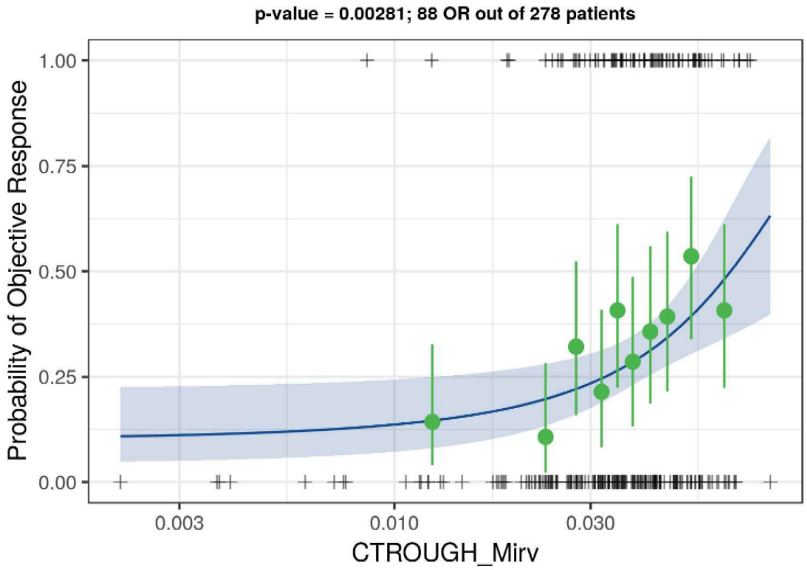
Figure 14: ER Curve of ORR vs. Mirvetuximab Soravtansine $Cmin_{ss}$ in Study 417



The plot shows the predicted probability (mean + 95% CI) in blue for the variable in the x axis at the median/mode value of any other variables. The green points and range depict the exact binomial estimate of the response for quantiles (4) of the exposure variable. Observed events are indicated by a + at the top (p=1.0) and bottom (p=0.0) of the plot. **OR**: Objective Response. **CI**: Confidence Interval.

Source: Applicant's ER report QPK28-007 – Figure 4.

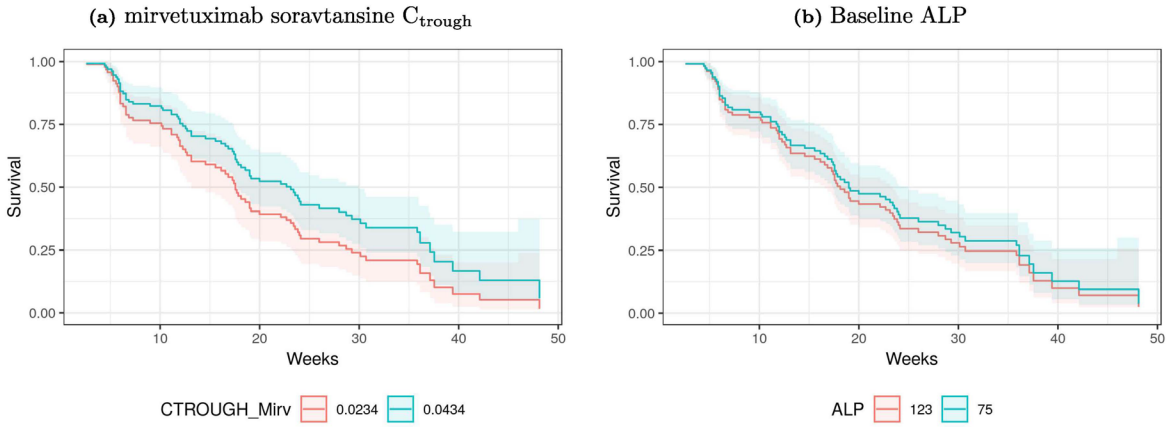
Figure 15: ER Curve of ORR vs. Mirvetuximab Soravtansine $Cmin_{ss}$ in Studies 401 and 403



The plot shows the predicted probability (mean + 95% CI) in blue for the variable in the x axis at the median/mode value of any other variables. The green points and range depict the exact binomial estimate of the response for quantiles (4) of the exposure variable. Observed events are indicated by a + at the top (p=1.0) and bottom (p=0.0) of the plot. **OR**: Objective Response. **CI**: Confidence Interval.

Source: Applicant's ER report QPK28-007 – Figure 10.

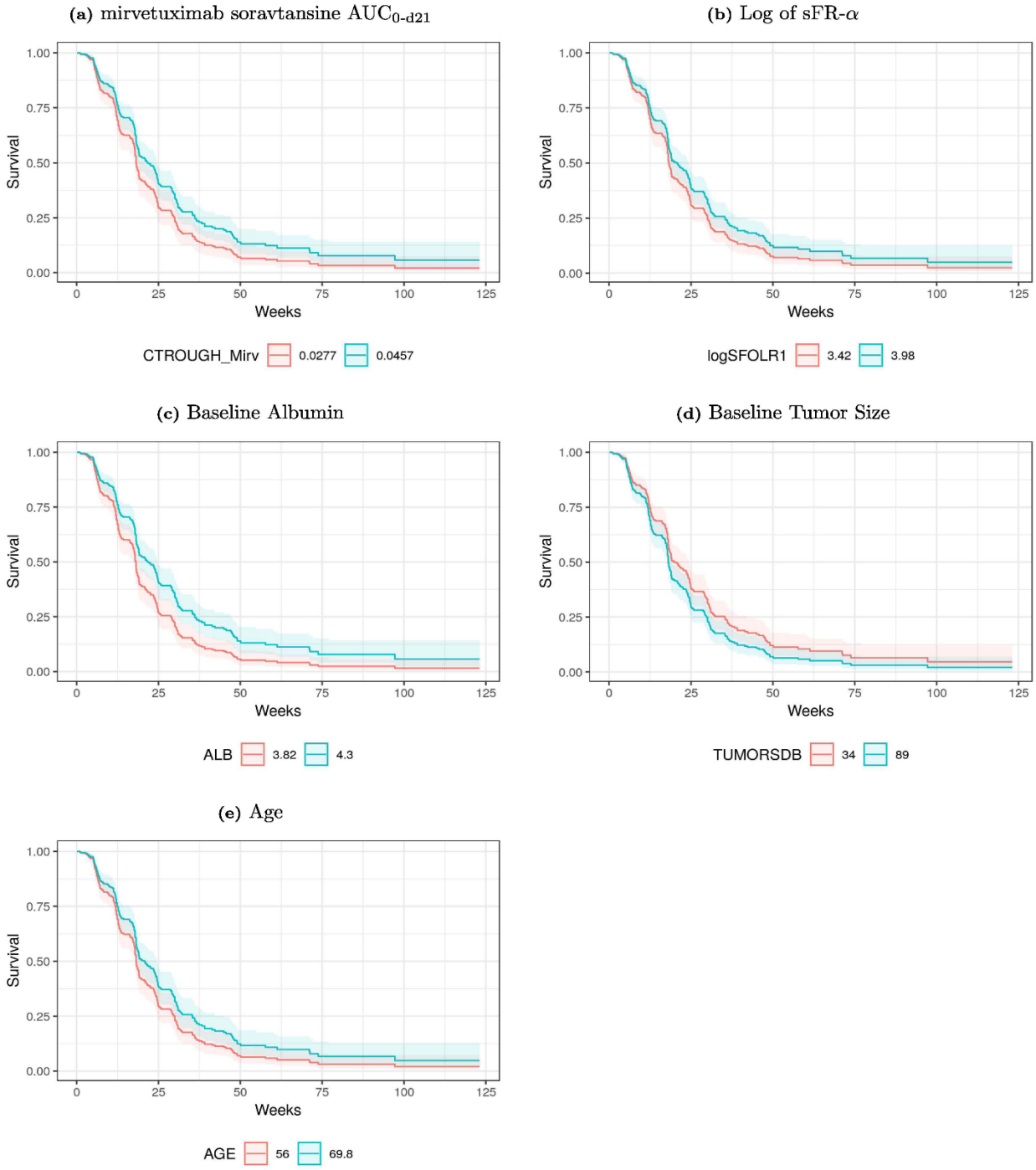
Figure 16: Model-Based Predictions of Investigator Reported Progression Free Survival for Covariates Included in the Final Model - Study 417



The model-based survival curves visualize the survival probability curves across the IQR (25th to 75th percentiles) for continuous variables.

Source: Applicant's ER report QPK28-007 – Figure 9.

Figure 17: Model-Based Predictions of Investigator Reported Progression Free Survival for Covariates Included in the Final Model – Studies 0401 and 0403



The model-based survival curves visualize the survival probability curves across the IQR (25th to 75th percentiles) for continuous variables.

Source: Applicant's ER report QPK28-007 – Figure 15

19.4.3. ER (safety) Executive Summary

The FDA's Assessment:
The Applicant's exposure response analyses on safety are considered acceptable for the purpose of supporting analyses objectives. The Applicant's analyses were verified by the reviewer, with no significant discordance identified.

ER (safety) Assessment Summary
The Applicant's Position:

General Information		
Goal of ER analysis		Characterize exposure-safety relationships for the AEs listed below Evaluate covariate relationships to explain potential differences in safety among subgroups of subjects
Studies Included		401, 403 and 417
Population Included		Ovarian cancer and other
Endpoint		Focusing on adverse events (AE) grade 2 or higher for (1) the ocular system, (2) peripheral neuropathy, and (3) pneumonitis
No. of Patients (total, and with individual PK)		N=542
Population Characteristics (Table 46)	General	Age: median 63.0 yr (min, max: 34.0, 89.0) Weight: median 68.3 kg (min, max: 36.1, 136) Sex: 6 (1.1%) male Race: 497 (91.7%) White, 12 (2.2%) Black, 2 (0.4%) American Indian, 15 (2.8%) Asian, 16 (3.0%) Other
	Pediatrics (if any)	Not applicable
Dose(s) Included		0.15 mg/kg to 7 mg/kg total body weight
Exposure Metrics Explored (range)		Cycle 1 area under the concentration vs. time curve over the first 21-day treatment cycle (AUC0-d21), maximum concentration (Cmax), and trough concentration (Ctrough) for mirvetuximab soravtansine, the payload DM4, and the metabolite, S-methyl-DM4 (safety only) were used as exposure metrics.
Covariates Evaluated		• Continuous Covariates: Age, AIBW, albumin, creatinine clearance (CLcr), baseline tumor burden, and soluble folate receptor α (sFR-α) • Categorical Covariates: Race (white vs. non-white, as the majority was white)
Final Model Parameters	**Summary**	**Acceptability [FDA's comments]**

Model Structure	For dichotomous safety endpoints: logistic regression models	**Acceptable**
Model Parameter Estimates	Table 48	Acceptable
Model Evaluation	Figure 18 and Figure 19	Acceptable
Covariates and Clinical Relevance	Ocular AEs: mirvetuximab soravtansine AUC0-d21 and baseline tumor size as predictor variables Peripheral neuropathy of Grade 2 or higher: mirvetuximab soravtansine Ctrough and AUC0-d21 as statistically significant covariates. Pneumonitis (including interstitial lung disease): None.	Few patients in the lowest AUC0-d21 decile developed a Grade 2+ ocular AE, but there was a trend that the incidence rate increased with increasing mirvetuximab soravtansine AUC0-d21 . ER relationship was relatively flat, suggesting limited impact of mirvetuximab soravtansine exposure on peripheral neuropathy.
Simulation for Specific Population	The ORR model based on mirvetuximab soravtansine AUC0-d2i, which was comparable to the final ORR model based on Ctrough, and the ocular toxicity model based on mirvetuximab soravtansine AUC0-d21 were used to predict the ORR response rate and ocular AE incidence rate over a wide range of exposures (See Table 18 and Figure 20 in the ER report).	Acceptable.
Visualization of E-R relationships	Figure 18 and Figure 19	Acceptable

Overall Clinical Relevance for ER	In general, both efficacy and ocular toxicity were found to increase with increasing exposure to mirvetuximab soravtansine. The covariates identified by the models overall had limited impact on efficacy and safety, and are likely not of clinical significance.	Acceptable.
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	Not applicable	

Table 48: Parameter Estimates Final Logistic Regression Model of Effect of Mirvetuximab Soravtansine AUC0-d21 on Odds of Ocular System Adverse Events (Grade 2 and Higher) and Parameter Estimates Final Logistic Regression Model of Effect of Mirvetuximab Soravtansine AUCo-d2l on Odds of Peripheral Neuropathy (Grade 2 and Higher)

Table 15: Parameter Estimates Final Logistic Regression Model of Effect of Mirvetuximab Soravtansine $AUC_{0\text{-}d21}$ on Odds of Ocular System Adverse Events (Grade 2 and Higher)

	Coefficient (95% CI)
Constant	−5.26883*** (−6.64479, −3.89287)
AUCTAU_Mirv	0.04033*** (0.02928, 0.05138)
TUMORSDB	−0.00536** (−0.01035, −0.00036)

**p<0.05; ***p<0.01

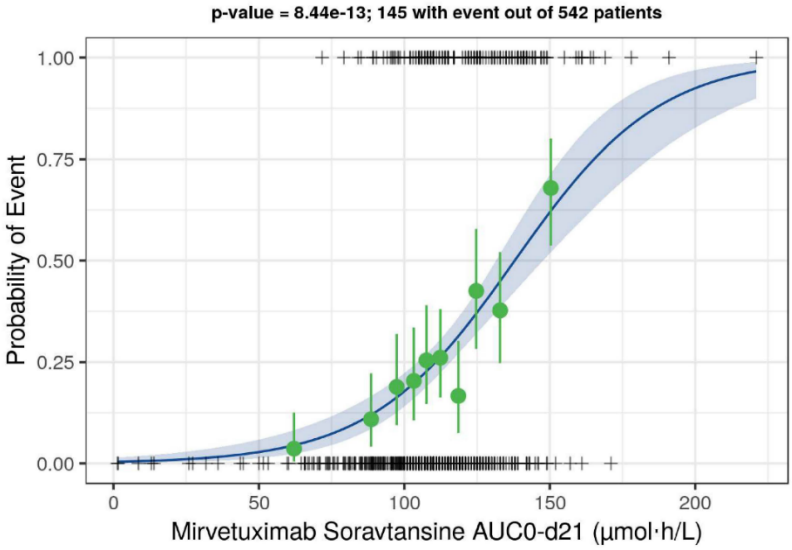
Table 16: Parameter Estimates Final Logistic Regression Model of Effect of Mirvetuximab Soravtansine $AUC_{0\text{-}d21}$ on Odds of Peripheral Neuropathy (Grade 2 and Higher)

	Coefficient (95% CI)
Constant	−4.02252*** (−5.44779, −2.59726)
AUCTAU_Mirv	0.01483*** (0.00361, 0.02606)
AST	0.01458** (0.00191, 0.02725)

**p<0.05; ***p<0.01

Source: Applicant's ER report QPK28-007

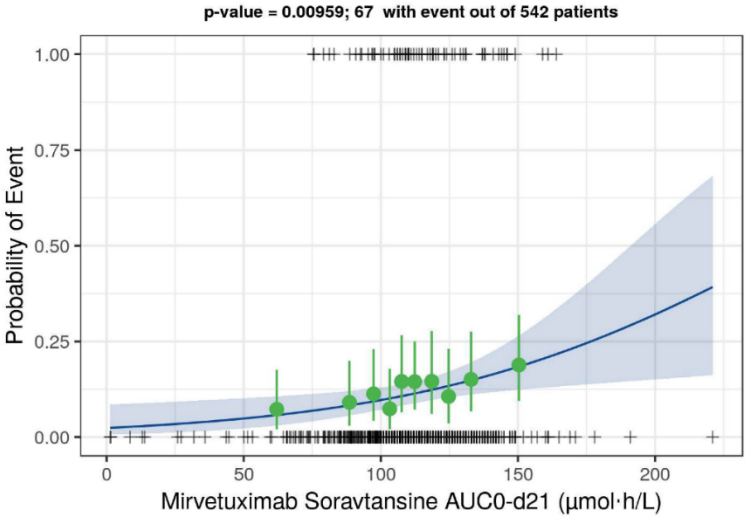
Figure 18: Observed Ocular System Adverse Event (Grade 2 and Higher) Occurrence vs. Mirvetuximab Soravtansine $AUC_{0\text{-}d21}$ with Model Predicted Probability Overlay



The plot shows the predicted probability (mean + 95% CI) in blue for the variable in the x axis at the median/mode value of any other variables. The green points and range depict the exact binomial estimate of the response for deciles (10) of the exposure variable. Observed events are indicated by a + at the top (p=1.0) and bottom (p=0.0) of the plot. **CI**: Confidence Interval.

Source: Applicant's ER report QPK28-007 – Figure 16

Figure 19: Observed Peripheral Neuropathy Adverse Event (Grade 2 and Higher) Occurrence vs. Mirvetuximab Soravtansine $AUC_{0\text{-}d21}$ with Model Predicted Probability Overlay



The plot shows the predicted probability (mean + 95% CI) in blue for the variable in the x axis at the median/mode value of any other variables. The green points and range depict the exact binomial estimate of the response for deciles (10) of the exposure variable. Observed events are indicated by a + at the top (p=1.0) and bottom (p=0.0) of the plot. **CI**: Confidence Interval.

Source: Applicant's ER report QPK28-007 – Figure 18

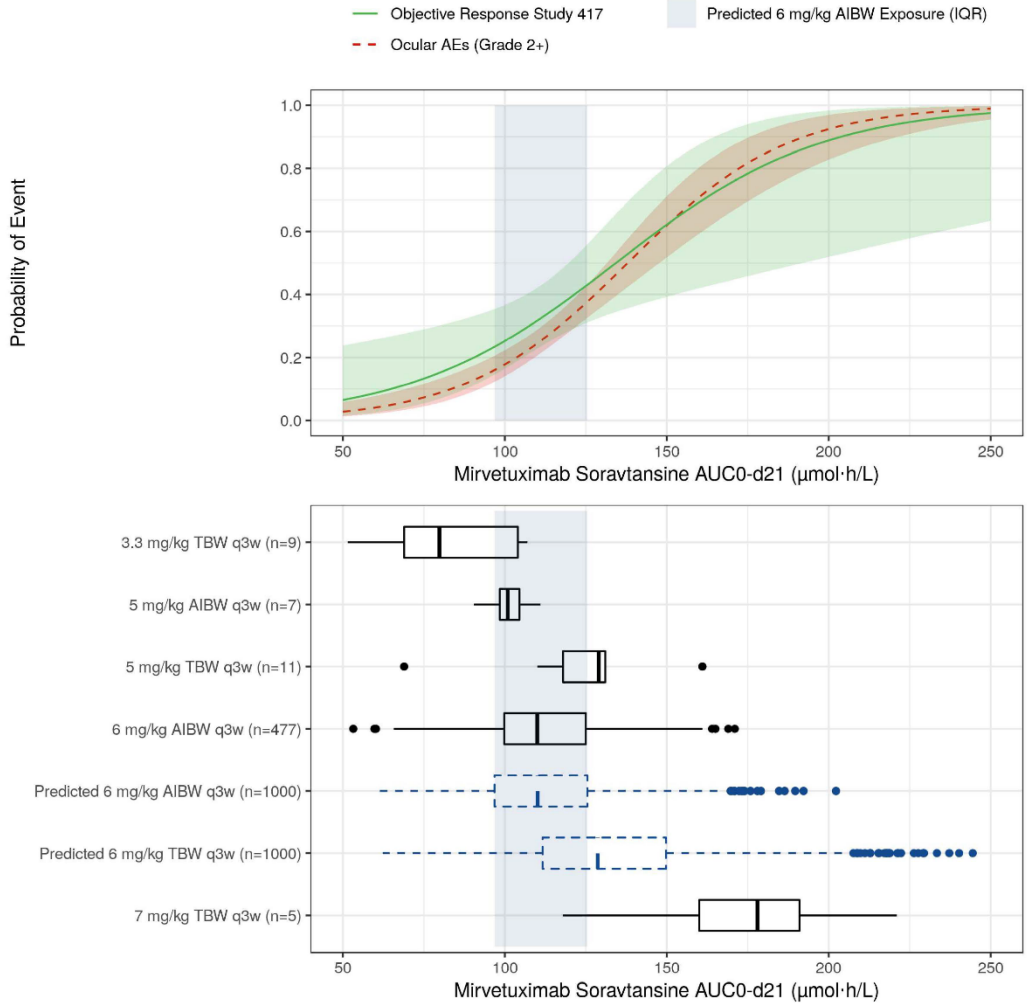
Table 49: Study IMGN853-0417 Model-Predicted ORR and Grade 2 or Higher Ocular Adverse Event Probability Summary - mirvetuximab soravtansine AUC0-d21

Regimen	Mean $AUC_{0\text{-}d21}$ [µmol*h/L]	Median (90% PI) $AUC_{0\text{-}d21}$ [µmol*h/L]	Predicted ORR Probability (95% CI) at Median $AUC_{0\text{-}d21}$	Predicted Ocular AE Probability (95% CI) at Median $AUC_{0\text{-}d21}$
3.3 mg/kg TBW q3w (n=9)	83.4	79.8 (57.2-106)	0.15 (0.08-0.29)	0.088 (0.037-0.22)
5 mg/kg AIBW q3w (n=7)	90.5	98.8 (46.2-109)	0.25 (0.058-0.31)	0.17 (0.024-0.24)
5 mg/kg TBW q3w (n=11)	126.0	129 (89.4-161)	0.46 (0.19-0.7)	0.41 (0.12-0.72)
6 mg/kg AIBW q3w (n=477)	112.0	110 (80.5-143)	0.32 (0.15-0.57)	0.24 (0.088-0.55)
Predicted 6 mg/kg AIBW q3w (n=1000)	112.0	110 (80.3-152)	0.32 (0.15-0.64)	0.24 (0.088-0.64)
Predicted 6 mg/kg TBW q3w (n=1O00)	133.0	129 (86.8-193)	0.46 (0.18-0.86)	0.41 (0.11-0.9)
7 mg/kg TBW q3w (n=5)	174.0	178 (126-215)	0.8 (0.43-0.93)	0.83 (0.38-0.96)

TBW: Total Body Weight. **AIBW:** Adjusted Ideal Body Weight. **AUC0-d21:** First 21-day treatment cycle mirvetuximab soravtansine **exposure**

Source: Applicant's ER report QPK28-007 – Table 18

Figure 20: Model-Predicted Relationships between AUC of Mirvetuximab Soravtansine and Responses in Efficacy (ORR) and Safety (Ocular Toxicity)



Upper Panel. **Lines**: Predicted probability across the $AUC_{0\text{-}d21}$ range with other model variables set at their median value. **Blue shaded area:** IQR (25th and 75th percentiles) of the popPK model-simulated 6 mg/kg AIBW mirvetuximab soravtansine $AUC_{0\text{-}d21}$ (n=1000 subjects).
Lower Panel. **Box and whisker plots:** The central line is the sample median, the boxes denote the interquartile range, the whiskers extend to 1.5 times the interquartile range, and any dots represent data outside the whiskers. **Black Boxplots**: Individual/Post-hoc estimate derived exposure values by treatment regimen. **Blue Boxplots**: Simulated exposure values by treatment regimen. **AE**: Adverse Event. **TBW**: Total Body Weight. **AIBW**: Adjusted Ideal Body Weight.

Source: Applicant's ER report QPK28-007 – Figure 20

<u>The FDA's Assessment:</u>

The Applicant's analyses results are considered acceptable for the purpose of supporting analyses objectives.

ER Review Issues

There are no review issues on ER.

Reviewer's Independent Analysis

The Applicant's analyses were verified by the reviewer, with no significant discordance identified.

Overall benefit-risk evaluation based on E-R analyses

The Applicant's Position:

The mirvetuximab soravtansine AUC0-d21 and Ctrough showed a relationship with efficacy in terms of ORR and PFS. Mirvetuximab soravtansine AUC0-d21 was the best exposure parameter to correlate with the adverse events of the ocular system. In general, both efficacy and ocular toxicity were found to increase with increasing exposure to mirvetuximab soravtansine. The covariates identified by the models overall had limited impact on efficacy and safety, and are likely not of clinical significance.

The FDA's Assessment:

We agree with the Applicant's position.

19.5. Summary of Bioanalytical Method Validation and Performance

ADC (mirvetuximab soravtansine), total antibody, unconjugated DM4, and s-methyl DM4 concentrations were measured throughout the drug development program. A list of the clinical trials and associated bioanalytical reports is provided in Table 50.

Table 50: Summary of Bioanalytical Methods for PK analysis in the clinical trial

Assay	Anticoagulant	Method	Assay Range	Application	Clinical Study
ADC	K2EDTA	ELISA	225 to 1500 ng/mL	PK	Study 0401 Study 0403 Study 0417
ADC	Sodium heparin	ELISA	75 to 1500 ng/mL	PK	Study 0401
TAb	K2EDTA	ELISA	500 to 5000 ng/mL	PK	Study 0401 Study 0403 Study 0417
TAb	Sodium heparin	ELISA	500 to 5000 ng/mL	PK	Study 0401
DM4 and S-methyl DM4 (ie, DM4-Me)	K2EDTA	LC/MS/MS	0.100 to 50 ng/mL for both DM4 and S-methyl DM4	PK	Study 0401 Study 0403 Study 0417

ADC (mirvetuximab soravtansine):

The bioanalytical methods for measuring mirvetuximab soravtansine plasma concentrations are shown in Table 51 and Table 52. ELISA assays were used to measure mirvetuximab soravtansine concentrations, which utilized a murine monoclonal antimaytansine antibody (α-maytansine) was used for capturing mirvetuximab soravtansine, a horseradish peroxidase (HRP) conjugated donkey antihuman immunoglobulin G (IgG) (heavy and light chain) was used for the detection, and the 3,3',5,5'-tetramethylbenzidine (TMB) was used as a chromogenic substrate.

Table 51: Bioanalytical Method Validation Summary ADC in Sodium Heparin

Bioanalytical Method Validation Report Name, Amendments, and Hyperlinks	**Validation of an ELISA Method for the Quantitation of IMGN853 Antibody-Drug Conjugate (ADC) in Sodium Heparin Human Plasma (ICD 604.2/PDY28-011)**	
Method description	ELISA	
Materials used for standard calibration curve and conc.	IMGN853: 35.0, 75.0, 120, 250, 450, 800, 1500, and 2500 ng/mL	
Validated assay range	75.0 to 2500 ng/mL	
Material used for QCs and concentration	IMGN853: 75.0, 120, 225, 600, 1875, 2250, and 2500 ng/mL	
MRDs	1:50 in assay diluent	
Source and lot of reagents	Monoclonal antimaytansinoid antibody (capture/coating reagent); ImmunoGen, Inc. Lot E002317-42-001 IMGN853 (reference standard) ImmunoGen, Inc. Lot RS14-001	
Regression model and weighting	4-parameter logistic, 1/response^2	
Validation Parameters	**Method Validation Summary**	
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	7
	Cumulative accuracy (%bias) from LLOQ to ULOQ IMGN853	-1.97% to 2.44%
	Cumulative precision (%CV) from LLOQ to ULOQ IMGN853	≤9.99%
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 7 QCs QCs for IMGN853	-2.51% to 11.2%
	Interbatch %CV QCs for IMGN853	≤13.4%
Selectivity and matrix effect	Human plasma samples fortified with IMGN853 at 225 ng/mL were prepared from 10 subjects to evaluate potential matrix effects bias that ranged from -19.3% to -7.69%.	
Interference and specificity	Human plasma samples from 10 subjects were analyzed for matrix interference. All samples were below the LLOQ (<75 ng/mL).	
Hemolysis effect	There was no effect from hemolysis on the quantitation of IMGN853.	
Lipemic effect	There was no effect from lipemia on the quantitation of IMGN853.	
Dilution linearity and hook effect	Dilution linearity was validated using 255000 ng/mL diluted 250-, 500-, and 1000-fold. The observed bias ranged from -2.93% to 7.01%. The hook effect was evaluated by analyzing a 255000 ng/mL QC sample undiluted and at 2-, 40-, 80-, 250-, and 500-fold dilutions. There was no apparent hook effect observed at concentrations up to 255000 ng/mL.	
Bench-top/process stability	Analyte stability in thawed matrix was demonstrated in sets of low- and high-level QCs, which were thawed and remained at room temperature for 24 hours prior to analysis.	
Freeze-thaw stability	Freeze-thaw stability was demonstrated using low- and high-level QCs samples, which were frozen at -80°C ± 10°C and thawed at room temperature during 5 cycles.	
Long-term storage	Up to 1522 days at -25°C ± 5°C and at -80°C ± 10°C	
Method Performance in Study 0401 (PDL28-009)		
Assay passing rate	83%	
Standard curve performance	Cumulative bias range: -1.5% to 1.5% Cumulative precision: ≤5% CV	
QC performance	Cumulative bias range: 3.2% to 4% Cumulative precision: ≤9.2% CV	
Method reproducibility	Incurred sample reanalysis was performed in 10.1% of the study samples, and 85% of the samples met the prespecified criteria.	
Study sample analysis/stability	The longest period of sample storage was 1331 days.	
Standard calibration curve performance during accuracy and precision runs	The number of standard calibrators was 7 from 75 to 2500 ng/mL. An additional standard calibrator (35 ng/mL) was used as an anchor concentration.	

Table 52: Bioanalytical Method Validation Summary ADC in K2EDTA

Bioanalytical Method Validation Report Name, Amendments, and Hyperlinks	**Validation of an ELISA Method for the Quantitation of IMGN853 Antibody-Drug Conjugate (ADC) in Dipotassium EDTA Human Plasma (ICD 604/PDY28-010)**	
Method description	ELISA	
Materials used for standard calibration curve and concentration	IMGN853 35.0, 75.0, 120, 250, 450, 800, 1200, and 1500 ng/mL	
Validated assay range	75.0 to 1500 ng/mL	
Material used for QCs and concentration	IMGN853 75.0, 120, 225, 600, 1200, 1300, and 1500 ng/mL	
MRDs	1:50 in assay diluent	
Source and lot of reagents	Monoclonal antimaytansinoid antibody (capture/coating reagent); ImmunoGen, Inc. Lot E002317-42-001 IMGN853 (reference standard) ImmunoGen, Inc. Lot RS14-001	
Regression model and weighting	4-parameter logistic, 1/response^2	
Validation parameters	Method Validation Summary	
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	7
	Cumulative accuracy (%bias) from LLOQ to ULOQ IMGN853	-0.8% to 1.2%
	Cumulative precision (%CV) from LLOQ to ULOQ IMGN853	≤4.7%
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 7 QCs QCs for IMGN853	-6.8% to 4.4%
	Interbatch %CV QCs for IMGN853	≤6.7%
Selectivity and matrix effect	Human plasma samples fortified with IMGN853 at 225 ng/mL were prepared from 10 subjects to evaluate potential matrix effects bias that ranged from -13.5% to 8.1%. Human plasma samples from 10 subjects diagnosed with endometrial or ovarian cancer were fortified with IMGN853 at the LLOQ (75 ng/mL) and HQC (1200 ng/mL) levels. The selectivity data were not acceptable at the LLOQ or back-up LLOQ (120 ng/mL) levels. Therefore, this method has a range of quantitation of 225 to 1500 ng/mL for reporting sample results. K2EDTA human plasma matrix blank, LLOQ, and HQC levels were fortified with 80 ng/mL pembrolizumab. Results indicated that there is no effect on the IMGN853 quantitation.	
Interference and specificity	Human plasma samples from 10 subjects were analyzed for matrix interference. All samples were below the LLOQ (<75 ng/mL).	
Hemolysis effect	There was no effect from hemolysis on the quantitation of IMGN853.	
Lipemic effect	There was no effect from lipemia on the quantitation of IMGN853.	
Dilution linearity and hook effect	Dilution linearity was validated using 255000 ng/mL diluted 250-, 500-, and 1000-fold. The observed bias ranged from -12.2% to -7.1%. The hook effect was evaluated by analyzing a 255000 ng/mL QC sample undiluted and at 2-, 40-, 100-, 250-, and 500-fold dilutions. No apparent hook effect was observed at concentrations up to 255000 ng/mL.	
Bench-top/process stability	Analyte stability in thawed matrix was demonstrated in sets of low- and high-level QCs, which were thawed and remained at room temperature for 25 hours prior	

	to analysis.
Freeze-thaw stability	Freeze-thaw stability was demonstrated using low- and high-level QCs samples, which were frozen at -80°C ± 10°C and thawed at room temperature during 5 cycles.
Long-term storage	Up to 732 days at -25°C ± 5°C and at -80°C ± 10°C
Method Performance in Study 0401 (PDL28-007)	
Assay passing rate	91%
Standard curve performance	Cumulative bias range: -0.7% to 1.1% Cumulative precision: ≤6.9% CV
QC performance	Cumulative bias range: 0.3% to 5.5% Cumulative precision: ≤8.4% CV
Method reproducibility	Incurred sample reanalysis was performed in 9.96% of the study samples, and 83.6% of the samples met the prespecified criteria.
Study sample analysis/stability	All samples that were analyzed within 732 days demonstrated long-term storage stability in human plasma containing K2EDTA at -80°C ± 10°C.
Standard calibration curve performance during accuracy and precision runs	The number of standard calibrators was 7 from 75 to 1500. An additional standard calibrator (35 ng/mL) was used as an anchor concentration.
Method Performance in Study 0403 (PDL28-013)	
Assay passing rate	82%
Standard curve performance	Cumulative bias range: -0.7% to 1.7% Cumulative precision: ≤4.3% CV
QC performance	Cumulative bias range: -0.1% to 0.1% Cumulative precision: ≤9.1% CV
Method reproducibility	Incurred sample reanalysis was performed in 8.56% of the study samples, and 89.7% of the samples met the prespecified criteria.
Study sample analysis/stability	All samples that were analyzed within 732 days demonstrated long-term storage stability in human plasma containing K2EDTA at -80°C ± 10°C.
Standard calibration curve performance during accuracy and precision runs	The number of standard calibrators was 7 from 75 to 1500. An additional standard calibrator (35 ng/mL) was used as an anchor concentration.
Method Performance in Study 0417 (ROQC)	
Assay passing rate	76%
Standard curve performance	Cumulative bias range: -1.14% to 1.58% Cumulative precision: ≤4.06% CV
QC performance	Cumulative bias range: -4.68% to -1.72% Cumulative precision: ≤7.44% CV
Method reproducibility	Incurred sample reanalysis was performed in 10% of the study samples, and 63.6% of the samples met the prespecified criteria.
Study sample analysis/stability	All samples that were analyzed within 732 days demonstrated long-term storage stability in human plasma containing K2EDTA at -80°C ± 10°C.
Standard calibration curve performance during accuracy and precision runs	The number of standard calibrators was 7 from 75 to 1500. An additional standard calibrator (35 ng/mL) was used as an anchor concentration.

Total antibody

The bioanalytical methods for measuring total antibody plasma concentrations are shown in Table 53 and Table 54. ELISA assays were used to measure total antibody concentrations, which utilized human folate receptor 1-Fc to capture TAb; a biotinylated antihuman IgG-Fc was used as a secondary antibody. The HRP-conjugated streptavidin was used for the detection and TMB as a colorimetric substrate.

Table 53: Bioanalytical Method Validation Summary TAb in K2EDTA

Bioanalytical Method Validation Report Name, Amendments, and Hyperlinks	**Validation of an ELISA Method to Quantitate IMGN853 Total Antibody (Tab) in Dipotassium EDTA Human Plasma (ICD 605/PDY28-008)**	
Method description	ELISA	
Materials used for standard calibration curve and concentration	IMGN853 TAb 500, 750, 1500, 2000, 3000, 3500, and 4000 ng/mL	
Validated assay range	500 to 4000 ng/mL	
Material used for QCs and concentration	IMGN853 TAb 500, 750, 1500, 2000, 3000, 3500, and 4000 ng/mL	
MRDs	1:50 in 1% casein in TBS	
Source and lot of reagents	IMGN853 TAb (reference standard): ImmunoGen, Inc. Lot RS14-001 HuFOLR1-Fc (capture reagent) ImmunoGen, Inc. Lot E002070-05-001 Biotinylated monoclonal antihuman IgG-Fc, clone HP-6017 (αIgGFc:B) (secondary antibody) ImmunoGen, Inc. Lot E002337-33-001	
Regression model and weighting	4-parameter logistic, 1/response^2	
Validation parameters	Method Validation Summary	
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	7
	Cumulative accuracy (%bias) from LLOQ to ULOQ IMGN853 TAb	-0.9% to 1.9%
	Cumulative precision (%CV) from LLOQ to ULOQ IMGN853 TAb	≤4.1%
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 7 QCs QCs for IMGN853 TAb	-7.8% to -0.2%
	Interbatch %CV QCs for IMGN853 TAb	≤7.3%
Selectivity and matrix effect	Human plasma samples fortified with 1500 ng/mL IMGN853 TAb were prepared from 10 subjects to evaluate potential matrix effects bias that ranged from -17.9% to 2.9%. Human plasma samples from 10 subjects diagnosed with ovarian cancer were fortified with IMGN853 TAb at the LLOQ (500 ng/mL) and HQC (3000 ng/mL) levels. The selectivity data met the acceptance criteria. K2EDTA human plasma matrix blank, LLOQ, and HQC levels were fortified with 80 ng/mL pembrolizumab. Results indicated that there is no effect on the IMGN853 TAb quantitation.	
Interference and specificity	Human plasma samples from 10 subjects were analyzed for matrix interference. All samples were below the LLOQ (<500 ng/mL).	
Hemolysis effect	There was no effect from hemolysis on the quantitation of IMGN853 TAb.	
Lipemic effect	There was no effect from lipemia on the quantitation of IMGN853 TAb.	
Dilution linearity and hook effect	Dilution linearity was validated using 255000 ng/mL IMGN853 TAb as 100-, 125-, and 200-fold dilutions. The observed bias ranged from -10.1% to 9.8%. The hook effect was evaluated by analyzing a 255000 ng/mL QC sample undiluted and at 2-, 20-, 50-, 125-, and 250-fold dilutions. No apparent hook effect observed at concentrations up to 255000 ng/mL.	
Bench-top/process stability	Analyte stability in thawed matrix was demonstrated in sets of low- and high-level QCs, which were thawed and remained at room temperature for 24 hours prior to analysis.	

Freeze-thaw stability	Freeze-thaw stability was demonstrated using low- and high-level QC samples, which were frozen at -80°C ± 10°C and thawed at room temperature during 5 cycles.
Long-term storage	Up to 756 days at -25°C ± 5°C and at -80°C ± 10°C
Method Performance in Study 0401 (PDL28-008)	
Assay passing rate	90%
Standard curve performance	Cumulative bias range: -1.3% to 3.1% Cumulative precision: ≤11.2% CV
QC performance	Cumulative bias range: -2.6% to -0.5% Cumulative precision: ≤6.2% CV
Method reproducibility	Incurred sample reanalysis was performed in 10.6% of the study samples, and 95.8% of the samples met the prespecified criteria.
Study sample analysis/stability	All samples that were analyzed within 756 days demonstrated long-term storage stability in human plasma containing K2EDTA at -80°C ± 10°C.
Standard calibration curve performance during accuracy and precision runs	The number of standard calibrators was 7 from 500 to 4000. An additional standard calibrator (200 ng/mL) was used as an anchor concentration.
Method Performance in Study 0403 (PDL28-014)	
Assay passing rate	94%
Standard curve performance	Cumulative bias range: -0.7% to 1.4% Cumulative precision: ≤4.6% CV
QC performance	Cumulative bias range: -3.5% to -1.8% Cumulative precision: ≤6.9% CV
Method reproducibility	Incurred sample reanalysis was performed in 8.6% of the study samples, and 98.6% of the samples met the prespecified criteria.
Study sample analysis/stability	All samples that were analyzed within 756 days demonstrated long-term storage stability in human plasma containing K2EDTA at -80°C ± 10°C.
Standard calibration curve performance during accuracy and precision runs	The number of standard calibrators was 7 from 500 to 4000. An additional standard calibrator (200 ng/mL) was used as an anchor concentration.
Method Performance in Study 0417 (ROQD)	
Assay passing rate	90%
Standard curve performance	Cumulative bias range: -0.610% to 1.43% Cumulative precision: ≤4.62% CV
QC performance	Cumulative bias range: -1.86% to 0.962% Cumulative precision: ≤11.9% CV
Method reproducibility	Incurred sample reanalysis was performed in 11.6% of the study samples, and 92.7% of the samples met the prespecified criteria.
Study sample analysis/stability	All samples that were analyzed within 756 days demonstrated long-term storage stability in human plasma containing K2EDTA at -80°C ± 10°C.
Standard calibration curve performance during accuracy and precision runs	The number of standard calibrators was 7 from 500 to 4000. An additional standard calibrator (200 ng/mL) was used as an anchor concentration.

Table 54: Bioanalytical Method Validation Summary TAb in Sodium Heparin

Bioanalytical Method Validation Report Name, Amendments, and Hyperlinks	**Validation of an ELISA Method to Quantitate IMGN853 Total Antibody (Tab) in Sodium Heparin Human Plasma (ICD 605.2/PDY28-006)**
Method description	ELISA
Materials used for standard calibration curve and concentration	IMGN853 TAb 200, 500, 750, 1500, 2000, 3000, 4000, and 5000 ng/mL
Validated assay range	500 to 5000 ng/mL
Material used for QCs and concentration	IMGN853 TAb 500, 750, 1500, 2000, 3500, 4500, and 5000 ng/mL
MRDs	1:50 in assay buffer
Source and lot of reagents	IMGN853 TAb (reference standard): ImmunoGen, Inc. Lot RS14-001

	HuFOLR1-Fc (capture reagent) ImmunoGen, Inc. Lot E002070-05-001 Biotinylated monoclonal antihuman IgG-Fc, clone HP-6017 (αIgGFc:B) (secondary antibody) ImmunoGen, Inc. Lot E002337-33-001	
Regression model and weighting	4-parameter logistic, 1/response²	
Validation Parameters	**Method Validation Summary**	
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	7
	Cumulative accuracy (%bias) from LLOQ to ULOQ IMGN853 TAb	-1.44% to 2.64%
	Cumulative precision (%CV) from LLOQ to ULOQ IMGN853 TAb	≤4.93%
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 7 QCs QCs for IMGN853 TAb	-3.00% to 2.54%
	Interbatch %CV QCs for IMGN853 TAb	≤9.06%
Selectivity and matrix effect	Human plasma samples fortified with 1500 ng/mL IMGN853 TAb were prepared from 10 subjects to evaluate potential matrix effects. Nine out of 10 of the fortified samples were within 20% from the theoretical concentration. Bias ranged from -14.7% to 21.8%.	
Interference and specificity	Human plasma samples from 10 subjects were analyzed for matrix interference. All samples were below LLOQ (<500 ng/mL).	
Hemolysis effect	There was no effect from hemolysis on the quantitation of IMGN853 TAb.	
Lipemic effect	There was no effect from lipemia on the quantitation of IMGN853 TAb.	
Dilution linearity and hook effect	Dilution linearity was validated using 255000 ng/mL IMGN853 TAb as 75-, 120-, and 200-fold dilutions. The observed bias ranged from -13.1% to -9.93%. The hook effect was evaluated by analyzing a 255000 ng/mL QC sample undiluted and at 5-, 10-, 20-, 100-, and 250-fold dilutions. No apparent hook effect observed at concentrations up to 255000 ng/mL.	
Bench-top/process stability	Analyte stability in thawed matrix was demonstrated in sets of low- and high-level QCs, which were thawed and remained at room temperature for 24 hours prior to analysis.	
Freeze-thaw stability	Freeze-thaw stability was demonstrated using low- and high-level QC samples, which were frozen at -80°C ± 10°C and thawed at room temperature during 5 cycles.	
Long-term storage	Up to 1344 days at -25°C ± 5°C and at -80°C ± 10°C	
Method Performance in Study 0401 (PDL28-006)		
Assay passing rate	98%	
Standard curve performance	Cumulative bias range: -1.5% to 1.8% Cumulative precision: ≤3.6% CV	
QC performance	Cumulative bias range: -1.1% to 2.5% Cumulative precision: ≤8.4% CV	
Method reproducibility	Incurred sample reanalysis was performed in 11% of the study samples, and 82.6% of the samples met the prespecified criteria.	
Study sample analysis/stability	All samples that were analyzed within 1344 days demonstrated long-term storage stability in human plasma containing K2EDTA at -25°C ± 5°C and at -80°C ± 10°C.	
Standard calibration curve performance during accuracy and precision runs	The number of standard calibrators was 7 from 500 to 5000 ng/mL. An additional standard calibrator (200 ng/mL) was used as an anchor concentration.	

DM4 and S-methyl DM4:

High performance liquid chromatography coupled to tandem mass spectrometry (MS/MS) detection was developed for the quantitation of DM4 and S-methyl DM4 analytes (Table 55).

Table 55: Bioanalytical Validation Summary DM4 and S-methyl DM4

Bioanalytical Method Validation Report Name, Amendments, and Hyperlinks	**Quantitation of DM4 and DM4-Me in Human Plasma via HPLC With MS/MS Detection (LCMSF 740.2/PDY28-009)** **5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies**	
Method description	HPLC with MS/MS detection	
Materials used for standard calibration curve and concentration	DM4 and DM4-Me at 0.100, 0.200, 0.350, 1.20, 4.00, 15.0, 40.0, and 50.0 ng/mL	
Validated assay range	0.100 to 50.0 ng/mL	
Material used for QCs and concentration	DM4 and DM4-Me at 0.100, 0.250, 0.600, 2.40, 8.00, and 37.5 ng/mL	
MRDs	NA	
Source and lot of reagents	DM4 ImmunoGen, Inc. Lot N08914001 DM4-Me ImmunoGen, Inc. Lot E002796-24 DM4-d6 ImmunoGen, Inc. Lot E002604-11 DM4-Me-d6 ImmunoGen, Inc. Lot E002796-27 IMGN853 ImmunoGen, Inc. Lot PO67614001	
Regression model and weighting	Linear, 1/concentration^2	
Validation Parameters	**Method Validation Summary**	
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8
	Cumulative accuracy (%bias) from LLOQ to ULOQ DM4 DM4-Me	 - 1.11% to 0.501% -1.34% to 1.04%
	Cumulative precision (%CV) from LLOQ to ULOQ DM4 DM4-Me	 ≤6.48% ≤6.63%
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 5 QCs QCs for DM4 QCs for DM4-Me	 -1.11% to 3.69% -1.515 to 2.86
	Interbatch %CV QCs for DM4 QCs for DM4-Me	 ≤8.93% ≤9.36%
Selectivity and matrix effect	Human plasma samples fortified with DM4 or DM4-Me at 0.100 ng/mL were prepared from 6 subjects to evaluate potential matrix effects. No significant matrix suppression effects were indicated that could compromise the sensitivity or accuracy of the assay. Human plasma blanks, with and without internal standard, and low- and high-level QC samples were fortified with 80 ng/mL pembrolizumab. Results indicated that there is no effect on the DM4 or DM4-Me quantitation.	
Interference and specificity	There were no significant interfering peaks noted in blank human plasma samples.	
Hemolysis effect	There was no effect from hemolysis on the quantification of DM4 or DM4-Me.	
Lipemic effect	There was no effect from lipemia on the quantitation of DM4 or DM4-Me.	

Dilution linearity and hook effect	Dilution linearity was validated using DM4 or DM4-Me at 2.40 ng/mL diluted 2-fold and 10 ng/mL diluted 10-fold. The observed bias ranged from -1.51% to 4.91% and from -0.879% to 5.35% for DM4 and DM4-Me.
Bench-top/process stability	DM4 or DM4-Me analytes stability in thawed matrix was demonstrated in sets of low- and high-level QCs (with or without 240 µg/mL IMGN853), which were thawed and remained at room temperature for 24 hours prior to analysis.
Freeze-thaw stability	DM4 or DM4-Me freeze-thaw stability was demonstrated using low- and high-level QC samples, which were frozen at -70°C or -20°C and thawed at room temperature during 5 cycles for each temperature.
Long-term storage	DM4 or DM4-Me was stable up to 1135 days at -70°C.
Carry over	Following blank sample evaluation in a sequence immediately after the ULOQ calibration standards, there were contributions from chromatographic peaks at the expected retention time of the analyte in the blank samples greater than 20% of the mean analyte response for the LLOQ calibration standards in the validation run.
Method Performance in Study 0401 (PDL28-011)	
Assay passing rate	DM4: 74% DM4-Me: 74%
Standard curve performance	DM4: • Cumulative bias range: -0.615% to 1.01% • Cumulative precision: ≤4.68% CV DM4-Me: • Cumulative bias range: -0.884% to 1.04% • Cumulative precision: ≤5.42% CV
QC performance	DM4: • Cumulative bias range: 0.0607% to 3.22% • Cumulative precision: ≤12.2% CV DM4-Me: • Cumulative bias range: -0.148% to 4.64% • Cumulative precision: ≤13.3% CV
Method reproducibility	DM4: Incurred sample reanalysis was performed in 10.2% of the study samples, and 97.4% of the samples met the prespecified criteria. DM4-Me: Incurred sample reanalysis was performed in 10.3% of the study samples, and 97.4% of the samples met the prespecified criteria.
Study sample analysis/stability	All samples that were analyzed within 588 days demonstrated long-term storage stability in human plasma containing K2EDTA with citric acid at -70°C.
Standard calibration curve performance during accuracy and precision runs	The number of standard calibrators was 8 from 0.100 to 50 ng/mL.
Method Performance in Study 0403 (PDL28-012)	
Assay passing rate	DM4: 95% DM4-Me: 92%
Standard curve performance	DM4: • Cumulative bias range: -0.569% to 0.906% • Cumulative precision: ≤5.24% CV DM4-Me:

	• Cumulative bias range: -1.65% to 1.1% • Cumulative precision: ≤5.87% CV
QC performance	DM4: • Cumulative bias range: -0.471% to 0.844% • Cumulative precision: ≤5.62% CV DM4-Me: • Cumulative bias range: -0.410% to 2.32% • Cumulative precision: ≤6.45% CV
Method reproducibility	DM4: Incurred sample reanalysis was performed in 10.2% of the study samples, and 98% of the samples met the prespecified criteria. DM4-Me: Incurred sample reanalysis was performed in 10.1% of the study samples, and 97.6% of the samples met the prespecified criteria.
Study sample analysis/stability	All samples that were analyzed within 785 days demonstrated long-term storage stability in human plasma containing K2EDTA with citric acid at -70°C.
Standard calibration curve performance during accuracy and precision runs	The number of standard calibrators was 8 from 0.100 to 50 ng/mL.
Method Performance in Study 0417 (ROQF)	
Assay passing rate	DM4: 87% DM4-Me: 93%
Standard curve performance	DM4: • Cumulative bias range: -1.79% to 3.59% • Cumulative precision: ≤5.01% CV DM4-Me: Cumulative bias range: -0.788% to 1.24% Cumulative precision: ≤4.27% CV
QC performance	DM4: • Cumulative bias range: -2.50% to 1.94% • Cumulative precision: ≤4.93% CV DM4-Me: Cumulative bias range: -1.58% to 0.114% Cumulative precision: ≤4.64% CV
Method reproducibility	DM4: Incurred sample reanalysis was performed in 9.01% of the study samples, and 90.7% of the samples met the prespecified criteria. DM4-Me: Incurred sample reanalysis was performed in 8.75% of the study samples, and 97.6% of the samples met the prespecified criteria.
Study sample analysis/stability	All samples that were analyzed within 1135 days demonstrated long-term storage stability in human plasma containing K2EDTA with citric acid at -80°C.
Standard calibration curve performance during accuracy and precision runs	The number of standard calibrators was 8 from 0.100 to 50 ng/mL.

19.6. Additional Clinical Outcome Assessment Analyses

Not applicable.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Ankit Shah	CDER/OTS/DCPII	Section: 6, 19.4, 19.5	**Select one:** ___X Authored ___ Approved
	Signature: Ankit B. Shah -S (Affiliate) Digitally signed by Ankit B. Shah -S (Affiliate) Date: 2022.11.09 14:10:01 -05'00'			
Clinical Pharmacology Team Leader	Salaheldin Hamed	CDER/OTS/DCPII	Section: 6, 19.4, 19.5	**Select one:** ___x Authored _____ Approved
	Signature: Salaheldin S. Hamed -S Digitally signed by Salaheldin S. Hamed -S Date: 2022.11.09 14:14:10 -05'00'			
Pharmacometrics Reviewer	Junshan Qiu	CDER/OTS/OCP/DPM	Section: 19.4	**Select one:** ___x Authored _____ Approved
	Signature: Junshan Qiu -S Digitally signed by Junshan Qiu -S Date: 2022.11.09 14:52:39 -05'00'			
Pharmacometrics Team Leader	Jingyu Yu	CDER/OTS/OCP/DPM	Section: 19.4	**Select one:** ___x Authored _____x Approved
	Signature: Jingyu Yu -S Digitally signed by Jingyu Yu -S Date: 2022.11.09 15:02:40 -05'00'			
Clinical Pharmacology Division Director	Nam Atiqur Rahman	CDER/OTS/DCPII	Section: 19.4	**Select one:** ___ Authored X___ Approved
	Signature: Nam A. Rahman -S Digitally signed by Nam A. Rahman -S Date: 2022.11.10 08:21:09 -05'00'			

Genomics Reviewer	Jeffrey Kraft	CDER/OTS/OCP/DTPM	Section: 6, 19.4, and 19.5	**Select one:** __x_ Authored ___ Approved
	Signature: Jeffrey B. Kraft Jr -S Digitally signed by Jeffrey B. Kraft Jr -S Date: 2022.11.10 10:06:13 -05'00'			
Genomics Division Director	Michael Pacanowski (signing as proxy for Robert Schuck)	CDER/OTS/OCP/DTPM	Section: 6, 19.4, and 19.5	**Select one:** x__ Authored ___ Approved
	Signature: Michael Pacanowski -S Digitally signed by Michael Pacanowski -S Date: 2022.11.10 10:27:41 -05'00'			
Nonclinical Reviewer	Wimolnut Manheng	CDER/OND/OOD/DHOT	Section: 5	**Select one:** x_ Authored x Approved
	Signature: Wimolnut Manheng -S Digitally signed by Wimolnut Manheng -S Date: 2022.11.10 10:40:01 -05'00'			
Nonclinical Team Leader	Tiffany Ricks	CDER/OND/OOD/DHOT	Section: 5	**Select one:** x_ Authored x__ Approved
	Signature: Tiffany K. Ricks -S Digitally signed by Tiffany K. Ricks -S Date: 2022.11.10 10:47:55 -05'00'			
Division Director (DHOT)	John Leighton	CDER/OND/OOD/DHOT	Section: 5	**Select one:** ___ Authored x_ Approved
	Signature: John K. Leighton -S Digitally signed by John K. Leighton -S Date: 2022.11.10 11:06:54 -05'00'			

Clinical Reviewer (efficacy)	Mirat Shah	CDER/OOD/DO1	Section: 1, 2, 3, 4, 7, 8.1, 9, 13, 19.2	**Select one:** x Authored ___ Approved
	Signature: Mirat Shah -S Digitally signed by Mirat Shah -S Date: 2022.11.10 11:22:30 -05'00'			
Clinical Reviewer (safety)	Asma Dilawari	CDER/OOD/DO1	Section: 8.2, 11	**Select one:** x Authored ___ Approved
	Signature: Asma Dilawari -S Digitally signed by Asma Dilawari -S Date: 2022.11.10 12:17:04 -05'00'			
Statistical Reviewer	Haley Gittleman	CDER/OTS/DBV	Section: 8	**Select one:** x Authored ___ Approved
	Signature: Haley R. Gittleman -S Digitally signed by Haley R. Gittleman -S Date: 2022.11.10 09:36:40 -05'00'			
Statistical Team Leader	Mallorie Fiero	CDER/OTS/DBV	Section: 8	**Select one:** x Authored x Approved
	Signature: Mallorie H. Fiero -S Digitally signed by Mallorie H. Fiero -S Date: 2022.11.10 10:16:23 -05'00'			
Acting Division Director (OB)	Shenghui Tang	CDER/OTS/DBV	Section: 8	**Select one:** ___ Authored x Approved
	Signature: Shenghui Tang -S Digitally signed by Shenghui Tang -S Date: 2022.11.10 11:33:50 -05'00'			
Associate Director for Labeling (ADL)	William Pierce	CDER/OOD	Section: 11, Prescribing Information, Medication Guide	**Select one:** X Authored X Approved
	Signature: William F. Pierce -S Digitally signed by William F. Pierce -S Date: 2022.11.10 11:46:42 -05'00'			

Cross-Disciplinary Team Leader (CDTL)	Gwynn Ison	CDER/OOD/DO1	Section: All	**Select one:** x Authored x Approved
	Signature: Gwynn Ison -S Digitally signed by Gwynn Ison -S Date: 2022.11.10 12:00:20 -05'00'			
Division Director	Laleh Amiri-Kordestani	CDER/OOD/DO1	Section: All	**Select one:** x Authored x Approved
	Signature: Laleh Amiri Kordestani -S Digitally signed by Laleh Amiri Kordestani -S Date: 2022.11.10 12:44:28 -05'00'			
Office Director	Richard Pazdur	CDER/OOD	Section: All	**Select one:** x Authored x Approved
	Signature: will be signing electronically in DARRTS			

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/

GWYNN ISON
11/10/2022 03:04:41 PM

RICHARD PAZDUR
11/10/2022 03:10:08 PM