EU RISK MANAGEMENT PLAN

ELAHERE
(MIRVETUXIMAB SORAVTANSINE)

RMP version to be assessed as part of this application:

RMP Version number: 0.3

Data lock point for this RMP	06 Mar 2023	Version number	0.3
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Other RMP versions under evaluation: Not applicable

QPPV name: Natalia Kocankova

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant's QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS

Abbreviation / Term	Definition
ADA	Anti-drug antibody
ADC	Antibody-drug conjugate
AE	Adverse event
AESI	Adverse event of special interest
AIBW	Adjusted ideal body weight
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APC	Annual Percent Change
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the concentration-time curve
BCVA	Best corrected visual acuity
BID	Two times a day
BRCA	Breast cancer susceptibility gene
CCI	Charlson Co-morbidity Index
CLcr	Creatinine clearance
C_{max}	Maximum plasma concentration
CNS	Central nervous system
CR	Complete response
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DM4	N2′-[4-[(3-carboxypropyl)dithio]-4-methyl-1-oxo-2-sulfopentyl]-N2′-deacetylmaytansine
ECHO	Echocardiography
ECIS	European Cancer Information System
ECL	Electrochemiluminescence
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form
EEA	European Economic Area
EMA	European Medicines Agency
EOC	Epithelial ovarian cancer, includes fallopian tube and primary peritoneal cancer

Abbreviation / Term	Definition
EOT	End of treatment
EPAR	European public assessment report
ER	Exposure-response
EU	European Union
FDA	Food and Drug Administration
FOLR1	Folate receptor 1, also known as FRα
FRα	Folate receptor α
G-CSF	Granulocyte-colony stimulating factor
GGT	Gamma-glutamyltransferase
hERG	Human ether-à-go-go-related gene
HIV	Human immunodeficiency virus
HNPCC	Hereditary nonpolyposis colon cancer
H2	Second half of the year
IARC	International Agency for Research on Cancer
IBW	Ideal body weight
IC	Investigator's choice
IC Chemo	Investigator's choice of select chemotherapies
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgG	Immunoglobulin G
ILD	Interstitial lung disease
IMGN853 (MIRV)	mirvetuximab soravtansine
INN	International nonproprietary name
IOP	Intraocular pressure
IRR	Infusion-related reaction
ISS	Integrated Summary of Safety
IV	Intravenous
K2EDTA	Dipotassium ethylenediaminetetraacetic acid
K_i	Concentration that causes half the maximal rate of inactivation
LVEF	Left ventricular ejection fraction
max	Maximum
MDR1	Multidrug resistance protein 1
MedDRA	Medical Dictionary for Regulatory Activities
min	Minimum
MIRV (IMGN853)	Mirvetuximab soravtansine
MMAE	Monomethyl auristatin E
MMAF	Monomethyl auristatin F
MUGA	Multigated acquisition

1.8.2 Risk Management Plan

Abbreviation / Term	Definition
NAb	Neutralising antibody
NaHep	Sodium heparin
NCI	National Cancer Institute
NCI-ODWG	National Cancer Institute Organ Dysfunction Working Group
ORR	Overall response rate
OS	Overall survival
Pac	Paclitaxel
P-gp	P-glycoprotein
PFS	Progression free survival
PK	Pharmacokinetic(s)
PL	Package leaflet
PLD	Pegylated liposomal doxorubicin
PopPK	Population PK
PR	Partial response
PROC	Platinum resistant ovarian cancer
PSOC	Platinum-sensitive ovarian cancer
PSUR	Periodic safety update report
PT	Preferred term
QPPV	Qualified Person Responsible for Pharmacovigilance
QTc	Corrected QT interval
QW	Weekly
Q3W	Every 3 weeks
Q4W	Every 4 weeks
RMP	Risk management plan
RR	Respiratory rate
RT	Radiotherapy
SAE	Serious adverse event
SCID	Severe combined immunodeficiency disease
SD	Standard deviation
SmPC	Summary of product characteristics
SMQ	Standardised MedDRA query
SOC	System organ class
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TF	Tissue Factor
Topo	Topotecan
UK	United Kingdom

1.8.2 Risk Management Plan

Abbreviation / Term	Definition
ULN	Upper limit of normal
US	United States
USPI	US Prescribing Information
WBC	White blood cell

PART I PRODUCT OVERVIEW

Table 1: Product Overview

Active substance (INN or common name)	Mirvetuximab soravtansine
Pharmacotherapeutic groups (ATC Code)	Antineoplastic and immunomodulating agents, monoclonal antibodies and antibody drug conjugates, other monoclonal antibodies and antibody drug conjugates (L01FX26)
Marketing Authorisation Applicant	AbbVie Deutschland GmbH & Co. KG, replacing ImmunoGen Biopharma (Ireland) Limited
Medicinal products to which this RMP refers	One
Invented name in the European Economic Area (EEA)	ELAHERE
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Antibody-drug conjugate
	Summary of mode of action: Mirvetuximab soravtansine is an antibody-drug conjugate (ADC). The antibody is an engineered immunoglobulin G1 (IgG1) directed against folate receptor alpha (FRα). The function of the antibody portion is to bind to FRα expressed on the surface of cancer cells. DM4 is a microtubule inhibitor attached to the antibody via a cleavable linker. Upon binding to FRα, mirvetuximab soravtansine is internalised followed by intracellular release of DM4 via proteolytic cleavage. DM4 disrupts the microtubule network within the cell, resulting in cell cycle arrest and apoptotic cell death.
	Important information about its composition: Mirvetuximab soravtansine is a FRα-directed ADC. The ADC consists of an anti-FRα monoclonal antibody of IgG1 subtype produced using recombinant DNA technology in Chinese Hamster Ovary cells and attached via a cleavable linker (butanoic acid, 4-(2-pyridinyldithio)-2-sulfo-1-(2,5-dioxo-1-pyrrolidinyl) ester) to a maytansinoid DM4, an anti-tubulin agent. Mirvetuximab soravtansine contains an average of 3.4 DM4 payload molecules bound to the anti-FRα antibody.

<table>
<tr><td></td><td>The excipients include acetic acid (E260), sodium acetate (E262), sucrose, polysorbate 20 (E432), and water for injections.</td></tr>
<tr><td>Hyperlink to the Product Information</td><td>ELAHERE Product Information (Module 1.3.1)</td></tr>
<tr><td rowspan="2">Indication in the EEA</td><td>Current: ELAHERE as monotherapy is indicated for the treatment of adult patients with folate receptor-alpha (FRα) positive, platinum-resistant high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received one to three prior systemic treatment regimens.</td></tr>
<tr><td>Proposed: Not applicable</td></tr>
<tr><td rowspan="2">Dosage in the EEA</td><td>Current: The recommended dose of ELAHERE 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. Dosing based on AIBW reduces exposure variability for patients who are either underweight or overweight.
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
For a female patient who is 165 cm in height and 80 kg in weight
<table>
<tr><td>First, calculate IBW:</td><td>IBW = 0.9*165 – 92 = 56.5 kg</td></tr>
<tr><td>Then calculate AIBW:</td><td>AIBW = 56.5 + 0.4*(80 – 56.5) = 65.9 kg</td></tr>
</table></td></tr>
<tr><td>Proposed: Not applicable</td></tr>
<tr><td rowspan="2">Pharmaceutical form and strengths</td><td>Current: Concentrate for solution for infusion (sterile concentrate).
Clear to slightly opalescent, colourless solution.
1 mL of concentrate for solution for infusion contains 5 mg of mirvetuximab soravtansine.
One vial contains 100 mg mirvetuximab soravtansine in 20 mL.</td></tr>
<tr><td>Proposed: Not applicable</td></tr>
<tr><td>Will the product be subject to additional monitoring in the EU?</td><td>Yes</td></tr>
</table>

PART II SAFETY SPECIFICATION

PART II: MODULE SI EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATION

ELAHERE as monotherapy is indicated for the treatment of adult patients with folate receptor-alpha (FRα) positive, platinum-resistant high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received one to three prior systemic treatment regimens.

Incidence

Ovarian cancer is one of the most common gynaecological cancers and has a high mortality rate. Globally it is estimated that there were 314,000 new cases of ovarian cancer diagnosed in 2020 and over 207,000 ovarian cancer deaths (Ferlay 2020). Of these new cases, the incidence was highest in Asia (54.4%), followed by Europe (21.2%), North America (8.5%), Africa (7.7%), Latin America and the Caribbean (7.5%) and Oceania (0.7%) (Ferlay 2020). The estimated incidence of ovarian cancer in the European Union (EU)-27 was 39,414 cases in 2020 based on data from the European Cancer Information System (ECIS) and this accounts for 3.2% of all cancers in females (ECIS 2023).

Prevalence

In 2020, the estimated number of ovarian cancer cases worldwide by the International Agency for Research on Cancer (IARC) was 823,315, comprising Asia (435,574), Europe (190,105), North America (80,532), Latin America and the Caribbean (62,165), Africa (48,940), and Oceania (5,999) (Ferlay 2020). A point prevalence of 4.6 per 10,000 European Economic Area (EEA) inhabitants is estimated as part of the draft EU orphan drug designation maintenance report for mirvetuximab soravtansine (EMA/H/C/0005036).

Demographics of the population in the proposed indication - age, gender, racial and/or ethnic origin and risk factors for the disease

Epithelial ovarian cancer is an age-related disease with the incidence more pronounced in patients over 65 years of age (Momenimovahed 2019). Incidence rates for ovarian cancer are lower in the Asian and Black racial groups, and in people of mixed race or multiple ethnicity, compared with the White racial group, in women in England (2013-2017) (Delon 2022). A study evaluating trends in ovarian cancer incidence overall (1973-1977 to 2003-2007) and by histologic subtype (1988-1992 to 2003-2007) found notable increases in ovarian cancer incidence rates in Eastern/Southern Europe (e.g., Poland: Annual Percent Change (APC) 1.6%, p=0.02) and Asia (e.g., Japan: APC 1.7%, p=0.01) and decreases in Northern Europe (e.g., Denmark: APC −0.7%, p=0.01) and North America (e.g., US Whites: APC −0.9%, $p < 0.01$) (Coburn 2017).

Risk factors for epithelial ovarian cancer include: increased age; having children later than 35 years of age or never having a full-term pregnancy; a family history of ovarian cancer; inherited mutations in the breast cancer susceptibility genes (BRCA) *BRCA1* and *BRCA2*; hereditary nonpolyposis colon cancer (HNPCC); *MUTYH*-associated polyposis; mutations in

genes linked to ovarian cancer including *ATM*, *BRIP1*, *RAD51C*, *RAD51D*, and *PALB2* (American Cancer Society 2023; Cancer Research UK 2023).

The main existing treatment options

Studies indicate that epithelial ovarian, primary peritoneal, and fallopian tube cancers are not distinct entities, but rather represent a spectrum of diagnoses that originate in the Müllerian tissue. Fallopian tube and primary peritoneal carcinomas are included in the ovarian cancer staging classification (Cobb 2015; Grant 2010; Naumann 2011; O'Shannessy 2013) and are considered part of epithelial ovarian cancer with the same treatment and outcomes. Epithelial ovarian, fallopian tube, and primary peritoneal cancer are collectively referenced as EOC.

Despite the incorporation of maintenance therapy into the treatment of ovarian cancer, most patients with advanced EOC relapse during or after treatment with platinum-containing regimens (Armstrong 2019). Disease recurring more than 6 months after completion of platinum is termed platinum sensitive. Patients with recurrent platinum-sensitive disease typically receive platinum-based combination therapy with or without subsequent maintenance therapy.

Disease recurring within 6 months of completion of platinum-based chemotherapy is classified as platinum resistant ovarian cancer (PROC). Once patients develop PROC, their prognosis is poor. Available therapies yield limited positive outcomes, with almost all PROC patients developing progressive disease and becoming increasingly symptomatic with abdominal pain due to malignant ascites, increasing tumour mass leading to bowel obstruction, inability to tolerate medication or take food, and declining performance status precluding further anticancer therapy.

The single-agent chemotherapies most commonly used in PROC include paclitaxel, pegylated liposomal doxorubicin (PLD), and topotecan, all of which were approved over 20 years ago. Paclitaxel is approved by the European Medicines Agency (EMA) at a dose of 175 mg/mg^2, though it is often given weekly (Paclitaxel SmPC). Two early European Phase 2 studies (n=41, n=102, respectively) of paclitaxel monotherapy given every 3 weeks (Q3W) in mixed platinum-sensitive ovarian cancer (PSOC) and PROC demonstrated encouraging overall response rate (ORR) of 17.1% (Pectasides 1998) and 20% (du Bois 1997), though median overall survival (OS) was 13.2 months and less than one year (45.9 weeks), respectively. The largest study of paclitaxel in PROC (n=652 evaluable) in the United States (US) reported an ORR of 22% and median OS of 9 months, complicated by 78% ≥ Grade 3 leukopenia (Trimble 1993). A subsequent Phase 2 study of weekly paclitaxel in ovarian cancer patients with resistance to platinum/paclitaxel on an every-3-week schedule demonstrated radiographic responses in 7 of 51 patients (14%) (Markman 2002).

Topotecan was approved in mixed platinum-sensitive and resistant recurrent ovarian cancer based on a study in second line use of topotecan versus paclitaxel with an ORR of 20.5% for topotecan and 12.5% for paclitaxel (Hycamtin SmPC; ten Bokkel Huinink 1997). In a PROC population, ORR was lower at 13.7%, with median OS less than one year (47 weeks). Notably, this regimen is associated with significant myelotoxicity, with Grade 4 neutropenia 82% and Grade 4 thrombocytopenia in 30% in recurrent ovarian cancer (Bookman 1998). PLD was approved following a 2001 study in second line treatment of mixed platinum-sensitive and platinum-refractory (defined as recurrence with < 6 month platinum-free interval) ovarian cancer (n=474) compared to topotecan (Caelyx SmPC). For the platinum-refractory subgroup (n=255), OS at one year was 13.8% with PLD and 9.5% with topotecan (Gordon 2001; Gordon 2004;

Caelyx SmPC). Outcomes with these single-agent chemotherapies, which remain standard of care in patients with PROC, have not meaningfully improved since their initial approvals. In a study of weekly paclitaxel in PROC published in the United Kingdom (UK) in 2023, median progression free survival (PFS) was 4.1 months with median OS 11.1 months, which was associated with a 36.7% rate of Grade 3 or 4 toxicity (Banerjee 2023).

Importantly, no large, randomised Phase 3 study in PROC has shown an OS benefit (Richardson 2023). The last regulatory approval in PROC was in 2014 for the use of bevacizumab in combination with chemotherapy (Pujade-Lauraine 2014). The last approval of a single agent chemotherapy for advanced ovarian cancer was over two decades ago.

In the past decade, clinical studies of many novel anti-cancer therapies, including immune checkpoint inhibitors, targeted therapies, and small molecule inhibitors, have failed to make a substantial impact in the treatment of PROC, with several negative Phase 3 studies (Pujade-Lauraine 2021; Hamanishi 2021; Gaillard 2021; Kurzeder 2016; Banerjee 2023; Richardson 2023). Despite improvements in supportive care for cancer patients, recent studies in PROC have not shown improvement in survival compared with historical studies, with median PFS of approximately 3 to 4 months and median OS remaining in the 11- to 14-month range, highlighting the unmet need in this population (Pujade-Lauraine 2014; Gaillard 2021; Pujade-Lauraine 2021; Moore 2021; Banerjee 2023).

Natural history of the indicated condition in the untreated population, including mortality and morbidity

Epithelial cancer of the ovary is thought to derive from malignant transformation of the epithelium of the ovarian surface, peritoneum, or fallopian tube. Somatic mutations in *BRCA1*, *BRCA2* and other genes can lead to cancer progression (Desai 2014).

The clinical presentation of EOC can either be acute or subacute (Desai 2014). Acute cases present with conditions such as pleural effusion, small bowel obstruction and venous thromboembolism. Subacute cases may present with non-specific symptoms such as abdominal fullness, bloating, an adnexal mass, vague pelvic or abdominal pain and gastrointestinal symptoms.

Resistance to platinum-based treatment can be intrinsic or acquired and may be caused by a variety of mechanisms in ovarian cancer with the role of candidate genes under investigation (Bélanger 2018; Xing 2020).

As discussed above, recent studies in PROC continue to show similar outcomes to historical studies, with median PFS of approximately 3 to 4 months and median OS remaining in the 11- to 14-month range, highlighting the unmet need in this population (Pujade-Lauraine 2014; Gaillard 2021; Pujade-Lauraine 2021; Moore 2021). Available therapies yield limited positive outcomes, with almost all patients with PROC developing progressive disease and becoming increasingly symptomatic with abdominal pain due to malignant ascites, increasing tumour mass leading to bowel obstruction, inability to tolerate medication or take food, and declining performance status precluding further anticancer therapy.

In the EU, ovarian cancer was estimated to account for 26,500 deaths in 2022 (Dalmartello 2022). The death rate from ovarian cancer in the EU and UK was predicted to fall in 2022 compared with 2017 by 7% and 17% respectively, due to the reduction in the incidence of ovarian cancer attributable to the use of oral contraceptives (Dalmartello 2022).

Important co-morbidities

Common co-morbidities prevalent in ovarian cancer patients include hypertension (11% to 26%), cardiovascular disease (4.5% to 12%) and diabetes (2.5% to 8.3%) based on a systematic review of literature using Charlson Co-morbidity Index (CCI) scores (Asthana 2020). Less commonly occurring co-morbidities are liver disease, renal disease, neurological problems and collagen vascular disease.

Cardiovascular diseases and diabetes mellitus have been shown to adversely affect advanced epithelial ovarian cancer survival (Slavchev 2021).

PART II: MODULE SII NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Mirvetuximab soravtansine (also known as IMGN853; MIRV) is an ADC that binds with high specificity and affinity to folate receptor alpha (FRα, also referred to as folate receptor 1 [FOLR1]), a glycosylphosphatidylinositol-linked protein). FRα has limited normal tissue expression and high expression in several solid tumours (Kelemen 2006), most notably serous epithelial ovarian cancer (Miotti 1987; O'Shannessy 2013).

The primary objectives of the MIRV nonclinical programme were to investigate:

- Distribution of FRα expression in normal tissues
- Expression of FRα in human solid tumour tissues
- Binding characteristics of the M9346A antibody and the antibody-maytansinoid conjugate MIRV
- Intracellular processing of MIRV
- Cytotoxicity mediated by:
  - Selective binding of MIRV
  - Induction of cell cycle arrest and apoptosis
  - Immune effector activity
- Identification of the appropriate animal model for conducting toxicity studies
- In vivo efficacy via human tumour xenograft models in severe combined immunodeficiency disease (SCID) mice
- Distribution, metabolism, and excretion of MIRV in Sprague Dawley rats
- In vitro metabolism studies for DM4 and S-methyl DM4
- The toxicity profile of MIRV in cynomolgus monkeys in single and repeat dose studies
- Ocular toxicity and ocular distribution of MIRV in Dutch Belted rabbits
- Pharmacokinetics (PK) of MIRV in cynomolgus monkeys and Dutch Belted rabbits

The cynomolgus and rhesus monkeys were identified as appropriate models to assess potential target-mediated toxicities of MIRV based on a comparative assessment of the FRα protein across different animal species (2.6.2 Pharmacology Written Summary, Section 2.3.1) and M9346A binding experiments performed using indirect flow cytometry with the M9346A antibody (2.6.2 Pharmacology Written Summary, Section 2.3.2). No other experimental species have tissues that cross reacted with MIRV.

Mouse and monkey were used to evaluate the toxicity of DM4, the cytotoxic payload, as these effects are independent of FRα mediation.

Table 2: Key safety findings from nonclinical studies and relevance to human usage

Key Safety findings (from nonclinical studies)	Relevance to human usage
Toxicity	
Single dose and repeat dose toxicity studies Administration of MIRV was tolerated in cynomolgus monkeys up to 10 mg/kg/dose in a single dose study (2.6.6 Toxicology Written Summary, Section 2.1) and up to 8 mg/kg/dose in	Ocular adverse events (AEs) (blurred vision, keratopathy, dry eye) have been observed in clinical studies of ADCs, containing the SPDB-DM4 and mc-MMAF linker payloads (Eaton 2015). These ADCs target different

Key Safety findings (from nonclinical studies)	Relevance to human usage
a repeat dose study (2.6.6 Toxicology Written Summary, Section 3.1), the highest doses tested. Findings were generally similar between single and repeat dose studies and consisted of clinical observations (dermal findings); effects on clinical pathology (white blood cell [WBC] and red blood cell mass); and microscopic findings in the skin (injection sites, epithelial ulceration/erosion, oedema in the subcutis, and superficial exudates; skin/subcutis, epithelial ulceration/erosion, and acanthosis/hyperkeratosis and oedema in the subcutis and superficial exudates). The repeat administration study of MIRV identified ocular tissues as an additional target organ. Ophthalmic examinations identified keratopathy, characterised by faint perilimbal corneal pigment migration into clear cornea and corneal microcysts. Microscopic findings of degeneration/necrosis, pigmentation, and attenuation were noted in the corneal epithelium, and epithelial degeneration/necrosis was noted for the eyelids, which correlated with the ophthalmic examinations. Most of the findings identified in the single and repeat dose studies with MIRV resolved by the respective recovery necropsies, with the exception of the ophthalmic observations of corneal pigmentation and a lesion noted in the females 8 mg/kg/dose group observed after repeat administration. Intravenous (IV) administration of MIRV Q3W to male Dutch Belted rabbits (Section 2.6.6 Toxicology Written Summary, Section 8.1.2) resulted in ophthalmic observations of corneal microcysts, and microscopic eye findings of slight attenuation and degeneration/necrosis of the corneal epithelium. The severity of the ocular findings increased with an increase in dose intensity (2.6.6 Toxicology Written Summary, Section 8.1.1; 2.6.6 Toxicology Written Summary, Section 8.1.3) as well as an increase in overall dose exposure. At the three-week recovery necropsy, signs of recovery were noted for all the findings up to the highest dose assessed of 12 mg/kg/dose. The overall toxicology findings observed in monkey and rabbit are supported by systemic exposures and distribution of MIRV in both species (2.6.4 Pharmacokinetic Written Summary, Sections 3-4). **Maytansinoid Toxicity Studies** Toxicity findings associated with a single IV dose of the small molecule payload, DM4, in mice	proteins, which are not expressed in the eye, suggesting that ocular events are a result of an off-target interaction. In addition, FRα expression was not observed in eye tissue providing further evidence of an off-target interaction (2.6.2 Pharmacology Written Summary, Section 2.1.1). As MIRV is a DM4 (payload) tubulin-directed compound, ocular disorders were expected adverse reactions in the clinical development programme and accordingly, the ocular AE profile of MIRV has been well characterised in patients receiving 6 mg/kg AIBW monotherapy. In the EOC population, a total of 405 of 682 patients (59%) treated with MIRV had at least 1 ocular treatment-emergent adverse event (TEAE) (5.3.5.3 Integrated Summary of Safety [ISS], Table 4.12.1). The majority were of Grade 1 or 2 severity; 75 patients (11%) had a ≥ Grade 3 ocular TEAE. The most common (≥ 3%) ≥ Grade 3 ocular TEAEs were vision blurred (32 patients; 5%), keratopathy (31 patients; 5%), and cataract (28 patients; 4%); all grouped terms (5.3.5.3 ISS, Table 4.12.1). Ocular disorders are an important identified risk of MIRV (Module SVII.1.2). The dermal findings observed in the single and repeat dose monkey studies were not as apparent in humans, with no significant skin disorder AEs observed in the clinical studies. The toxicity attributed to DM4 in the cynomolgus monkey included transient elevations in alkaline phosphatase (ALP), neutropenia, decreases in red blood cell parameters and increases in platelet counts. Transient elevations in liver function tests have been associated with MIRV. In the EOC population (N=682), the most common (≥ 5%) hepatic enzyme elevation TEAEs observed in patients treated with MIRV include aspartate aminotransferase (AST) increased (111 patients; 16%), alanine aminotransferase (ALT) increased (90 patients; 13%), and blood ALP increased (46 patients; 7%) (5.3.5.3 ISS, Table 4.2.1.1). The majority of TEAEs were of Grade 1 or 2 severity; ≥ Grade 3 TEAEs included gamma-glutamyltransferase (GGT) increased (8 patients; 1%), AST increased (8 patients; 1%), ALT increased (6 patients; < 1%), and blood ALP increased (3 patients; < 1%) (5.3.5.3 ISS, Table 4.8.1.1).

Key Safety findings (from nonclinical studies)	Relevance to human usage
(2.6.6 Toxicology Written Summary, Section 8.3.2) included morbidity and microscopic observations in the gastrointestinal tract and hypocellularity in the bone marrow and lymph organs at doses ≥ 3.12 mg/kg/dose. Survival was also affected at the lowest dose administered, 1.17 mg/kg/dose; one animal was euthanised early on day 6 due to a ≥ 20% decrease in body weight. DM4 was administered as a single IV dose at 0.1 mg/kg/dose in the cynomolgus monkey (2.6.6 Toxicology Written Summary, Section 2.2) to assess the toxicity profile. DM4-related clinical pathology alterations included mild leukopenia primarily due to neutropenia, which corresponded microscopically to bone marrow depletion. Transient elevations in ALP values were noted with no correlating microscopic findings in the liver. Decreases in red blood cell parameters and increases in platelet counts were seen in most animals across both groups. The toxicity profile of the small molecule in mouse and cynomolgus monkey is similar to that seen with MIRV, indicating the toxicities identified are driven by the cytotoxic payload.	Analysis of liver function test results did not find any patients with post-baseline ALT or AST > 3 × upper limit of normal (ULN) and total bilirubin (TBL) ≥ 2 × ULN and ALP < 2 × ULN in either Study 0416 or the EOC population (5.3.5.3 ISS, Table 5.1.4). No patient met the Hy's Law criteria. Hepatotoxicity is not an important risk (Module SVII.1.1). MIRV has been associated with blood dyscrasias but with few Grade 3-4 AEs (5.3.5.3 ISS, Table 4.2.1.1; 5.3.5.3 ISS, Table 4.8.1.1). In the EOC population (N=682), the most common blood dyscrasias experienced by patients treated with MIRV included anaemia (80 patients; 12%), thrombocytopenia (69 patients; 10%), neutropenia (64 patients; 9%), and leukopenia (13 patients; 2%) TEAEs (5.3.5.3 ISS, Table 4.2.1.1). The majority of TEAEs were of Grade 1 or 2 severity. The only ≥ Grade 3 blood dyscrasia that occurred in ≥ 1% of patients was anaemia (10 patients; 1%) (5.3.5.3 ISS, Table 4.8.1.1). For the EOC population (N=682), the incidences of haematology laboratory abnormalities ≥ 10% that worsened from baseline to Grade 3-4 in patients treated with MIRV included 53 (8.2%) patients with lymphocyte count decreased, 14 (2.1%) patients with haemoglobin decreased, 7 (1.1%) patients with neutrophil count decreased, 5 (0.8%) patients with platelets decreased, and 4 (0.6%) patients with leukocytes decreased (5.3.5.3 ISS, Table 5.1.6).
Reproductive/developmental toxicity In line with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) S9 guidance, no reproductive or developmental toxicity studies were conducted as MIRV is intended to treat patients with advanced cancer.	DM4 binds microtubules, leading to a disruption of microtubule networks, G2/M phase arrest, and cell death. Therefore, MIRV can be expected to cause embryo-foetal harm when administered to a pregnant woman. There are no available human data on MIRV use in pregnant women (Module SIV.3). Embryo-foetal toxicity is a risk not considered important as discussed in Module SVII.1.1.
Genotoxicity The in vitro genotoxicity assessment utilising the bacterial reverse mutation assay (2.6.6 Toxicology Written Summary, Section 4.1) was negative for DM4 and the metabolite S-methyl DM4. Consistent with its mode of action (2.6.2 Pharmacology Written Summary, Section 2.4.1), DM4 and S-methyl DM4 scored positively in the rat bone marrow micronucleus assay (2.6.6	MIRV contains a genotoxic compound (DM4) that affects actively dividing cells.

Key Safety findings (from nonclinical studies)	Relevance to human usage
Toxicology Written Summary, Section 4.2). DM4 and S-methyl DM4 resulted in micronuclei in polychromatic erythrocytes. This result was expected based on the mechanism of action of DM4 which is to inhibit tubulin polymerisation and microtubule assembly. DM4 is an antimitotic agent that induces G2/M phase arrest of dividing cells resulting in cell death (2.6.2 Pharmacology Written Summary, Section 2.5.2).	
Carcinogenicity In line with ICH S9 guidance, no carcinogenicity studies were conducted as MIRV is intended to treat patients with advanced cancer.	Not applicable.
Safety pharmacology	
Cardiac safety An in vitro study (CTT14-001) evaluating the in vitro effects of DM4 and S-methyl DM4 on the human ether-à-go-go-related gene (hERG) channel current [a surrogate for the rapidly activating, delayed rectifier cardiac potassium current (IKr)] at near-physiological temperature found a low likelihood of DM4 or its metabolite S-methyl DM4 interaction with the hERG channel (2.6.2 Pharmacology Written Summary, Section 4.1). A 10-week IV (slow push) toxicity and toxicokinetic study (CVT28-001), including a telemetry component, in cynomolgus monkeys evaluated the toxicity profile of MIRV when administered after repeated IV injection (slow push) of 2, 4, and 8 mg/kg/dose Q3W for four consecutive doses with a 5-week recovery period. No changes attributed to MIRV in vital signs, blood pressure, PR interval, QRS duration, QT interval, corrected QT (QTc) interval, RR interval, or heart rate were observed during the dosing or recovery phases in animals administered 2, 4, or 8 mg/kg/dose (2.6.2 Pharmacology Written Summary, Section 4.2).	Similar to the nonclinical in vitro and in vivo findings, MIRV is not cardiotoxic in humans. An analysis was conducted to evaluate the MIRV PK-electrocardiogram relationship using data from patients enrolled in both the dose escalation and expansion Phases of the Study 0401 clinical study (IMK28-013). The QTc analyses indicate that MIRV has a low likelihood of inducing clinically significant QTc prolongation in humans (2.7.2 Summary of Clinical Pharmacology Studies, Section 3.5.1.3).
Mechanisms for drug interactions	
In vitro studies (CVG14-003 and CVG14-002) were conducted to evaluate PK drug interaction potentials (2.7.2 Summary of Clinical Pharmacology Studies, Section 3.3). Both DM4 and S-methyl-DM4 showed no direct inhibition on cytochrome P450 (CYP)1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5. However, DM4 showed time-dependent inhibition on CYP3A4 (inactivation constant [Ki] of 2.92 µM and 5.95 µM for	No specific clinical study was conducted to evaluate the effect of concomitant medicines on the exposures to MIRV, DM4, or S-methyl-DM4. Exposures in patients with or without concomitant medication were evaluated as part of the population PK (PopPK) analysis (2.7.2 Summary of Clinical Pharmacology Studies, Section 3.3).

Key Safety findings (from nonclinical studies)	Relevance to human usage
testosterone 6β-hydroxylase, midazolam 1'-hydroxylase, respectively). S-methyl DM4 showed weak time-dependent inhibition of CYP2C8 and CYP2C9. In vitro studies also indicated no evidence for induction of CYP1A2, CYP2B6, and CYP3A4 in human hepatocytes following exposure to DM4 and S-methyl DM4. DM4 and S-methyl-DM4 are substrates of the multidrug resistance protein 1 (MDR1), also known as P-gp, efflux transporter (SVG28-001); however, neither compound inhibited the MDR1 efflux transporter. In Study 0403 at 6 mg/kg AIBW, the maximum plasma concentration (C_{max}) of DM4 was 4.11 ng/mL or 0.0052 µM, which is almost three orders of magnitude lower than the K_i of 2.92 or 5.95 µM for DM4 on CYP3A4 (CVG14-003), indicating that DM4 is unlikely to act as a perpetrator inhibiting CYP3A4. The C_{max} of S-methyl-DM4 was 6.98 ng/mL or 0.0085 µM, indicating that S-methyl-DM4 is unlikely to be a perpetrator inhibiting CYP2C8 and CYP2C9.	During the four clinical studies (0416, 0417, 0401, and 0403), there were 49 patients treated with MIRV 6 mg/kg AIBW who were taking concomitant P-glycoprotein (P-gp) inhibitors at any time during the first three cycles of treatment in these studies. There were also 19 and 59 patients taking concomitant weak or moderate CYP3A4 inhibitors, respectively, at any time during the first three cycles of treatment in these studies. There were no differences in exposure to the ADC, DM4, and S-methyl-DM4 between patients who received concomitant weak or moderate CYP3A4 inhibitors or P-gp inhibitors and those who did not. Drug-drug interactions are a risk not considered important (Module SVII.1.1).
Other toxicity-related information or data	
Phototoxicity DM4 was assayed for phototoxicity to Balb/c 3T3 fibroblast cells using the neutral red uptake assay (2.6.6 Toxicology Written Summary, Section 8.2). DM4 was phototoxic in this in vitro test system when tested up to 100 µg/mL. As ICH S10 does not generally apply to ADCs, no further phototoxicity studies were conducted with MIRV.	In the EOC population (N=682), photosensitivity reaction (all treatment related) occurred in 6 patients (< 1%); none of which were of ≥ Grade 3 severity (5.3.5.3 ISS, Table 4.2.1.1; 5.3.5.3 ISS, Table 4.7.1.1; 5.3.5.3 ISS, Table 4.8.1.1).
Local tolerance The 10-week IV (slow push) toxicity and toxicokinetic study (CVT28-001) in cynomolgus monkeys described above, found MIRV-related microscopic observations at the terminal sacrifice in the IV injection sites of animals given 8 mg/kg/dose (2.6.6 Toxicology Written Summary, Section 7.1). The microscopic findings at the IV injection sites were epithelial ulceration/erosion, oedema in the subcutis, and superficial exudates. The microscopic findings noted at the terminal sacrifice were not found at the recovery necropsy indicating signs of recovery.	Local injection site reactions are not considered a safety concern for MIRV. Events of administration site swelling, bruising, extravasation, and pain have been reported in 6 (< 1%) of patients in the EOC population (N=682) who received MIRV (1.8.2 RMP, Table 4.3.1.11). The majority of events were mild to moderate in severity (1.8.2 RMP, Table 4.3.1.11a). One patient was hospitalised one week after receiving their cycle 5 dose, due to a Grade 3 event of poor pain control secondary to extravasation of drug. The event resolved with dose delay.

Conclusions from the nonclinical development programme

The overall nonclinical assessment of MIRV supports its use for the treatment of cancer patients.

A nonclinical finding, which has relevance for use in humans is ocular toxicity observed in the cynomolgus monkey and Dutch-Belted rabbit. Ocular disorders are an important identified risk of MIRV (Module SVII.1.2).

The reproductive/development toxicity of DM4 and its effect on actively dividing cells is another significant finding because of the potential toxicity to the foetus. Embryo-foetal toxicity is a risk not considered important as discussed in Module SVII.1.1.

PART II: MODULE SIII CLINICAL TRIAL EXPOSURE

In the clinical development programme, the safety and efficacy of MIRV have been evaluated in four studies:

- Study IMGN853-0401 (0401): A Phase 1, first in human, dose escalation and dose expansion study in patients with EOC and other FRα-positive tumours.
- Study IMGN853-0403 (0403): A Phase 3, randomised, open-label, multicentre study evaluating the efficacy and safety of MIRV compared to investigator's choice (IC) of select chemotherapies (IC Chemo) (paclitaxel [Pac], pegylated liposomal doxorubicin [PLD], or topotecan [Topo]) in patients (randomised 2:1) with FRα -positive platinum-resistant, advanced high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancers (PROC) who had received 1 to 3 prior systemic anticancer therapies.
- Study IMGN853-0417 (0417): A Phase 3, multicentre, single-arm study of MIRV in patients with FRα-positive PROC who had received 1 to 3 prior therapies, including bevacizumab.
- Study IMGN853-0416 (0416): A Phase 3, open-label, randomised study designed to compare the efficacy and safety of MIRV vs. IC Chemo (Pac, PLD, or Topo) in patients with FRα-positive PROC.

Patients who received at least one dose of MIRV 6 mg/kg Q3W AIBW were pooled according to the groups listed in Table 3.

Table 3: Pooled Safety Analysis Populations

Group	Analysis Population	No of Patients
All Patients (6 mg/kg AIBW Q3W)	All patients (EOC and endometrial cancer) treated with MIRV 6 mg/kg AIBW Q3W (Studies 0401, 0403, 0416, 0417) - Patients in expansion cohorts of Study IMGN853-0401 (n=137) [a] - Patients who received MIRV 6 mg/kg AIBW Q3W in Study IMGN853-0403 (n=245) [b] - Patients who received MIRV 6 mg/kg AIBW Q3W in Study IMGN853-0416 (n=218) - All patients in Study IMGN853-0417 (n=106)	706
EOC Patients (6 mg/kg AIBW Q3W)	All EOC patients treated with MIRV 6 mg/kg AIBW Q3W (Studies 0401, 0403, 0416, 0417) - EOC patients (cohorts 1, 3, and 5) in Study IMGN853-0401 (n=113) - Patients who received MIRV 6 mg/kg AIBW Q3W in Study IMGN853-0403 (n=245) [b] - Patients who received MIRV 6 mg/kg AIBW Q3W in Study IMGN853-0416 (n=218) - All patients in Study IMGN853-0417 (n=106)	682
0416 MIRV (6 mg/kg AIBW Q3W)	All patients treated with MIRV 6 mg/kg AIBW Q3W in Study 0416 (n=218)	218

Group	Analysis Population	No of Patients
0416 IC Chemo[c]	All patients treated with IC Chemo in Study 0416 (n=207)	207

Abbreviations: AIBW = adjusted ideal body weight; EOC = epithelial ovarian cancer; IC Chemo = Investigator's choice/selected standard-of-care chemotherapy; MIRV = mirvetuximab soravtansine; Pac = paclitaxel; PLD = pegylated liposomal doxorubicin; QW = weekly; Q3W = every 3 weeks; Q4W = every 4 weeks; Topo = topotecan.
[a] All EOC patients from cohorts 1, 3, and 5 (n=113) and endometrial cancer patients from cohort 2 (n=24).
[b] 243 patients from Phase 3 portion and 2 patients from Stage 1.
[c] IC Chemo: Pac (80 mg/m^2 administered QW within a 4-week cycle); PLD (40 mg/m^2 administered Q4W); Topo (4 mg/m^2 administered either on Days 1, 8 or 15 of a 4 week cycle or for 5 consecutive days at 1.25 mg/m^2 Days 1-5 Q3W).

MIRV is administered at a dose of 6 mg/kg AIBW Q3W. Exposure by duration (Table 4), age group and sex (Table 5), racial group (Table 6) and ethnicity (Table 7) in the safety populations are presented below.

Table 4: Duration of Exposure (Safety Populations)

Parameter	All Patients (6 mg/kg AIBW Q3W (N=706)	EOC (6 mg/kg AIBW Q3W) (N=682)	Study 0416	
			MIRV (6 mg/kg AIBW Q3W) (N=218)	IC Chemo (N=207)
Duration of treatment (weeks), n (%)				
≤ 12	215 (30)	202 (30)	58 (27)	97 (47)
> 12 to 24	224 (32)	218 (32)	59 (27)	60 (29)
> 24 to 36	122 (17)	117 (17)	48 (22)	29 (14)
> 36 to 48	59 (8)	59 (9)	22 (10)	14 (7)
> 48	86 (12)	86 (13)	31 (14)	7 (3)
Duration of dosing (weeks) [1]				
n	706	682	218	207
Mean (SD)	25.1 (20.84)	25.5 (21.01)	26.6 (19.15)	17.3 (13.51)
Median	19.0	19.1	21.6	12.9
Min, Max	3, 132	3, 132	3, 119	2, 79

Abbreviations: AIBW = adjusted ideal body weight; EOC = epithelial ovarian cancer; IC Chemo = Investigator's choice/selected standard-of-care chemotherapy; Max = maximum; Min = minimum; MIRV = mirvetuximab soravtansine; Pac = paclitaxel; PLD = pegylated liposomal doxorubicin; QW = weekly; Q3W = every 3 weeks; Q4W = every 4 weeks; SD = standard deviation; Topo = topotecan.
IC Chemo: Pac (80 mg/m^2 administered QW within a 4-week cycle); PLD (40 mg/m^2 administered Q4W); Topo (4 mg/m^2 administered either on Days 1, 8 or 15 of a 4 week cycle or for 5 consecutive days at 1.25 mg/m^2 Days 1-5 Q3W).
[1] Duration of dosing in weeks are calculated as the following: IMGN853: (last dose date – first dose date + 21) / 7; Pac: (last dose date – first dose date + 7) / 7; PLD: (last dose date – first dose date + 28) / 7; Topo (Q4W): (last dose date – first dose date + 14) / 7; Topo (Q3W): (last dose date – first dose date + 16) / 7.
Data cut-off dates for studies IMGN853-0401: 10 Feb 2018; IMGN853-0403: 18 Mar 2020; IMGN853-0417: 22 Dec 2022; IMGN853-0416: 06 Mar 2023
Source data: 5.3.5.3 ISS, Table 3.1.1

Table 5: Exposure by Age Group and Sex (Safety Populations)

Characteristic	All Patients (6 mg/kg AIBW Q3W) (N=706)	EOC (6 mg/kg AIBW Q3W) (N=682)	Study 0416	
			MIRV (6 mg/kg AIBW Q3W) (N=218)	IC Chemo (N=207)
Age (years)				
n	706	682	218	207
Mean (SD)	62.7 (9.67)	62.5 (9.71)	63.5 (9.78)	62.6 (9.28)
Median	63.0	63.0	64.0	63.0
Min, Max	32, 89	32, 89	32, 88	29, 87
Age category, n (%)				
18 to 64	389 (55)	379 (56)	115 (53)	119 (57)
≥ 65	317 (45)	303 (44)	103 (47)	88 (43)
65 to 74	240 (34)	229 (34)	75 (34)	73 (35)
75 to 84	73 (10)	70 (10)	27 (12)	14 (7)
≥ 85	4 (< 1)	4 (< 1)	1 (< 1)	1 (< 1)
18 to 69	529 (75)	514 (75)	153 (70)	154 (74)
≥ 70	177 (25)	168 (25)	65 (30)	53 (26)
Sex, n (%)				
Male	0	0	0	0
Female	706 (100)	682 (100)	218 (100)	207 (100)

Abbreviations: AIBW = adjusted ideal body weight; EOC = epithelial ovarian cancer; IC Chemo = Investigator's choice/selected standard-of-care chemotherapy; Max = maximum; Min = minimum; MIRV = mirvetuximab soravtansine; Pac = paclitaxel; PLD = pegylated liposomal doxorubicin; QW = weekly; Q3W = every 3 weeks; Q4W = every 4 weeks; SD = standard deviation; Topo = topotecan.
IC Chemo: Pac (80 mg/m^2 administered QW within a 4-week cycle); PLD (40 mg/m^2 administered Q4W); Topo (4 mg/m^2 administered either on Days 1, 8 or 15 of a 4 week cycle or for 5 consecutive days at 1.25 mg/m^2 Days 1-5 Q3W).
Data cut-off dates for studies IMGN853-0401: 10 Feb 2018; IMGN853-0403: 18 Mar 2020; IMGN853-0417: 22 Dec 2022; IMGN853-0416: 06 Mar 2023
Source data: 5.3.5.3 ISS, Table 2.1

Table 6: Exposure by Race (Safety Populations)

Characteristic	All Patients (6 mg/kg AIBW Q3W) (N=706)	EOC (6 mg/kg AIBW Q3W) (N=682)	Study 0416	
			MIRV (6 mg/kg AIBW Q3W) (N=218)	IC Chemo (N=207)
Race, n (%)				
White	594 (84)	571 (84)	147 (67)	128 (62)
Black or African American	18 (3)	18 (3)	8 (4)	5 (2)
Native Hawaiian or Other Pacific Islander	0	0	0	0
Asian	41 (6)	41 (6)	28 (13)	23 (11)

Characteristic	All Patients (6 mg/kg AIBW Q3W) (N=706)	EOC (6 mg/kg AIBW Q3W) (N=682)	Study 0416	
			MIRV (6 mg/kg AIBW Q3W) (N=218)	IC Chemo (N=207)
American Indian or Alaska Native	2 (< 1)	2 (< 1)	0	0
Other	5 (< 1)	5 (< 1)	3 (1)	2 (< 1)
Not reported	46 (7)	45 (7)	32 (15)	49 (24)

Abbreviations: AIBW = adjusted ideal body weight; EOC = epithelial ovarian cancer; IC Chemo = Investigator's choice/selected standard-of-care chemotherapy; MIRV = mirvetuximab soravtansine; Pac = paclitaxel; PLD = pegylated liposomal doxorubicin; QW = weekly; Q3W = every 3 weeks; Q4W = every 4 weeks; Topo = topotecan.
IC Chemo: Pac (80 mg/m^2 administered QW within a 4-week cycle); PLD (40 mg/m^2 administered Q4W); Topo (4 mg/m^2 administered either on Days 1, 8 or 15 of a 4 week cycle or for 5 consecutive days at 1.25 mg/m^2 Days 1-5 Q3W).
Data cut-off dates for studies IMGN853-0401: 10 Feb 2018; IMGN853-0403: 18 Mar 2020; IMGN853-0417: 22 Dec 2022; IMGN853-0416: 06 Mar 2023
Source data: 5.3.5.3 ISS, Table 2.1

Table 7: Exposure by Ethnicity (Safety Populations)

Characteristic	All Patients (6 mg/kg AIBW Q3W) (N=706)	EOC (6 mg/kg AIBW Q3W) (N=682)	Study 0416	
			MIRV (6 mg/kg AIBW Q3W) (N=218)	IC Chemo (N=207)
Ethnicity, n (%)				
Hispanic or Latino	26 (4)	26 (4)	12 (6)	15 (7)
Not Hispanic or Latino	616 (87)	593 (87)	168 (77)	145 (70)
Not reported	60 (8)	59 (9)	35 (16)	45 (22)
Missing	4 (< 1)	4 (< 1)	3 (1)	2 (< 1)

Abbreviations: AIBW = adjusted ideal body weight; EOC = epithelial ovarian cancer; IC Chemo = Investigator's choice/selected standard-of-care chemotherapy; MIRV = mirvetuximab soravtansine; Pac = paclitaxel; PLD = pegylated liposomal doxorubicin; QW = weekly; Q3W = every 3 weeks; Q4W = every 4 weeks; Topo = topotecan.
IC Chemo: Pac (80 mg/m^2 administered QW within a 4-week cycle); PLD (40 mg/m^2 administered Q4W); Topo (4 mg/m^2 administered either on Days 1, 8 or 15 of a 4 week cycle or for 5 consecutive days at 1.25 mg/m^2 Days 1-5 Q3W).
Data cut-off dates for studies IMGN853-0401: 10 Feb 2018; IMGN853-0403: 18 Mar 2020; IMGN853-0417: 22 Dec 2022; IMGN853-0416: 06 Mar 2023
Source data: 5.3.5.3 ISS, Table 2.1

PART II: MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Exclusion criteria from Study IMGN853-0416 (0416) that are common to most other clinical studies for oncology products and that are not discussed further include:

- Patients with prior treatment with (investigational product) MIRV or other FRα-targeting agents
- Patients with untreated or symptomatic central nervous system (CNS) metastases
- Patients with a history of other malignancy within 3 years prior to randomisation

  Note: did not include tumours with a negligible risk for metastasis or death (e.g., adequately controlled basal-cell carcinoma or squamous-cell carcinoma of the skin, or carcinoma in situ of the cervix or breast
- Prior known hypersensitivity reactions to study drugs and/or any of their excipients
- Patients with prior hypersensitivity to monoclonal antibodies (same class of product)
- Patients with serious concurrent illness or clinically relevant active infection, including, but not limited to the following:

  a. Active hepatitis B or C infection (whether or not on active antiviral therapy)
  b. Human immunodeficiency virus (HIV) infection
  c. Active cytomegalovirus infection
  d. Any other concurrent infectious disease requiring IV antibiotics within 2 weeks before starting study drug

  Note: Testing at screening was not required for the above infections unless clinically indicated
- People who were detained through a court or administrative decision, receiving psychiatric care against their will, adults who are the subject of a legal protection order (under tutorship/curatorship), people who were unable to express their consent, and people who were subject to a legal guardianship order
- Simultaneous participation in another research study, in countries or localities where this was the health authority guidance

The important exclusion criteria from Study 0416 are presented below and may be grouped together.

- Patients with endometrioid, clear cell, mucinous, or sarcomatous histology, mixed tumours containing any of the above histologies, or low-grade or borderline ovarian tumour
- Patients with primary platinum-refractory disease, defined as disease that did not respond to (complete response [CR] or partial response [PR]) or has progressed within 3 months of the last dose of first line platinum containing chemotherapy

- Patients with prior wide-field radiotherapy (RT) affecting at least 20% of the bone marrow

Reason for exclusion: Patients were excluded from clinical study participation if they did not meet the specifications of the target population or were considered to have disease that was progressing too rapidly as this may have impacted the efficacy or safety outcome of the study.

Is it considered to be included as missing information? No

Rationale: There is no known increased risk for use of MIRV in these populations. While a clinical study targets a specific population to demonstrate efficacy and safety in that population, in clinical practice there may some patients who would benefit from MIRV treatment who have more severe disease or a complicated diagnosis.

- Patients with > Grade 1 peripheral neuropathy per Common Terminology Criteria for Adverse Events (CTCAE) v5.0

Reason for exclusion: As MIRV consists of an engineered anti-FRα monoclonal IgG1 antibody conjugated via a cleavable disulfide-containing linker to the cytotoxic maytansine derivative DM4, specific interest was paid to peripheral neuropathy in clinical studies.

Is it considered to be included as missing information? No

Rationale: Peripheral neuropathy is a risk not considered important (Module SVII.1.1).

Peripheral neuropathy can be managed in clinical practice through patient monitoring and dose modifications. The ELAHERE summary of product characteristics (SmPC) warns healthcare professionals that MIRV can cause peripheral neuropathy, including Grade ≥ 3 reactions. Patients should be monitored for signs and symptoms of neuropathy, such as paraesthesia, tingling or a burning sensation, neuropathic pain, muscle weakness, or dysesthesia. Recommended dose modifications for new or worsening peripheral neuropathy include withholding treatment, reducing the dose or permanently discontinuing treatment depending on the severity grade.

Healthcare professionals are advised that MIRV has moderate influence on the ability to drive and use machines. If patients experience peripheral neuropathy during treatment with MIRV, they should be instructed not to drive or use machines until complete resolution of symptoms is confirmed.

Peripheral neuropathy will continue to be monitored using routine pharmacovigilance activities.

- Patients with active or chronic corneal disorders, history of corneal transplantation, or active ocular conditions requiring ongoing treatment/monitoring such as uncontrolled glaucoma, wet age-related macular degeneration requiring intravitreal injections, active diabetic retinopathy with macular oedema, macular degeneration, presence of papilledema, and /or monocular vision

Reason for exclusion:

Some ADCs containing tubulin-directed payloads have been associated with ocular AEs related to keratopathy, including blurred vision. Several recently approved ADCs containing auristatin payloads, including monomethyl auristatin E (Padcev SmPC; Tivdak USPI) and

monomethyl auristatin F (Blenrep SmPC), have been associated with corneal-related AEs. These ADCs are comprised of unique antibodies, linkers, and tubulin-directed payloads, and each produce a distinct spectrum of effects upon the cornea. For example, the antibody component of Tivdak is directed toward the Tissue Factor (TF) protein which is present on the cornea. Some of the associated toxicity is a direct effect of this ADC's antibody binding to TF. Essentially, each ADC is unique in its AE profile and its subsequent management.

In the MIRV nonclinical development programme, ocular changes with MIRV in the Dutch-Belted rabbit and cynomolgus monkey were observed but limited to the formation of corneal microcysts without any inflammatory response (Module SII). Punctate microcystic lesions in the cornea in the Dutch-Belted rabbit are suggestive of a close phenotypic match to the keratopathy observed in human subjects treated with MIRV. Histopathologic evaluation of the keratopathy showed marked attenuation and disorganisation of the corneal epithelium in MIRV-treated animals. These corneal effects occurred in a dose-dependent manner with respect to onset, duration, and severity with evidence of reversibility.

Is it considered to be included as missing information? No

Rationale: Ocular disorders are an important identified risk of MIRV (Module SVII.1.2).

Ocular disorders can be managed in clinical practice through ophthalmic examinations, use of lubricating eye drops, patient monitoring, use of ophthalmic topical steroids as secondary prophylaxis for ≥ Grade 2 corneal adverse reactions, and dose modifications for keratitis/keratopathy including withholding treatment, reducing the dose or permanently discontinuing treatment depending on severity grade.

Ocular disorders will be further characterised through using routine pharmacovigilance activities.

- Patients with history of multiple sclerosis or other demyelinating disease and/or Lambert Eaton syndrome (paraneoplastic syndrome)

Reason for exclusion: Including patients with a history of multiple sclerosis or other demyelinating disease and/or Lambert Eaton syndrome (conditions affecting the nerves) may have impacted the safety or efficacy evaluation of MIRV or IC Chemo, or led to premature withdrawal of subjects from the study.

Is it considered to be included as missing information? No

Rationale: There are no known safety or efficacy concerns for using MIRV in this patient population in clinical practice. As the use of MIRV in patients with a history of multiple sclerosis or other demyelinating disease and/or Lambert Eaton syndrome is expected to be very limited, this population is not considered missing information.

- Patients with clinically significant cardiac disease including, but not limited to, any one of the following:

  a. Myocardial infarction ≤ 6 months prior to first dose

  b. Unstable angina pectoris

  c. Uncontrolled congestive heart failure (New York Heart Association > class II)

  d. Uncontrolled ≥ Grade 3 hypertension (per CTCAE)

e. Uncontrolled cardiac arrhythmias

- Patients assigned to PLD stratum only:

  Left ventricular ejection fraction (LVEF) below the institutional limit of normal as measured by echocardiography (ECHO) or multigated acquisition (MUGA) scan

Reason for exclusion: MIRV is not cardiotoxic in humans. An analysis was conducted to evaluate the MIRV PK-electrocardiogram relationship using data from patients enrolled in both the dose escalation and expansion Phases of the Study 0401 clinical study (IMK28-013). The QTc analyses indicate that MIRV has a low likelihood of inducing clinically significant QTc prolongation in humans (2.7.2 Summary of Clinical Pharmacology Studies, Section 3.5.1.3).

While MIRV is not recognised to be cardiotoxic, Pac and PLD are cardiotoxic (Paclitaxel SmPC; Caelyx SmPC). There was also an additional exclusion criterion applied to the patients randomised to PLD that required patients to have LVEF above the institutional lower limit of normal as measured by ECHO or MUGA scan.

Patients with clinically significant cardiac disease were excluded from study participation as their inclusion could have affected the safety and efficacy assessment of MIRV versus IC Chemo.

Is it considered to be included as missing information? No

Rationale: As MIRV is not cardiotoxic it is not necessary to further characterise use in patients with clinically significant cardiac disease.

- Patients with a history of haemorrhagic or ischemic stroke within six months prior to randomisation

Reason for exclusion: Patients with a recent history of haemorrhagic or ischemic stroke were excluded from study participation as their inclusion could have affected the safety and efficacy assessment of MIRV versus IC Chemo.

Is it considered to be included as missing information? No

Rationale: Use of MIRV in patients with a recent history of haemorrhagic or ischemic stroke is not considered missing information as there are no known or expected risks for use of MIRV in this population.

- Patients with a history of cirrhotic liver disease (Child-Pugh Class B or C)

Reason for exclusion: In a nonclinical study, liver toxicity was found to be attributable to the DM4 payload (Module SII).

Patients with a history of cirrhotic liver disease (Child-Pugh Class B or C) were excluded from study participation as their inclusion could have affected the safety and efficacy assessment of MIRV versus IC Chemo. Furthermore, patients were required to have adequate liver function defined as AST and ALT $\leq 3.0 \times$ ULN; serum bilirubin $\leq 1.5 \times$ ULN (patients with documented diagnosis of Gilbert syndrome were eligible if TBL $< 3.0 \times$ ULN); and serum albumin ≥ 2 g/dL.

Is it considered to be included as missing information? Yes. Use in patients with moderate hepatic impairment has been identified as missing information (Module SVII.1.2).

The ELAHERE SmPC informs healthcare professionals that no clinically significant difference in the PK of MIRV was observed based on mild hepatic impairment (TBL ≤ ULN and any AST > ULN or TBL > 1 to 1.5 times ULN and any AST). The PK of MIRV in patients with moderate to severe hepatic impairment (TBL > 1.5 ULN with any AST) is unknown. Healthcare professionals are advised that no dose adjustment of MIRV is recommended for patients with mild hepatic impairment (TBL ≤ ULN and AST > ULN or TBL > 1 to 1.5 times ULN and any AST) and that MIRV should be avoided in patients with moderate to severe hepatic impairment (TBL > 1.5 ULN with any AST).

Use of MIRV in patients with moderate hepatic impairment will be further characterised in Study IMGN853-0425 (Part III.2).

- Patients with a previous clinical diagnosis of non-infectious interstitial lung disease (ILD), including non-infectious pneumonitis

Reason for exclusion: Pneumonitis was an AE of special interest (AESI) in Study 0403 as lower grade events of non-infectious pneumonitis were seen in Study 0401. Review of the pneumonitis AESI information from Study 0403, demonstrating that the majority of pneumonitis events (88%) were ≤ Grade 2 in severity with no Grade 4 or 5 pneumonitis events, led to the decision to remove the AESI designation for pneumonitis in Study 0417 and Study 0416. However, pneumonitis was observed in both these studies leading to a warning in the ELAHERE US Prescribing Information (USPI) (ELAHERE USPI).

Furthermore, pneumonitis has been reported with Paclitaxel (Paclitaxel SmPC) and topotecan has been associated with reports of ILD (Topotecan SmPC).

Patients with a previous clinical diagnosis of non-infectious ILD, including non-infectious pneumonitis, were excluded from study participation as their inclusion could have affected the safety and efficacy assessment of MIRV versus IC Chemo.

Is it considered to be included as missing information? No

Rationale: Pneumonitis is a risk not considered important (Module SVII.1.1).

Pneumonitis can be managed in clinical practice through monitoring patients for pulmonary signs and symptoms of pneumonitis (which may include hypoxia, cough, dyspnoea, or interstitial infiltrates on radiologic exams), excluding other infectious, neoplastic, or other causes for any symptoms of pneumonitis, and dose modifications depending on severity grade.

Pneumonitis will be further monitored using routine pharmacovigilance activities.

- Patients with required use of folate-containing supplements (e.g., folate deficiency)

Reason for exclusion: As discussed in Module SII, MIRV is an ADC and the antibody is a IgG1 directed against FRα. Patients who required use of folate-containing supplements were excluded in the clinical study in case the use of these supplements interfered with the efficacy evaluation of MIRV.

Is it considered to be included as missing information? No

Rationale: In clinical practice, the use of MIRV in patients with required use of folate-containing supplements is expected to be very limited, and the safety of MIRV is not expected to differ in this population.

- Patients who are pregnant or lactating

Reason for exclusion: Patients who are pregnant or lactating were excluded from clinical study participation because of the potential harm that MIRV could have on the foetus or the nursing infant.

Is it considered to be included as missing information? No

Rationale: Embryo-foetal toxicity is a risk not considered important (Module SVII.1.1).

Embryo-foetal toxicity will be managed in clinical practice by verifying the pregnancy status of patients of childbearing potential prior to initiating MIRV treatment, using effective contraception during treatment and for 7 months after the last dose, and advising patients of the potential risk to the foetus. Patients who become pregnant must immediately contact their doctor. If a patient becomes pregnant during treatment with MIRV or within 7 months following the last dose, close monitoring is recommended.

Embryo-foetal toxicity will be further monitored using routine pharmacovigilance activities.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged exposure.

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table 8: Exposure of Special Populations Included or Not in Clinical Study Development Programmes

<table>
<tr><th>Type of Special Population</th><th>Exposure</th></tr>
<tr><td>Pregnant patients</td><td rowspan="2">Not included in the clinical development programme.</td></tr>
<tr><td>Breastfeeding patients</td></tr>
<tr><td>Patients with relevant comorbidities:
• Patients with hepatic impairment</td><td>In Study 0416, patients with a history of cirrhotic liver disease (Child-Pugh Class B or C) were excluded from clinical study participation (Module SIV.1). Furthermore, patients were required to have adequate liver function defined as AST and ALT ≤ 3.0 x ULN, serum bilirubin ≤ 1.5 x ULN (patients with documented diagnosis of Gilbert syndrome are eligible if TBL < 3.0 x ULN), and serum albumin ≥ 2 g/dL.
Clinically significant liver function of the patients in the safety populations is presented in the table below. All patients in Study 0416 had adequate liver function and there were very few patients (< 1%) in the EOC group with hepatic impairment.

Clinically significant liver function (Safety Populations)
<table>
<tr><th rowspan="2">Characteristic</th><th rowspan="2">All Patients (6 mg/kg AIBW Q3W) (N=706)</th><th rowspan="2">EOC (6 mg/kg AIBW Q3W) (N=682)</th><th colspan="2">Study 0416</th></tr>
<tr><th>MIRV (6 mg/kg AIBW Q3W) (N=218)</th><th>IC Chemo (N=207)</th></tr>
<tr><td colspan="5">Concurrent (AST or ALT) and TBL, n (%)</td></tr>
<tr><td>Patients with non-missing AST or ALT and non-missing TBL value</td><td>690 (97.7)</td><td>666 (97.7)</td><td>213 (97.7)</td><td>193 (93.2)</td></tr>
<tr><td>Concurrent (AST or ALT) > 3 x ULN and TBL > 1.5 x ULN</td><td>5 (0.7)</td><td>4 (0.6)</td><td>0</td><td>0</td></tr>
<tr><td>Concurrent (AST or ALT) > 3 x ULN and TBL > 2 x ULN</td><td>3 (0.4)</td><td>2 (0.3)</td><td>0</td><td>0</td></tr>
<tr><td colspan="5">Concurrent (AST or ALT) and ALP and TBL, n (%)</td></tr>
<tr><td>Patients with non-missing AST or ALT and non-missing ALP value and no-missing TBL</td><td>689 (97.6)</td><td>665 (97.5)</td><td>212 (97.2)</td><td>193 (93.2)</td></tr>
<tr><td>Concurrent (AST or ALT) > 3 x ULN and ALP < 2 x ULN and TBL ≥ 2 x ULN</td><td>1 (0.1)</td><td>0</td><td>0</td><td>0</td></tr>
</table>
Abbreviations: AIBW = adjusted ideal body weight; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; EOC = epithelial ovarian cancer; IC Chemo = Investigator’s choice/selected standard-of-care chemotherapy;</td></tr>
</table>

Type of Special Population	Exposure
	MIRV = mirvetuximab soravtansine; Pac = paclitaxel; PLD = pegylated liposomal doxorubicin; QW = weekly; Q3W = every 3 weeks; Q4W = every 4 weeks; TBL = total Bilirubin; Topo = topotecan; ULN = upper limit of normal. IC Chemo: Pac (80 mg/m^2 administered QW within a 4-week cycle); PLD (40 mg/m^2 administered Q4W); Topo (4 mg/m^2 administered either on Days 1, 8 or 15 of a 4 week cycle or for 5 consecutive days at 1.25 mg/m^2 Days 1-5 Q3W). Data cut-off dates for studies IMGN853-0401: 10 Feb 2018; IMGN853-0403: 18 Mar 2020; IMGN853-0417: 22 Dec 2022; IMGN853-0416: 06 Mar 2023 Source data: 5.3.5.3 ISS Table 5.1.4 No clinical study assessing the effect of hepatic impairment on the PK of MIRV was conducted. Individual exposures were predicted using the developed PopPK model for patients from studies 0401, 0403, 0417 and 0416 and compared according to hepatic function categories defined according to the National Cancer Institute (NCI) scoring system for hepatic dysfunction (2.7.2 Summary of Clinical Pharmacology Studies, Section 3.2). For patients with mild hepatic impairment, the exposures to the MIRV, DM4, and S-methyl-DM4 were similar to those patients with normal hepatic function. Inadequate data were available for patients with moderate or severe hepatic impairment. Overall, these data support that no dose adjustment is required for patients with mild hepatic impairment (TBL ≤ ULN and AST > ULN or TBL > 1 to 1.5 times ULN and any AST), as recommended in the ELAHERE SmPC. The PK of MIRV in patients with moderate to severe hepatic impairment is unknown and therefore use of MIRV should be avoided in patients with moderate to severe hepatic impairment (TBL > 1.5 ULN with any AST). Use in patients with moderate hepatic impairment is missing information (Module SVII.1.2). Use of MIRV in patients with moderate hepatic impairment will be further characterised in Study IMGN853-0425 (Part III.2). Use of MIRV in patients with severe hepatic impairment will not be further characterised. As a precautionary measure, the ELAHERE SmPC advises healthcare professionals that MIRV should be avoided in patients with moderate to severe hepatic impairment (TBL > 1.5 ULN with any AST).
• Patients with renal impairment	In Study 0416, patients were required to have adequate kidney function defined as serum creatinine ≤ 1.5 x ULN. Creatinine levels at baseline as assessed by CTCAE grade for the safety populations is presented in the table below.

Type of Special Population	Exposure

Creatinine levels at baseline (Safety Populations)

Characteristic	All Patients (6 mg/kg AIBW Q3W) (N=706)	EOC (6 mg/kg AIBW Q3W) (N=682)	Study 0416	
			MIRV (6 mg/kg AIBW Q3W) (N=218)	IC Chemo (N=207)
Creatinine (umol/L): Creatinine increased, n (%)				
Grade 0	585 (84.5)	565 (84.6)	189 (88.3)	169 (87.6)
Grade 1	101 (14.6)	98 (14.7)	23 (10.7)	23 (11.9)
Grade 2	6 (0.9)	5 (0.7)	2 (0.9)	1 (0.5)
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Total:	692 (100.0)	668 (100.0)	214 (100.0)	193 (100.0)

Abbreviations: AIBW = adjusted ideal body weight; EOC = epithelial ovarian cancer; IC Chemo = Investigator's choice/selected standard-of-care chemotherapy; MIRV = mirvetuximab soravtansine; Pac = paclitaxel; PLD = pegylated liposomal doxorubicin; QW = weekly; Q3W = every 3 weeks; Q4W = every 4 weeks; Topo = topotecan.
IC Chemo: Pac (80 mg/m^2 administered QW within a 4-week cycle); PLD (40 mg/m^2 administered Q4W); Topo (4 mg/m^2 administered either on Days 1, 8 or 15 of a 4 week cycle or for 5 consecutive days at 1.25 mg/m^2 Days 1-5 Q3W).
Data cut-off dates for studies IMGN853-0401: 10 Feb 2018; IMGN853-0403: 18 Mar 2020; IMGN853-0417: 22 Dec 2022; IMGN853-0416: 06 Mar 2023
Source data: 5.3.5.3 ISS, Table 5.1.2

No clinical study assessing the effect of renal impairment on the PK of MIRV was conducted. Individual exposures were predicted using the validated PopPK model for patients from studies 0401, 0403, 0417, and 0416 and compared according to renal function categories defined according to Food and Drug Administration (FDA) Guidance (2.7.2 Summary of Clinical Pharmacology Studies, Section 3.2).

For patients with mild and moderate renal impairment, the exposures to MIRV, DM4, and S-methyl-DM4 were similar to those patients with normal renal function. Inadequate data were available for patients with severe or end-stage renal impairment.

Overall, these data support that no dose adjustment is required for patients with mild to moderate renal impairment (creatinine clearance [CLcr] 30 to < 90 mL/min), as recommended in the ELAHERE SmPC. Although the effect of severe renal impairment (CLcr 15 to < 30 mL/min) or end-stage renal disease on MIRV is unknown and the potential need for dose adjustment in these patients cannot be determined, metabolite assessment in patient urine in Study 0403 suggests that urinary excretion is not a major route for the elimination of DM4 and its related metabolites.

<table>
<tr><th>Type of Special Population</th><th>Exposure</th></tr>
<tr><td>• Patients with cardiovascular impairment</td><td>
In Study 0416 patients were required to have adequate cardiovascular function. The following patients were excluded from clinical study participation:
Patients with clinically significant cardiac disease including, but not limited to, any one of the following:
a. Myocardial infarction ≤ 6 months prior to first dose
b. Unstable angina pectoris
c. Uncontrolled congestive heart failure (New York Heart Association > class II)
d. Uncontrolled ≥ Grade 3 hypertension (per CTCAE)
e. Uncontrolled cardiac arrhythmias
Patients assigned to PLD stratum only:
LVEF below the institutional limit of normal as measured by ECHO or MUGA scan (Module SIV.1).
Patients with a medical history of cardiac disorders (≥ 2%) in the safety populations are presented in the table below.

Medical history cardiac disorders in ≥ 2% patients (Safety Populations)
<table>
<tr><th rowspan="2">System Organ Class, n (%)
Preferred Term, n (%)</th><th rowspan="2">All Patients (6 mg/kg AIBW Q3W) (N=706)</th><th rowspan="2">EOC (6 mg/kg AIBW Q3W) (N=682)</th><th colspan="2">Study 0416</th></tr>
<tr><th>MIRV (6 mg/kg AIBW Q3W) (N=218)</th><th>IC Chemo (N=207)</th></tr>
<tr><td>Cardiac disorders</td><td>97 (14)</td><td>87 (13)</td><td>25 (11)</td><td>25 (12)</td></tr>
<tr><td>Atrial fibrillation</td><td>18 (3)</td><td>16 (2)</td><td>7 (3)</td><td>6 (3)</td></tr>
<tr><td>Palpitations</td><td>15 (2)</td><td>11 (2)</td><td>1 (< 1)</td><td>0</td></tr>
<tr><td>Coronary artery disease</td><td>13 (2)</td><td>13 (2)</td><td>5 (2)</td><td>1 (< 1)</td></tr>
<tr><td>Tachycardia</td><td>11 (2)</td><td>9 (1)</td><td>2 (< 1)</td><td>4 (2)</td></tr>
<tr><td>Cardiac failure chronic</td><td>5 (< 1)</td><td>5 (< 1)</td><td>4 (2)</td><td>2 (< 1)</td></tr>
<tr><td>Left ventricular dysfunction</td><td>4 (< 1)</td><td>4 (< 1)</td><td>4 (2)</td><td>1 (< 1)</td></tr>
</table>
Abbreviations: AIBW = adjusted ideal body weight; EOC = epithelial ovarian cancer; IC Chemo = Investigator's choice/selected standard-of-care chemotherapy; MIRV = mirvetuximab soravtansine; Pac = paclitaxel; PLD = pegylated liposomal doxorubicin; QW = weekly; Q3W = every 3 weeks; Q4W = every 4 weeks; Topo = topotecan.
IC Chemo: Pac (80 mg/m^2 administered QW within a 4-week cycle); PLD (40 mg/m^2 administered Q4W); Topo (4 mg/m^2 administered either on Days 1, 8 or 15 of a 4 week cycle or for 5 consecutive days at 1.25 mg/m^2 Days 1-5 Q3W).
Data cut-off dates for studies IMGN853-0401: 10 Feb 2018; IMGN853-0403: 18 Mar 2020; IMGN853-0417: 22 Dec 2022; IMGN853-0416: 06 Mar 2023
Source data: 5.3.5.3 ISS, Table 2.2.1
</td></tr>
</table>

<table>
<tr><th>Type of Special Population</th><th>Exposure</th></tr>
<tr><td></td><td>As MIRV is not cardiotoxic it is not necessary to further characterise use in patients with cardiovascular impairment.</td></tr>
<tr><td>• Immunocompromised patients</td><td>In Study 0416, patients were required to have adequate haematologic function including an absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (1,500/µL) without granulocyte colony-stimulating factor (G-CSF) in the prior 10 days or long-acting WBC growth factors in the prior 20 days. Furthermore, patients with HIV infection were excluded from clinical study participation (Module SIV.1).
No patients had a medical history of HIV in the safety populations (5.3.5.3 ISS, Table 2.2.1).</td></tr>
<tr><td>• Patients with a disease severity different from inclusion criteria in clinical studies</td><td>In Study 0416, most patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1. The ECOG status for patients in the safety populations is presented in the table below.

Exposure by ECOG (Safety Populations)
<table>
<tr><th rowspan="2">Characteristic</th><th rowspan="2">All Patients (6 mg/kg AIBW Q3W) (N=706)</th><th rowspan="2">EOC (6 mg/kg AIBW Q3W) (N=682)</th><th colspan="2">Study 0416</th></tr>
<tr><th>MIRV (6 mg/kg AIBW Q3W) (N=218)</th><th>IC Chemo (N=207)</th></tr>
<tr><td>ECOG, n (%)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>0</td><td>385 (55)</td><td>380 (56)</td><td>128 (59)</td><td>113 (55)</td></tr>
<tr><td>1</td><td>321 (45)</td><td>302 (44)</td><td>90 (41)</td><td>91 (44)</td></tr>
<tr><td>2</td><td>0</td><td>0</td><td>0</td><td>3 (1)</td></tr>
</table>
Abbreviations: AIBW = adjusted ideal body weight; ECOG = Eastern Cooperative Oncology Group; EOC = epithelial ovarian cancer; IC Chemo = Investigator's choice/selected standard-of-care chemotherapy; MIRV = mirvetuximab soravtansine; Pac = paclitaxel; PLD = pegylated liposomal doxorubicin; QW = weekly; Q3W = every 3 weeks; Q4W = every 4 weeks; Topo = topotecan.
IC Chemo: Pac (80 mg/m^2 administered QW within a 4-week cycle); PLD (40 mg/m^2 administered Q4W); Topo (4 mg/m^2 administered either on Days 1, 8 or 15 of a 4 week cycle or for 5 consecutive days at 1.25 mg/m^2 Days 1-5 Q3W).
Data cut-off dates for studies IMGN853-0401: 10 Feb 2018; IMGN853-0403: 18 Mar 2020; IMGN853-0417: 22 Dec 2022; IMGN853-0416: 06 Mar 2023
Source data: 5.3.5.3 ISS, Table 2.1</td></tr>
<tr><td>Population with relevant different ethnic origin</td><td>In Study 0416, the ethnicity of the majority of patients treated with MIRV (N=218) were not Hispanic or Latino (77%); the other patients were Hispanic or Latino (6%) or classified as not reported (16%) or missing (1%) (Table 7). Similarly, in the EOC population (N=682), 87% of patients were not Hispanic or Latino, 4% were Hispanic or Latino, 9% were classified as not reported and < 1% as missing.</td></tr>
</table>

<table>
<tr><th>Type of Special Population</th><th>Exposure</th></tr>
<tr><td>Subpopulations carrying relevant genetic polymorphisms</td><td>Not included in the clinical development programme.</td></tr>
<tr><td>Subpopulations by tumour biomarker</td><td>
The study protocols defined the required FRα expression levels by Ventana FOLR1 (FOLR1-2.1) CDx assay, referred to as Ventana FOLR1 Assay, for enrolment in the studies.

FRα expression for the patients in the safety populations is presented in the table below. The different scoring methods for FRα positivity in each study is presented as a footnote to the table.

In Study 0416, an inclusion criterion was for the patient's tumour to be positive for FRα expression as defined by the Ventana FOLR1 (FOLR-2.1) CDx assay. FRα expression for patients in the safety populations is presented in the table below.

FRα expression (Safety Populations)
<table>
<tr><th rowspan="2">Characteristic</th><th rowspan="2">All Patients (6 mg/kg AIBW Q3W) (N=706)</th><th rowspan="2">EOC (6 mg/kg AIBW Q3W) (N=682)</th><th colspan="2">Study 0416</th></tr>
<tr><th>MIRV (6 mg/kg AIBW Q3W) (N=218)</th><th>IC Chemo (N=207)</th></tr>
<tr><td>FRα expression level per protocol[a], n (%)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>0-24%</td><td>1 (< 1)</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>25-49%</td><td>34 (5)</td><td>23 (3)</td><td>0</td><td>0</td></tr>
<tr><td>50-74%</td><td>133 (19)</td><td>130 (19)</td><td>0</td><td>0</td></tr>
<tr><td>≥ 75%</td><td>538 (76)</td><td>529 (78)</td><td>218 (100)</td><td>207 (100)</td></tr>
</table>
Abbreviations: AIBW = adjusted ideal body weight; EOC = epithelial ovarian cancer; FRα = folate receptor alpha; IC Chemo = Investigator's choice/selected standard-of-care chemotherapy; MIRV = mirvetuximab soravtansine; Pac = paclitaxel; PLD = pegylated liposomal doxorubicin; QW = weekly; Q3W = every 3 weeks; Q4W = every 4 weeks; Topo = topotecan.
IC Chemo: Pac (80 mg/m^2 administered QW within a 4-week cycle); PLD (40 mg/m^2 administered Q4W); Topo (4 mg/m^2 administered either on Days 1, 8 or 15 of a 4 week cycle or for 5 consecutive days at 1.25 mg/m^2 Days 1-5 Q3W).
[a] FRα positivity was based on the following: Study 0401: ≥ 25% cells stained at 2+ intensity; Study 0403: ≥ 50% of cells with any FRα membrane using the 10× scoring method, including a medium level of FRα (50%-74%) and high FRα (≥ 75%); Studies 0417 and 0416: ≥ 75% cells stained at 2+ intensity (PS2+ scoring method).
Data cut-off dates for studies IMGN853-0401: 10 Feb 2018; IMGN853-0403: 18 Mar 2020; IMGN853-0417: 22 Dec 2022; IMGN853-0416: 06 Mar 2023
Source data: 5.3.5.3 ISS Table 2.3; Module 2.7.4 Table 12

BRCA mutations for the patients in the safety populations is presented in the table below.
</td></tr>
</table>

<table>
<tr><th>Type of Special Population</th><th>Exposure</th></tr>
<tr><td></td><td>

BRCA mutations (Safety Populations)

<table>
<tr><th rowspan="2">Characteristic</th><th rowspan="2">All Patients (6 mg/kg AIBW Q3W) (N=706)</th><th rowspan="2">EOC (6 mg/kg AIBW Q3W) (N=682)</th><th colspan="2">Study 0416</th></tr>
<tr><th>MIRV (6 mg/kg AIBW Q3W) (N=218)</th><th>IC Chemo (N=207)</th></tr>
<tr><td>Any BRCA mutations, n (%)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>BRCA1 or BRCA2 positive</td><td>69 (10)</td><td>69 (10)</td><td>27 (12)</td><td>35 (17)</td></tr>
<tr><td>BRCA1 positive</td><td>55 (8)</td><td>55 (8)</td><td>23 (11)</td><td>28 (14)</td></tr>
<tr><td>BRCA2 positive</td><td>19 (3)</td><td>19 (3)</td><td>8 (4)</td><td>7 (3)</td></tr>
<tr><td>Negative/unknown</td><td>637 (90)</td><td>613 (90)</td><td>191 (88)</td><td>172 (83)</td></tr>
</table>

Abbreviations: AIBW = adjusted ideal body weight; BRCA = breast cancer susceptibility gene; EOC = epithelial ovarian cancer; IC Chemo = Investigator's choice/selected standard-of-care chemotherapy; MIRV = mirvetuximab soravtansine; Pac = paclitaxel; PLD = pegylated liposomal doxorubicin; QW = weekly; Q3W = every 3 weeks; Q4W = every 4 weeks; Topo = topotecan.
IC Chemo: Pac (80 mg/m^2 administered QW within a 4-week cycle); PLD (40 mg/m^2 administered Q4W); Topo (4 mg/m^2 administered either on Days 1, 8 or 15 of a 4 week cycle or for 5 consecutive days at 1.25 mg/m^2 Days 1-5 Q3W).
Data cut-off dates for studies IMGN853-0401: 10 Feb 2018; IMGN853-0403: 18 Mar 2020; IMGN853-0417: 22 Dec 2022; IMGN853-0416: 06 Mar 2023
Source data: 5.3.5.3 ISS Table 2.4

</td></tr>
</table>

PART II: MODULE SV POST-AUTHORISATION EXPERIENCE

SV.1 Post-Authorisation Exposure

On 22 March 2024, the FDA granted full approval to mirvetuximab soravtansine-gynx (brand name ELAHERE) for 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.

MIRV is not currently approved for marketing in any other country other than the US.

SV.1.1 Method Used to Calculate Exposure

Patient exposure was calculated based on the estimated number of vials per cycle per patient, in addition to the number of vials per order, the order size of each account and the duration between orders.

Based on an average AIBW for a female patient of 50 to 60 kg, it is estimated that each patient receives 3 to 4 vials every cycle and this equates to 4 to 5 vials over 4 weeks / 1 month, respectively.

Every shipping order per account and facility is reviewed to determine whether there is a consistent order size (e.g., 3 or 4 vials every 3 weeks is assumed to be for 1 patient) or an increase in order size (e.g., 6 or 8 vials over a similar period of 3 weeks is assumed to be for 2 patients).

SV.1.2 Exposure

Cumulatively in the commercial setting in the US, 717 patients have been exposed to ELAHERE as of 13 May 2023.

PART II: MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

There is no nonclinical or clinical evidence that MIRV has potential for drug abuse. Specific clinical studies evaluating abuse potential have not been conducted.

PART II: MODULE SVII IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- **Gastrointestinal toxicity**

In Study 0416, 153 of 218 patients (70%) treated with MIRV and 137 of 207 patients (66%) treated with IC Chemo experienced TEAEs pertaining to the Gastrointestinal Disorders system organ class (SOC) (5.3.5.3 ISS, Table 4.2.1.1). The most common (≥ 10%) gastrointestinal disorders TEAEs (by preferred term [PT]) in the MIRV arm were abdominal pain (66 patients; 30%), diarrhoea (64 patients; 29%), constipation (59 patients; 27%), nausea (58 patients; 27%), and vomiting (39 patients; 18%). In the IC Chemo arm, the most common (≥ 10%) gastrointestinal disorders TEAEs (PT) were nausea (60 patients; 29%), constipation (40 patients; 19%), vomiting (37 patients; 18%), diarrhoea (36 patients; 17%), abdominal pain (31 patients; 15%), and stomatitis (23 patients; 11%).

The majority of the TEAEs were considered related to MIRV treatment (110 patients; 50%); the most frequent treatment-related TEAEs were diarrhoea (54 patients; 25%), nausea (50 patients; 23%), constipation (32 patients; 15%), abdominal pain (27 patients; 12%), and vomiting (20 patients; 9%) (5.3.5.3 ISS, Table 4.7.1.1). Likewise, in the IC Chemo arm, the majority of the Gastrointestinal Disorder TEAEs were considered related to study treatment (93 patients; 45%); the most common treatment-related TEAEs in the IC Chemo arm were nausea (46 patients; 22%), diarrhoea and vomiting (both 24 patients; 12%), and constipation and stomatitis (both 22 patients; 11%).

The majority of Gastrointestinal Disorders TEAEs were of Grade 1 or Grade 2 severity in both groups; 28 patients (13%) in the MIRV arm and 31 patients (15%) in the IC Chemo arm experienced a ≥ Grade 3 TEAE pertaining to the Gastrointestinal Disorders SOC but only 4% and 4% experienced a ≥ Grade 3 TEAE considered related to study treatment, respectively (5.3.5.3 ISS, Table 4.8.1.1; 5.3.5.3 ISS, Table 4.9.1).

Gastrointestinal Disorder serious adverse events (SAEs) occurred in 25 patients (11%) treated with MIRV and 27 patients (13%) treated with IC Chemo (5.3.5.3 ISS, Table 4.11.1). The most frequent SAEs (> 1%) in the MIRV arm were abdominal pain (6 patients; 3%), intestinal obstruction (5 patients; 2%), and ascites and small intestinal obstruction (both 4 patients, 2%). In the IC Chemo arm, the most frequent SAEs were small intestinal obstruction (10 patients, 5%) and intestinal obstruction (4 patients, 2%). Treatment-related Gastrointestinal Disorder SAEs occurred in 7 patients (3%) treated with MIRV and in 2 patients (< 1%) treated with IC Chemo; abdominal pain (1%) was the only treatment-related SAE to occur in ≥ 1% patients in the MIRV arm (5.3.5.3 ISS, Table 4.11.2).

In the MIRV and IC Chemo arms, Gastrointestinal Disorder TEAEs led to dose reduction or dose delay in 15 patients (7%) and 13 patients (6%), respectively (5.3.5.3 ISS, Table 4.10.2).

Treatment discontinuation due to a Gastrointestinal Disorders TEAE only occurred in 3 patients (1%) in the MIRV arm, compared with 9 patients (4%) in the IC Chemo arm (5.3.5.3 ISS, Table 4.10.1). Two deaths in the MIRV arm were due to Gastrointestinal Disorder TEAEs (< 1%) including intestinal obstruction and subileus (1 patient each, < 1%) but neither was related to MIRV treatment; there were no deaths in the IC Chemo arm due to Gastrointestinal Disorders TEAEs (5.3.5.3 ISS, Table 4.10.3.1; 5.3.5.3 ISS, Table 4.7.1.1).

In the EOC population (N=682), 540 patients (79%) experienced TEAEs pertaining to the Gastrointestinal Disorders SOC (5.3.5.3 ISS, Table 4.2.1.1). The most common (≥ 10%) TEAEs were nausea (279 patients; 41%), diarrhoea (263 patients; 39%), abdominal pain (202 patients; 30%), constipation (175 patients; 26%), vomiting (159 patients; 23%), and abdominal distension (66 patients; 10%) (5.3.5.3 ISS, Table 4.2.1.1). The majority of the TEAEs were considered related to MIRV treatment (396 patients; 58%); the most frequent treatment related TEAEs were nausea (237 patients; 35%), diarrhoea (205 patients; 30%), vomiting (91 patients; 13%), abdominal pain (72 patients; 11%), and constipation (68 patients; 10%) (5.3.5.3 ISS, Table 4.7.1.1).

The majority of TEAEs were of Grade 1 or Grade 2 severity; 124 patients (18%) experienced a ≥ Grade 3 TEAE pertaining to the Gastrointestinal Disorders SOC but only 5% experienced a ≥ Grade 3 TEAE considered related to MIRV treatment (5.3.5.3 ISS, Table 4.8.1.1; 5.3.5.3 ISS, Table 4.9.1). The most frequent ≥ Grade 3 TEAEs included abdominal pain (25 patients; 4%), small intestinal obstruction (23 patients; 3%), vomiting (19 patients; 3%), diarrhoea (18 patients; 3%), intestinal obstruction (18 patients; 3%), ascites (15 patients; 2%), and nausea (14 patients; 2%) (5.3.5.3 ISS, Table 4.8.1.1). The ≥ Grade 3 Gastrointestinal Disorder TEAEs related to treatment occurring at ≥ 1% were diarrhoea (13 patients; 2%), nausea and vomiting (both 9 patients; 1%), and abdominal pain (7 patients; 1%) (5.3.5.3 ISS, Table 4.9.1).

Gastrointestinal Disorder SAEs occurred in 96 patients (14%) (5.3.5.3 ISS, Table 4.11.1). The most frequent SAEs (> 1%) were small intestinal obstruction (23 patients; 3%), intestinal obstruction (19 patients, 3%), and abdominal pain (13 patients; 2%). Treatment-related Gastrointestinal Disorder SAEs occurred much less frequently; occurring in 17 patients (2%) with no individual treatment-related SAE reported in ≥ 1% patients (5.3.5.3 ISS, Table 4.11.2).

Gastrointestinal Disorder TEAEs led to dose reduction or delay in 41 patients (6%) treated with MIRV and led to treatment discontinuation in 25 patients (4%); small intestinal obstruction, ascites, intestinal obstruction, and abdominal pain were the most common reasons for treatment discontinuation (5.3.5.3 ISS, Table 4.10.2; 5.3.5.3 ISS, Table 4.10.1).

Six deaths occurred due to TEAEs within the Gastrointestinal Disorders SOC (< 1%) which included intestinal obstruction (2 patients; < 1%) and single events of ascites, large intestinal obstruction, intestinal perforation, and subileus (1 patient each, < 1%) (5.3.5.3 ISS, Table 4.10.3.1); the events were likely due to disease progression.

Overall, patients in Study 0416 experienced less treatment related diarrhoea and nausea than patients in the EOC population (25% and 23% versus 30% and 35%, respectively), which is likely due to the recommended early implementation of symptom-directed treatment and prophylactic pre-medications, antiemetics and early use of antidiarrheals in this study. Related gastrointestinal disorders were mainly mild in severity. In Study 0416 there were no intestinal obstructions related to MIRV; intestinal obstruction can be attributed to disease progression. Gastrointestinal toxicity is not considered an important risk as it does not impact the benefit/risk balance of MIRV.

The risk of gastrointestinal toxicity will be minimised in clinical practice through the administration of oral or IV antiemetics before each dose to reduce the incidence and severity of nausea and vomiting. For patients experiencing nausea and/or vomiting, additional antiemetics may be considered thereafter as needed. In addition, early use of antidiarrheals may be used to minimise this AE. Healthcare professionals are advised in the ELAHERE SmPC that gastrointestinal disorder adverse reactions may occur with MIRV with similar guidance in the package leaflet (PL).

Gastrointestinal toxicity will continue to be monitored using routine pharmacovigilance activities.

- **Hepatotoxicity**

In a nonclinical study (CRT14-001), liver toxicity was found to be attributable to the DM4 payload (Module SII). A single IV administration of DM4 (0.1 mg/kg/dose) in cynomolgus monkey was associated with transient elevations in ALP values but with no correlating microscopic findings in the liver. Hepatotoxicity (increases in ALT, AST, ALP, GGT, and TBL) was also observed in the definitive rat study with DM1, a maytansinoid (microtubule inhibitor), with the same mechanism of action as DM4.

In Study 0416, the most common (≥ 2%) hepatic enzyme elevation TEAEs observed in patients treated with MIRV (N=218) include AST increased (24 patients; 11%), ALT increased (19 patients; 9%), blood ALP increased (9 patients; 4%), and GGT increased (7 patients; 3%) (5.3.5.3 ISS, Table 4.2.1.1). The majority of these TEAEs were of Grade 1 or Grade 2 severity; 1 patient (< 1%) had a ≥ Grade 3 AST increased and 1 patient (< 1%) had a ≥ Grade 3 ALT increased (5.3.5.3 ISS, Table 4.8.1.1). In patients treated with IC Chemo (N=207), the most common (≥ 3%) hepatic enzyme elevation TEAEs include AST increased and ALT increased (both 9 patients; 4%) and blood ALP increased (4 patients; 2%); none were of ≥ Grade 3 severity (5.3.5.3 ISS, Table 4.2.1.1; 5.3.5.3 ISS, Table 4.8.1.1).

Hepatic enzyme elevation TEAEs did not lead to dose reduction or dose delay or to treatment discontinuation in any patients treated with MIRV or IC Chemo (5.3.5.3 ISS, Table 4.10.2; 5.3.5.3 ISS, Table 4.10.1). There were no deaths in either arm due to hepatic enzyme elevation TEAEs (5.3.5.3 ISS, Table 4.10.3.1).

An evaluation of laboratory data found that in Study 0416 only 3 patients treated with MIRV had worst post-baseline values of Grade 3 for the following liver tests: 1 patient (0.5%) had Grade 3 ALT values, 1 patient (0.5%) had Grade 3 ALP values and 1 patient (0.5%) had Grade 3 TBL values (5.3.5.3 ISS, Table 5.1.5). No patients had post-baseline Grade 3 AST values or any Grade 4 liver function tests.

In the EOC population (N=682), the most common (≥ 5%) hepatic enzyme elevation TEAEs observed in patients treated with MIRV include AST increased (111 patients; 16%), ALT increased (90 patients; 13%), and blood ALP increased (46 patients; 7%) (5.3.5.3 ISS, Table 4.2.1.1). Most of these TEAEs were considered related to MIRV treatment; AST increased (89 patients; 13%), ALT increased (71 patients; 10%), and blood ALP increased (30 patients; 4%), (68 patients; 10%) (5.3.5.3 ISS, Table 4.7.1.1). The majority of TEAEs were of Grade 1 or 2 severity; ≥ Grade 3 TEAEs included GGT increased (8 patients; 1%), AST increased (8 patients; 1%), ALT increased (6 patients; < 1%), blood ALP increased (3 patients; < 1%), and transaminases increased (1 patient; < 1%) (5.3.5.3 ISS, Table 4.8.1.1). The ≥ Grade 3 hepatic enzyme elevation TEAEs related to treatment included GGT increased (7 patients; 1%), AST increased (6 patients; < 1%), ALT increased (5 patients; < 1%), blood ALP increased (2 patients;

< 1%), and transaminases increased (1 patient; < 1%) (5.3.5.3 ISS, Table 4.9.1). There were no hepatic enzyme elevation SAEs in patients treated with MIRV (5.3.5.3 ISS, Table 4.11.1).

There were very few hepatic enzyme elevation TEAEs that led to dose reduction or delay; ALT increased (6 patients; < 1%), AST increased (6 patients; < 1%), blood ALP increased (3 patients; < 1%), GGT increased (3 patients; < 1%), and transaminases increased (1 patient; < 1%) (5.3.5.3 ISS, Table 4.10.2). No hepatic enzyme elevation TEAEs led to treatment discontinuation (5.3.5.3 ISS, Table 4.10.1) or death (5.3.5.3 ISS, Table 4.10.3.1).

In the EOC population the laboratory data showed that 14 patients (2.1%) had Grade 3 ALT values, 9 patients (1.3%) had Grade 3 AST values, 5 patients (0.7%) had Grade 3 ALP values, and 3 patients (0.4%) had Grade 3 TBL values (5.3.5.3 ISS, Table 5.1.5). There were no post-baseline Grade 4 liver function tests.

Analysis of liver function test results did not find any patients with post-baseline concurrent ALT or AST > 3 × ULN and TBL ≥ 2 × ULN and ALP < 2 × ULN in either Study 0416 or the EOC population (5.3.5.3 ISS, Table 5.1.4). No patient met the Hy's Law criteria.

No clinically relevant changes were observed over time for mean liver function tests including parameters AST, ALT, or blood bilirubin parameters (Module 2.7.4, Section 3.3). Slight increases in values were seen at most of the treatment cycles.

Based on these data, hepatotoxicity is not considered an important risk as it does not impact the benefit/risk balance of MIRV.

The risk of hepatotoxicity will be minimised in clinical practice through advising healthcare professionals in the ELAHERE SmPC that elevations in hepatic enzymes may occur with MIRV with similar guidance in the PL. MIRV should be avoided in patients with moderate to severe hepatic impairment (TBL > 1.5 ULN with any AST) and no dose adjustment of MIRV is recommended for patients with mild hepatic impairment (TBL ≤ ULN and AST > ULN or TBL > 1 to 1.5 times ULN and any AST).

Hepatotoxicity will continue to be monitored using routine pharmacovigilance activities.

- **Immunogenicity**

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation against MIRV is highly dependent on the sensitivity and specificity of the assay. Two sensitive and specific electrochemiluminescence (ECL)-based assays were developed and validated for the detection of anti-drug antibody (ADAs) in human plasma samples containing sodium heparin (NaHep) and dipotassium ethylenediaminetetraacetic acid (K2EDTA), and an assay was validated for the detection of neutralising antibody (NAb) in human plasma.

During the clinical development programme, ADA responses were assessed in studies 0416, 0417, 0403, and 0401.

Among patients in the Study 0416 MIRV arm (N=218), a total of 213 patients had at least 1 sample tested; 209 patients had at least 1 baseline ADA sample tested, with 203 patients having at least 1 valid post-baseline ADA sample tested. Most patients (150 patients; 74%) were seronegative at screening (5.3.5.3 ISS, Table 5.3.1). A total of 24 patients (12%) developed treatment-emergent ADA, 3 patients (1%) experienced treatment-enhanced ADA (greater than baseline titre by 4-fold), and 26 patients (13%) experienced treatment-unaffected ADA (negative or not greater than baseline titre by 4-fold). A total of 10 patients experienced NAb.

In the EOC population (N=682), a total of 663 patients had at least 1 sample tested; 639 patients had at least 1 baseline ADA sample tested, with 626 patients having at least 1 valid post-baseline ADA sample tested (5.3.5.3 ISS, Table 5.3.1). Most patients (518 patients; 83%) were seronegative at screening. A total of 52 patients (8%) developed treatment-emergent ADA, 5 patients (< 1%) experienced treatment-enhanced ADA, and 51 patients (8%) experienced treatment-unaffected ADA. A total of 34 patients experienced NAb.

Overall, there was no apparent impact of ADAs identified on MIRV clearance or exposure based on patients with concurrent PK and positive immunogenicity data (5.3.5.3 ISI, Section 5). Due to the limited numbers in the groups analysed, differences between the antitumour activity data for the seropositive and seronegative patients could not be determined.

There were no significant differences identified in safety outcomes between seronegative and ADA-positive patients. In the EOC population (N=682), among the 626 patients with ADA evaluable samples, the percentage of patients with TEAEs ≥ Grade 3 was 47% for seronegative patients (241 of 518 patients), 54% for ADA positive patients categorised as treatment-emergent (28 of 52 patients), 20% for treatment-enhanced (1 of 5 patients), and 35% for treatment-unaffected (18 of 51 patients) (5.3.5.3 ISS, Table 5.3.2). The percentage of patients with ≥ Grade 3 SAEs was 24% for seronegative patients (123 of 518 patients), 25% for treatment-emergent (13 of 52 patients), 20% for treatment-enhanced (1 of 5 patients), and 8% for treatment-unaffected (4 of 51 patients) (5.3.5.3 ISS, Table 5.3.2).

TEAEs leading to dose reduction were similar between seronegative and ADA-positive patients; seronegative patients (142 of 518 patients; 27%), ADA positive patients categorised as treatment-emergent (10 of 52 patients; 19%), treatment-enhanced (1 of 5 patients; 20%), or treatment-unaffected (14 of 51 patients; 27%) (5.3.5.3 ISS, Table 5.3.2). There were more patients with treatment-enhanced ADA who had a TEAE leading to dose delay (3 of 5 patients; 60%) than the other 3 groups (ranging from 38% to 42%) but numbers are limited in this group (5.3.5.3 ISS, Table 5.3.2).

A greater percentage of patients with treatment-emergent ADA had TEAEs that led to study drug discontinuation (12 of 52 patients; 23%) compared to seronegative patients (60 of 518 patients; 12%) (5.3.5.3 ISS, Table 5.3.2). There were no TEAEs that led to study drug discontinuation reported for patients with treatment-enhanced ADA and only 1 patient (2%) with treatment-unaffected ADA who had a TEAE that led to study drug discontinuation. TEAEs ≥ Grade 3 that led to study drug discontinuation and considered related to study treatment were slightly higher in patients with treatment-emergent ADA (3 of 52 patients; 6%) compared to seronegative patients (16 of 518 patients; 3%). There were no specific TEAEs identified that accounted for the higher percentage of discontinuations among patients with treatment-emergent ADAs. The increase compared to seronegative patients should be interpreted with caution due to the small number of patients with treatment-emergent ADAs.

Using the standardised Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ) infusion-related reactions (IRRs) (hypersensitivity AE that occurred within 3 days of dosing and match SMQ Hypersensitivity narrow and PTs flushing, erythema, and erythema of eyelid), IRRs occurred in greater percentages of patients with treatment-emergent ADA (13 of 52 patients; 25%) and with treatment-enhanced ADA (2 of 5 patients; 40%) compared to seronegative patients (38 of 518 patients; 7%), and treatment-unaffected (3 of 51 patients; 6%) ADA patients (5.3.5.3 ISS, Table 5.3.2). Of the 13 patients with treatment-emergent ADAs who reported IRRs: 1 discontinued treatment due to drug hypersensitivity, and 12 had acute IRR, 2 of which met the criteria for an SAE leading to discontinuation (5.3.5.3 ISI, Section 4.2.13). These TEAEs

resolved following study drug discontinuation, indicating a manageable safety profile. Deaths due to TEAEs occurred in 6 seronegative patients (1%) (2 related to treatment) and in 1 patient (2%) with treatment-emergent ADA (not related to treatment) (5.3.5.3 ISS, Table 5.3.2).

In summary, there was no apparent impact of ADAs identified on MIRV clearance or exposure. Due to the limited numbers in the groups analysed, differences between the antitumour activity data for the seropositive and seronegative patients could not be determined. In patients with treatment-emergent ADA, there is the potential for a small increase in IRRs but these are manageable. The incidence of NAb was low; therefore, the impact of NAb on safety or efficacy could not be established. Based on the low frequency of ADA in the study population and the low potential for impact of ADA on MIRV efficacy and safety, immunogenicity is not considered to be an important risk.

The risk of immunogenicity will be minimised in clinical practice through increasing healthcare professional awareness via the ELAHERE SmPC that ADA were commonly detected and that no evidence of ADA impact on the PK, efficacy, or safety was observed, however, data are still limited. Furthermore, the risk of IRRs will be minimised through the use of pre-medications (corticosteroids, antihistamines, and antipyretics) to reduce the incidence and severity of IRRs. For patients who experience an IRR Grade ≥ 2, additional pre-medication with dexamethasone 8 mg two times a day (BID) (or equivalent) the day before MIRV administration should be considered.

Immunogenicity will continue to be monitored using routine pharmacovigilance activities.

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

- None

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorised):

- **Pneumonitis**

MIRV is an ADC; some but not all ADCs are recognised to cause pneumonitis (Yong 2022; Zhu 2023). The exact mechanism by which ADCs causes pneumonitis is unknown. Pneumonitis or drug-induced ILD is one of the foremost causes of treatment-related AEs and mortality in patients receiving ADCs, with an incidence range of 1% to 15.8% (Yong 2022). A systematic review and meta-analysis of ADCs in 169 clinical studies, found that respiratory diseases (pneumonitis, 12.4% incidence) were the most common cause of treatment-related death in patients treated with ADCs (Zhu 2023).

Pneumonitis was designated as an AESI in Study 0403 to gain additional information (reports of radiographic imaging) on this event based on the lower grade events of non-infectious pneumonitis observed in Study 0401. Review of the pneumonitis AESI information from Study 0403, demonstrating that the majority of pneumonitis events (88%) were ≤ Grade 2 in

severity with no Grade 4 or 5 pneumonitis events, led to the decision to remove the AESI designation for pneumonitis in Study 0417 and Study 0416.

Patients with a previous clinical diagnosis of non-infectious ILD including non-infectious pneumonitis were excluded from participation in Study 0416 (Module SIV.1). To ensure patient safety in Study 0416, any treatment-emergent pneumonitis must have recovered to ≤ Grade 1 prior to patients receiving any additional doses of MIRV.

Pneumonitis grouped term includes the PTs pneumonitis, interstitial lung disease, pulmonary fibrosis, respiratory failure, and organising pneumonia.

In Study 0416, 27 pneumonitis TEAEs (grouped term) occurred in 21 of 218 patients (10%) treated with MIRV and 2 pneumonitis TEAEs occurred in 1 of 207 patients (< 1%) treated with IC Chemo (5.3.5.3 ISS, Table 4.13.1). The most frequently reported PT in the MIRV arm was pneumonitis that occurred in 15 patients (7%); pneumonitis occurred in 1 patient (< 1%) in the IC Chemo arm (Table 9).

Two patients had pneumonitis TEAEs ≥ Grade 3 severity in the MIRV arm (1 patient had Grade 3 respiratory failure and 1 patient had Grade 5 respiratory failure; both not related to treatment) (Table 9; 5.3.5.3 ISS, Table 4.9.1). The pneumonitis TEAE in the IC Chemo arm was of Grade 2 severity (5.3.5.3 ISS, Table 4.13.1).

Table 9: Pneumonitis TEAEs by Preferred Term and Maximum Grade (All Patients, EOC population and Study 0416)

Preferred Term	All Patients (6 mg/kg AIBW Q3W) (N=706)	EOC (6 mg/kg AIBW Q3W) (N=682)	0416	
			MIRV (6 mg/kg AIBW Q3W) (N=218)	IC Chemo (N=207)
Patients with any pneumonitis TEAEs, n (%)				
All grades	75 (11)	70 (10)	21 (10)	1 (< 1)
Grade ≥ 3	11 (2)	9 (1)	2 (< 1)	0
Pneumonitis, n (%)				
All grades	62 (9)	59 (9)	15 (7)	1 (< 1)
Grade ≥ 3	5 (< 1)	5 (< 1)	0	0
Interstitial lung disease, n (%)				
All grades	5 (< 1)	5 (< 1)	3 (1)	0
Grade ≥ 3	0	0	0	0
Organising pneumonia, n (%)				
All grades	4 (< 1)	4 (< 1)	1 (< 1)	0
Grade ≥ 3	1 (< 1)	1 (< 1)	0	0
Respiratory failure, n (%)				
All grades	5 (< 1)	3 (< 1)	2 (< 1)	0
Grade ≥ 3	5 (< 1)	3 (< 1)	2 (< 1)	0
Pulmonary fibrosis, n (%)				
All grades	2 (< 1)	2 (< 1)	0	0
Grade ≥ 3	0	0	0	0

Abbreviations: AIBW = adjusted ideal body weight; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic case report form; EOC = epithelial ovarian cancer; IC Chemo = Investigator's choice/selected standard-of-care chemotherapy; MedDRA = Medical Dictionary for Regulatory Activities; MIRV = mirvetuximab soravtansine; Pac = paclitaxel; PLD = pegylated liposomal doxorubicin; QW = weekly; Q3W = every 3 weeks; Q4W = every 4 weeks; TEAE = treatment-emergent adverse event; Topo = topotecan.
IC Chemo: Pac (80 mg/m^2 administered QW within a 4-week cycle); PLD (40 mg/m^2 administered Q4W); Topo (4 mg/m^2 administered either on Days 1, 8 or 15 of a 4 week cycle or for 5 consecutive days at 1.25 mg/m^2 Days 1-5 Q3W).
Coding was performed using MedDRA 24.0 and CTCAE version 5.0.
Note: TEAEs are defined as adverse events with an onset date on or after the first dose of study drug, and within 30 days of the last dose of study drug or prior to the start of a new anti-cancer treatment, whichever occurs first.
Note: When counting events, each event is counted once for each adverse event entered into the eCRF. For the remaining frequencies, each patient is counted once, with the worst grade for each preferred term.
Note: Pneumonitis TEAEs are defined as TEAEs with the following preferred terms: 'Pneumonitis', 'Interstitial lung disease', 'Pulmonary fibrosis', 'Respiratory failure', 'Organising pneumonia'.
Data cut-off dates for studies IMGN853-0401: 10 Feb 2018; IMGN853-0403: 18 Mar 2020; IMGN853-0417: 22 Dec 2022; IMGN853-0416: 06 Mar 2023
Source data: 5.3.5.3 ISS, Table 4.13.1

The median time to first onset was 21 weeks (range: 3.1 to 49.1 weeks) for the pneumonitis TEAEs in 21 patients treated with MIRV and the time to onset was 6 weeks for the 1 patient who had a pneumonitis TEAE in the IC Chemo arm (Table 10).

In the MIRV arm the actions taken for the pneumonitis TEAEs were dose delayed (10 patients; 5%), drug permanently discontinued (4 patients; 2%), and dose reduced and dose not given (both 2 patients; < 1%) (Table 10). In the IC Chemo arm, 1 patient had a pneumonitis TEAE (< 1%), and the only action taken (and reported worst outcome) was dose not given (< 1%). The reported worst outcomes in the MIRV arm were dose delayed or not given (9 patients; 4%), drug permanently discontinued (4 patients, 2%), and dose reduced (1 patient; < 1%). No action was taken in 7 patients (3%).

Table 10: Time to First Onset and Action Taken for Pneumonitis TEAEs (All Patients, EOC population and Study 0416)

Preferred Term	All Patients (6 mg/kg AIBW Q3W) (N=706)	EOC (6 mg/kg AIBW Q3W) (N=682)	0416	
			MIRV (6 mg/kg AIBW Q3W) (N=218)	IC Chemo (N=207)
Time to first onset of pneumonitis TEAEs (weeks)				
N	75	70	21	1
Mean (SD)	20.09 (17.058)	20.89 (17.352)	21.37 (14.424)	6.00 (--)
Median	17.14	18.07	21.00	6.00
Min, Max	1.6, 97.0	1.6, 97.0	3.1, 49.1	6.0, 6.0
Action taken, n (%) [a]				
Drug permanently discontinued	19 (3)	18 (3)	4 (2)	0
Dose reduced	8 (1)	8 (1)	2 (< 1)	0
Infusion interrupted	2 (< 1)	2 (< 1)	0	0
Dose delayed/ not given	29 (4)	29 (4)	12 (6)	1 (< 1)
Dose delayed	23 (3)	23 (3)	10 (5)	0

Preferred Term	All Patients (6 mg/kg AIBW Q3W) (N=706)	EOC (6 mg/kg AIBW Q3W) (N=682)	0416	
			MIRV (6 mg/kg AIBW Q3W) (N=218)	IC Chemo (N=207)
Dose not given	6 (< 1)	6 (< 1)	2 (< 1)	1 (< 1)
Worst outcome, n (%) [b]				
Drug permanently discontinued	19 (3)	18 (3)	4 (2)	0
Dose reduced	5 (< 1)	5 (< 1)	1 (< 1)	0
Infusion interrupted	1 (< 1)	1 (< 1)	0	0
Dose delayed/ not given	18 (3)	18 (3)	9 (4)	1 (< 1)
No action taken	32 (5)	28 (4)	7 (3)	0

Abbreviations: AIBW = adjusted ideal body weight; EOC = epithelial ovarian cancer; IC Chemo = Investigator's choice/selected standard-of-care chemotherapy; max = maximum; min = minimum; MIRV = mirvetuximab soravtansine; Pac = paclitaxel; PLD = pegylated liposomal doxorubicin; QW = weekly; Q3W = every 3 weeks; Q4W = every 4 weeks; SD = standard deviation; TEAE = treatment-emergent adverse event; Topo = topotecan.
IC Chemo: Pac (80 mg/m^2 administered QW within a 4-week cycle); PLD (40 mg/m^2 administered Q4W); Topo (4 mg/m^2 administered either on Days 1, 8 or 15 of a 4 week cycle or for 5 consecutive days at 1.25 mg/m^2 Days 1-5 Q3W).
[a] A patient could have multiple actions taken.
[b] A patient was counted once based on the worst outcome. The order of the worst outcome chosen was 'Dose Permanently Discontinued', 'Dose Reduced', 'Infusion Interrupted', 'Dose Delayed/Not Given' and 'No Action Taken'.
Note: TEAEs are defined as adverse events with an onset date on or after the first dose of study drug, and within 30 days of the last dose of study drug or prior to the start of a new anti-cancer treatment, whichever occurs first.
Note: Pneumonitis TEAEs are defined as TEAEs with the following preferred terms: 'Pneumonitis', 'Interstitial lung disease', 'Pulmonary fibrosis', 'Respiratory failure', 'Organising pneumonia'.
Data cut-off dates for studies IMGN853-0401: 10 Feb 2018; IMGN853-0403: 18 Mar 2020; IMGN853-0417: 22 Dec 2022; IMGN853-0416: 06 Mar 2023
Source data: 5.3.5.3 ISS, Table 4.13.2

In the EOC population (N=682), 70 patients (10%) treated with MIRV had 103 pneumonitis TEAEs (grouped term) (5.3.5.3 ISS, Table 4.13.1). The most frequently reported PT was pneumonitis (59 patients; 9%), followed by interstitial lung disease (5 patients; < 1%), organising pneumonia (4 patients; < 1%), respiratory failure (3 patients; < 1%), and pulmonary fibrosis (2 patients; < 1%) (Table 9). The majority of pneumonitis TEAEs were of Grade 1 or 2 severity, only 9 patients (1%) experienced a ≥ Grade 3 TEAE of which 1 patient had Grade 4 organising pneumonia and 2 patients had Grade 5 respiratory failures (5.3.5.3 ISS, Table 4.13.1).

The median time to first onset was 18.07 weeks (range: 1.6 to 97.0 weeks) for the pneumonitis TEAEs in 70 patients in the EOC population (Table 10).

The actions taken for the pneumonitis TEAEs were dose delayed (23 patients; 33%), drug permanently discontinued (18 patients; 3%), dose reduced (8 patients; 1%), and dose not given (6 patients; < 1%) (Table 10). The reported worst outcomes were drug permanently discontinued (18 patients, 3%), dose delayed or not given (18 patients; 3%), dose reduced (5 patients; < 1%), and infusion interrupted (1 patient; < 1%). No action was taken in 28 patients (4%).

Pneumonitis can be life-threatening, but as it has been characterised in the clinical development programme it is not considered an important risk in the risk management plan (RMP).

The risk of pneumonitis will be minimised in clinical practice through increased healthcare professional awareness, patient monitoring and early detection and treatment. The ELAHERE SmPC warns healthcare professionals that severe, life-threatening, or fatal ILD, including pneumonitis, can occur in patients treated with MIRV. Patients should be monitored for pulmonary signs and symptoms of pneumonitis, which may include hypoxia, cough, dyspnoea, or interstitial infiltrates on radiologic exams. Infectious, neoplastic, or other causes for any symptoms of pneumonitis should be excluded through appropriate investigations. MIRV treatment should be withheld for patients who develop persistent or recurrent Grade 2 pneumonitis until symptoms resolve to ≤ Grade 1 and dose reduction should be considered. MIRV should be permanently discontinued in all patients with Grade 3 or 4 pneumonitis. Patients who are asymptomatic may continue dosing of MIRV with close monitoring.

Pneumonitis will continue to be monitored using routine pharmacovigilance activities.

- **Peripheral neuropathy**

Peripheral neuropathy is a known AE associated with cytotoxic agents that target tubulin. It has been reported with anti-tubulin chemotherapies (e.g., paclitaxel and docetaxel) as well as with ADCs containing tubulin-directed payloads (e.g., auristatins and maytansines). As DM4, the cytotoxic payload in MIRV, is a maytansinoid payload with anti-tubulin activity, special attention was paid to peripheral neuropathy in clinical development. (Zhu 2023; Masters 2018). A meta-analysis of 70 publications summarising the key clinical safety data for ADCs by payload, found a low Grade 3 or 4 toxicity rate for peripheral neuropathy across all ADCs (Masters 2018). In this study, the most frequent incidence of Grade 3/4 peripheral neuropathy was in ADCs with a monomethyl auristatin E (MMAE) payload (6.5%), followed by the DM4 payload (2.1%), the DM1 payload (0.3%), and the monomethyl auristatin F (MMAF) payload (0); all of which are anti-tubulins (Masters 2018).

The mechanism behind peripheral neuropathy is hypothesised to be peripheral axonopathy induced by free payload released in the systemic circulation (Nguyen 2023; Guffroy 2018). This mechanism may explain the preferential effects on sensory nerves due to the longer projections of axons in those nerves, making them more susceptible to neurotoxic effects (Guffroy 2018). Even though peripheral neurons are not actively proliferating, a functional microtubule is critical for protein transport from the cell body to the distal synapses and therefore, the disruption of microtubules by tubulin-inhibiting payloads may result in peripheral neuropathy.

Patients with > Grade 1 peripheral neuropathy per CTCAE v5.0 were excluded from participation in Study 0416 (Module SIV.1), but patients with ≤ Grade 1 peripheral neuropathy were allowed to enrol and participate in Studies 0401, 0403, 0417, and pivotal Study 0416.

Peripheral neuropathy grouped term includes the PTs neuropathy peripheral, peripheral sensory neuropathy, peripheral motor neuropathy, paraesthesia, hypoaesthesia, neurotoxicity, polyneuropathy, and peripheral sensorimotor neuropathy.

In Study 0416, 132 peripheral neuropathy TEAEs (grouped term) occurred in 81 of 218 (37%) patients treated with MIRV and 91 peripheral neuropathy TEAEs (grouped term) occurred in 47 of 207 (23%) patients treated with IC Chemo (5.3.5.3 ISS, Table 4.14.1). In the MIRV arm, the most frequently reported PTs (≥ 3%) were neuropathy peripheral (47 patients; 22%), peripheral sensory neuropathy (20 patients; 9%), and paraesthesia (11 patients; 5%) (Table 11). In the IC Chemo arm, the most frequently reported PTs (≥ 3%) were neuropathy peripheral and peripheral sensory neuropathy that occurred in 30 patients (14%) and 12 patients (6%), respectively.

The majority of peripheral neuropathy TEAEs in both the MIRV and IC Chemo arms were of Grade 1 or 2 severity, and only 4% of patients in each arm had a ≥ Grade 3 peripheral neuropathy TEAE (Table 11). No Grade 4 or Grade 5 TEAEs were observed in either treatment arm (5.3.5.3 ISS, Table 4.14.1).

In the IC Chemo arm, 82 patients received Pac, 76 received PLD and 49 received Topo. The peripheral neuropathy TEAEs in the IC Chemo arm were driven by Pac (38 patients; 46%), with fewer patients treated with PLD (8 patients; 11%) or Topo (1 patient; 2%) reporting peripheral neuropathy TEAEs (Clinical Study Report [CSR] 0416, Table 50). This was expected as Pac is recognised to cause peripheral neuropathy, based on its anti-tubulin mechanism of action (Paclitaxel SmPC).

Table 11: Peripheral Neuropathy TEAEs by Preferred Term and Maximum Grade (All Patients, EOC population and Study 0416)

Preferred Term	All Patients (6 mg/kg AIBW Q3W) (N=706)	EOC (6 mg/kg AIBW Q3W) (N=682)	0416	
			MIRV (6 mg/kg AIBW Q3W) (N=218)	IC Chemo (N=207)
Patients with any Peripheral Neuropathy TEAEs, n (%)				
All grades	254 (36)	248 (36)	81 (37)	47 (23)
Grade ≥ 3	21 (3)	18 (3)	8 (4)	8 (4)
Neuropathy peripheral, n (%)				
All grades	136 (19)	134 (20)	47 (22)	30 (14)
Grade ≥ 3	7 (< 1)	7 (1)	3 (1)	4 (2)
Peripheral sensory neuropathy, n (%)				
All grades	63 (9)	62 (9)	20 (9)	12 (6)
Grade ≥ 3	7 (< 1)	7 (1)	2 (< 1)	2 (< 1)
Paraesthesia, n (%)				
All grades	40 (6)	40 (6)	11 (5)	1 (< 1)
Grade ≥ 3	0	0	0	0
Neurotoxicity, n (%)				
All grades	19 (3)	19 (3)	5 (2)	5 (2)
Grade ≥ 3	1 (< 1)	1 (< 1)	1 (< 1)	2 (< 1)
Hypoaesthesia, n (%)				
All grades	8 (1)	8 (1)	1 (< 1)	0
Grade ≥ 3	0	0	0	0
Peripheral motor neuropathy, n (%)				
All grades	9 (1)	6 (< 1)	0	2 (< 1)
Grade ≥ 3	4 (< 1)	1 (< 1)	0	0
Polyneuropathy, n (%)				
All grades	2 (< 1)	2 (< 1)	1 (< 1)	0
Grade ≥ 3	1 (< 1)	1 (< 1)	1 (< 1)	0
Peripheral sensorimotor neuropathy, n (%)				

Preferred Term	All Patients (6 mg/kg AIBW Q3W) (N=706)	EOC (6 mg/kg AIBW Q3W) (N=682)	0416	
			MIRV (6 mg/kg AIBW Q3W) (N=218)	IC Chemo (N=207)
All grades	1 (< 1)	1 (< 1)	1 (< 1)	0
Grade ≥ 3	1 (< 1)	1 (< 1)	1 (< 1)	0

Abbreviations: AIBW = adjusted ideal body weight; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic case report form; EOC = epithelial ovarian cancer; IC Chemo = Investigator's choice/selected standard-of-care chemotherapy; MedDRA = Medical Dictionary for Regulatory Activities; MIRV = mirvetuximab soravtansine; Pac = paclitaxel; PLD = pegylated liposomal doxorubicin; QW = weekly; Q3W = every 3 weeks; Q4W = every 4 weeks; TEAE = treatment-emergent adverse event; Topo = topotecan.
IC Chemo: Pac (80 mg/m^2 administered QW within a 4-week cycle); PLD (40 mg/m^2 administered Q4W); Topo (4 mg/m^2 administered either on Days 1, 8 or 15 of a 4 week cycle or for 5 consecutive days at 1.25 mg/m^2 Days 1-5 Q3W).
Coding was performed using MedDRA 24.0 and CTCAE version 5.0.
Note: TEAEs are defined as adverse events with an onset date on or after the first dose of study drug, and within 30 days of the last dose of study drug or prior to the start of a new anti-cancer treatment, whichever occurs first.
Note: When counting events, each event is counted once for each adverse event entered into the eCRF. For the remaining frequencies, each patient is counted once, with the worst grade for each preferred term.
Note: Peripheral Neuropathy TEAEs are defined as TEAEs with the following preferred terms: 'Neuropathy peripheral', 'Peripheral sensory neuropathy', 'Peripheral motor neuropathy', 'Paraesthesia', 'Hypoaesthesia', 'Neurotoxicity', 'Polyneuropathy' and 'Peripheral sensorimotor neuropathy'.
Data cut-off dates for studies IMGN853-0401: 10 Feb 2018; IMGN853-0403: 18 Mar 2020; IMGN853-0417: 22 Dec 2022; IMGN853-0416: 06 Mar 2023
Source data: 5.3.5.3 ISS, Table 4.14.1

The median time to first onset for the peripheral neuropathy TEAEs was 5.86 weeks (range: 0.1 to 52.1 weeks) in the MIRV arm and 7.29 weeks (range: 0.1 to 28.4 weeks) in the IC Chemo arm (Table 12).

In the MIRV arm the actions taken for the peripheral neuropathy TEAEs included dose reduced (14 patients; 6%), dose delayed (5 patients; 2%), dose not given (4 patients; 2%), and drug permanently discontinued (3 patients; 1%) (Table 12). The reported worst outcomes were dose reduced (13 patients; 6%), drug permanently discontinued (3 patients; 1%), and dose delayed or not given (1 patient; < 1%). No action was taken in 29% of those patients with a reported peripheral neuropathy TEAE.

In the IC Chemo arm, the actions taken for the peripheral neuropathy TEAEs included dose reduced (17 patients; 8%), dose not given (12 patients; 6%), drug permanently discontinued (5 patients; 2%), and dose delayed (3 patients; 1%) (Table 12). The reported worst outcomes were dose reduced (14 patients; 7%), dose delayed or not given (5 patients; 2%), and drug permanently discontinued (5 patients, 2%); no action was taken in 23 patients (11%).

Overall, the peripheral neuropathy TEAEs in the 81 patients treated with MIRV completely resolved in 13 patients (16%) and partially improved in 8 patients (10%) (5.3.5.3 ISS, Table 4.14.3.1). There was no documented improvement in 60 patients (74%); these patients were reported to have Grade 1 (37 patients; 46%), Grade 2 (22 patients; 27%), and Grade 3 (1 patient; 1%) peripheral neuropathy TEAEs at the final assessment. In the IC Chemo arm, the peripheral neuropathy TEAEs in 47 patients completely resolved in 10 patients (21%) and partially improved in 7 patients (15%). There was no documented improvement in 30 patients

(64%); these patients were reported to have Grade 1 (18 patients; 38%), Grade 2 (9 patients; 19%), and Grade 3 (3 patients; 6%) peripheral neuropathy TEAEs at the final assessment.

Table 12: Time to First Onset and Action Taken for Peripheral Neuropathy TEAEs (All Patients, EOC population and Study 0416)

Preferred Term	All Patients (6 mg/kg AIBW Q3W) (N=706)	EOC (6 mg/kg AIBW Q3W) (N=682)	0416	
			MIRV (6 mg/kg AIBW Q3W) (N=218)	IC Chemo (N=207)
Time to first onset of peripheral neuropathy TEAEs (weeks)				
n	254	248	81	47
Mean (SD)	9.53 (14.189)	9.68 (14.326)	7.50 (7.625)	8.45 (6.281)
Median	5.86	5.86	5.86	7.29
Min, Max	0.1, 126.7	0.1, 126.7	0.1, 52.1	0.1, 28.4
Action taken, n (%) [a]				
Drug permanently discontinued	6 (< 1)	5 (< 1)	3 (1)	5 (2)
Dose reduced	29 (4)	29 (4)	14 (6)	17 (8)
Infusion interrupted	0	0	0	0
Dose delayed/ not given	22 (3)	21 (3)	8 (4)	13 (6)
Dose delayed	18 (3)	17 (2)	5 (2)	3 (1)
Dose not given	6 (< 1)	6 (< 1)	4 (2)	12 (6)
Worst outcome, n (%) [b]				
Drug permanently discontinued	6 (< 1)	5 (< 1)	3 (1)	5 (2)
Dose reduced	28 (4)	28 (4)	13 (6)	14 (7)
Infusion interrupted	0	0	0	0
Dose delayed/not given	6 (< 1)	5 (< 1)	1 (< 1)	5 (2)
No action taken	214 (30)	210 (31)	64 (29)	23 (11)

Abbreviations: AIBW = adjusted ideal body weight; EOC = epithelial ovarian cancer; IC Chemo = Investigator's choice/selected standard-of-care chemotherapy; max = maximum; min = minimum; MIRV = mirvetuximab soravtansine; Pac = paclitaxel; PLD = pegylated liposomal doxorubicin; QW = weekly; Q3W = every 3 weeks; Q4W = every 4 weeks; SD = standard deviation; TEAE = treatment-emergent adverse event; Topo = topotecan.
IC Chemo: Pac (80 mg/m^2 administered QW within a 4-week cycle); PLD (40 mg/m^2 administered Q4W); Topo (4 mg/m^2 administered either on Days 1, 8 or 15 of a 4 week cycle or for 5 consecutive days at 1.25 mg/m^2 Days 1-5 Q3W).
[a] A patient could have multiple actions taken.
[b] A patient was counted once based on the worst outcome. The order of the worst outcome chosen was 'Dose Permanently Discontinued', 'Dose Reduced', 'Infusion Interrupted', 'Dose Delayed/Not Given' and 'No Action Taken'.
Note: TEAEs are defined as adverse events with an onset date on or after the first dose of study drug, and within 30 days of the last dose of study drug or prior to the start of a new anti-cancer treatment, whichever occurs first.
Note: Peripheral Neuropathy TEAEs are defined as TEAEs with the following preferred terms: 'Neuropathy peripheral', 'Peripheral sensory neuropathy', 'Peripheral motor neuropathy', 'Paraesthesia', 'Hypoaesthesia', 'Neurotoxicity', 'Polyneuropathy' and 'Peripheral sensorimotor neuropathy'.
Data cut-off dates for studies IMGN853-0401: 10 Feb 2018; IMGN853-0403: 18 Mar 2020; IMGN853-0417: 22 Dec 2022; IMGN853-0416: 06 Mar 2023
Source data: 5.3.5.3 ISS, Table 4.14.2

In the EOC population (N=682), 404 peripheral neuropathy TEAEs (grouped term) occurred in 248 (36%) patients treated with MIRV (5.3.5.3 ISS, Table 4.14.1). The majority of neuropathy peripheral TEAEs were of Grade 1 or 2 severity, 18 patients (3%) experienced a ≥ Grade 3 TEAE (Table 11). No Grade 4 or 5 peripheral neuropathy events were reported (5.3.5.3 ISS, Table 4.14.1). The most frequently reported PTs (≥ 3%) were neuropathy peripheral (134 patients; 20%), peripheral sensory neuropathy (62 patients; 9%), paraesthesia (40 patients; 6%), and neurotoxicity (19 patients; 3%) (Table 11).

The median time to first onset was 5.86 weeks (range: 0.1 to 126.7 weeks) for peripheral neuropathy TEAEs in 248 patients in the EOC population (Table 12).

The actions taken for the peripheral neuropathy TEAEs were dose reduced (29 patients; 4%), dose delayed (17 patients; 2%), dose not given (6 patients; < 1%), and drug permanently discontinued (5 patients; < 1%) (Table 12). The reported worst outcomes were dose reduced (28 patients; 4%), dose delayed or not given (5 patients; < 1%), and drug permanently discontinued (5 patients, < 1%). In the majority of patients, no action was taken (210 patients; 31%).

Overall, the peripheral neuropathy TEAEs in 248 patients treated with MIRV completely resolved in 58 patients (23%) and partially improved in 30 patients (12%) (5.3.5.3 ISS, Table 4.14.3.1). Where there was no documented improvement in 160 patients (65%); these patients were reported to have Grade 1 (103 patients; 42%), Grade 2 (54 patients; 22%), and Grade 3 (3 patients; 1%) peripheral neuropathy TEAEs at the final assessment.

The risk of peripheral neuropathy will be minimised in clinical practice through increased healthcare professional awareness, dose modifications, patient monitoring and early detection and treatment. The ELAHERE SmPC warns healthcare professionals that peripheral neuropathy has occurred with MIRV, including Grade ≥ 3 reactions. Patients should be monitored for signs and symptoms of neuropathy, such as paraesthesia, tingling or a burning sensation, neuropathic pain, muscle weakness, or dysesthesia. For patients experiencing new or worsening peripheral neuropathy, the MIRV dose should be withheld, reduced, or permanently discontinued based on the severity of peripheral neuropathy.

Healthcare professionals are advised that MIRV has moderate influence on the ability to drive and use machines. If patients experience peripheral neuropathy during treatment with MIRV, they should be instructed not to drive or use machines until complete resolution of symptoms is confirmed.

Peripheral neuropathy will continue to be monitored using routine pharmacovigilance activities.

- **Embryo-foetal toxicity**

There are no available human data on MIRV use in pregnant patients (Module SIV.1).

No reproductive or developmental animal toxicity studies were conducted with MIRV (Module SII). However, the DM4 component of MIRV can be expected to cause embryo-foetal harm when administered to a pregnant patient as MIRV targets actively dividing cells suggesting it has the potential to cause embryotoxicity and teratogenicity. In addition, human IgG are known to cross the placenta barrier; therefore, MIRV has the potential to be transmitted from the pregnant person to the developing foetus.

While MIRV can potentially cause toxicity to the foetus, embryo-foetal toxicity is not an important risk because it is not expected to be further characterised during the post-marketing period and the risk can be minimised by adhering to the SmPC guidance.

The ELAHERE SmPC warns healthcare professionals that based on its mechanism of action, MIRV can cause embryo-foetal harm when administered to a pregnant patient because it contains a genotoxic compound (DM4) and affects actively dividing cells. Human IgG is known to cross the placental barrier; therefore, MIRV has the potential to be transmitted from the pregnant patient to the developing foetus. Healthcare professionals are advised that there are no available human data on MIRV use in pregnant patients to inform a drug-associated risk and that no reproductive or developmental animal toxicity studies were conducted with MIRV.

Healthcare professionals are advised that MIRV is not recommended during pregnancy. Patients should be informed of the potential risk to the foetus if they become or wish to become pregnant. Patients who become pregnant must immediately contact their doctor. If a patient becomes pregnant during treatment with MIRV or within 7 months following the last dose, close monitoring is recommended.

The pregnancy status in patients of childbearing potential should be verified prior to initiating MIRV treatment and patients of childbearing potential should use effective contraception during treatment with MIRV and for 7 months after the last dose.

Embryo-foetal toxicity will continue to be monitored using routine pharmacovigilance activities.

Known risks that do not impact the risk-benefit profile:

- **Infusion related reactions / hypersensitivity**

In clinical studies, patients received corticosteroid, antihistamine, and antipyretic pre-medications to reduce the risk of IRRs. With these measures, the risk of IRRs was low.

The SMQ for Hypersensitivity narrow in addition to the PTs erythema, flushing, and erythema of eyelid were used to identify potential relevant hypersensitivity reactions occurring within 3 days of an infusion.

In Study 0416, 23 IRR TEAEs occurred in 18 of 218 patients (8%) treated with MIRV and 45 IRR TEAEs occurred in 27 of 207 patients (13%) treated with IC Chemo within 3 days of the infusion using the SMQ Hypersensitivity narrow (5.3.5.3 ISS, Table 4.15.2). In the MIRV arm, all of the TEAEs were of mild (5% patients) or moderate (4% patients) severity and no ≥ Grade 3 IRR TEAEs were reported in patients; ≥ Grade 3 IRRs were reported in 2 patients (< 1%) in the IC Chemo arm. The most common IRR TEAEs reported in the MIRV arm were rash, erythema, and infusion-related reaction (2% each). The most common IRR TEAEs reported in the IC Chemo arm were infusion-related reaction (4%), erythema, rash, and rash maculo-papular (2% each).

In the EOC population (N=682), 59 patients (9%) treated with MIRV experienced 76 IRR TEAEs within 3 days of the infusion using the SMQ Hypersensitivity narrow (5.3.5.3 ISS, Table 4.15.2). The most common (≥ 1%) PTs were infusion related reaction (17 patients; 2%), flushing (12 patients; 2%), rash (11 patients; 2%), and erythema (10 patients; 1%). The majority of the TEAEs were of mild or moderate severity; only 4 patients (< 1%) had a Grade 3 IRR. No Grade 4 or 5 IRR TEAEs were reported.

Throughout the clinical studies IRR / hypersensitivity TEAEs were not life-threatening. IRRs / hypersensitivity are not considered an important risk as they do not impact the benefit/risk balance of MIRV.

The risk of IRRs / hypersensitivity will be minimised in clinical practice through adhering to the guidance in the ELAHERE SmPC which recommends use of pre-medications (corticosteroids, antihistamines, and antipyretics) to reduce the incidence and severity of IRRs. For patients who experienced an IRR Grade ≥ 2, additional pre-medication with dexamethasone 8 mg BID (or equivalent) the day before MIRV administration should be considered. Dose modifications include interrupting the infusion, administering supportive treatment, administering additional pre-medication with dexamethasone, reducing the infusion rate, or permanently discontinuing treatment depending on severity grade. The SmPC also advises healthcare professionals that IRRs / hypersensitivity may occur with MIRV with similar guidance in the PL.

Infusion related reactions / hypersensitivity will continue to be monitored using routine pharmacovigilance activities.

- **Thrombocytopenia**

In Study 0416, 16 of 218 patients (7%) treated with MIRV and 33 of 207 patients (16%) treated with IC Chemo experienced thrombocytopenia TEAEs; the majority were considered related to treatment (13 patients; 6% and 31 patients; 15%, respectively) (5.3.5.3 ISS, Table 4.2.1.1; 5.3.5.3 ISS, Table 4.7.1.1). The thrombocytopenia TEAEs in the IC Chemo arm (33 patients, 16%) were driven by Topo (29 patients, 59%), with 3 patients (4%) treated with Pac and 1 patient (1%) treated with PLD experiencing thrombocytopenia TEAEs (CSR 0416, Table 37). This was expected as Topo is recognised to cause thrombocytopenia (Topotecan SmPC).

The majority of thrombocytopenia TEAEs were of Grade 1 or Grade 2 severity in the MIRV arm; 2 patients (< 1%) experienced a ≥ Grade 3 TEAE and one of which was considered related to study treatment (5.3.5.3 ISS, Table 4.8.1.1; 5.3.5.3 ISS, Table 4.9.1). In the IC Chemo arm, 13 patients (6%) had ≥ Grade 3 thrombocytopenia TEAEs; all in the Topo group (5.3.5.3 ISS, Table 4.8.1.1; CSR 0416, Table 37).

Two patients (< 1%) treated with MIRV had SAEs; one of which was considered related to treatment (5.3.5.3 ISS, Table 4.11.1; 5.3.5.3 ISS, Table 4.11.2). In the IC Chemo arm, 3 patients (1%) had SAEs; all related to study treatment.

In the MIRV arm, thrombocytopenia TEAEs led to dose reduction or dose delay in 6 patients (3%) and led to treatment discontinuation in 1 patient (< 1%) (5.3.5.3 ISS, Table 4.10.2; 5.3.5.3 ISS, Table 4.10.1). In the IC Chemo arm, thrombocytopenia TEAEs led to dose reduction or dose delay in 13 patients (6%) and led to treatment discontinuation in 3 patients (1%). No deaths occurred due to thrombocytopenia TEAEs in either the MIRV or IC Chemo arms (5.3.5.3 ISS, Table 4.10.3.1).

In MIRV treated patients (N=218) in Study 0416, laboratory value shifts from baseline to maximum grade for haematology parameters identified 2 patients (0.9%) with worst post-baseline Grade 4 laboratory values for platelet count decreased (5.3.5.3 ISS, Table 5.1.1). Overall, the patients who experienced at least a 2-grade change in platelet count decreased from baseline include; normal to Grade 2: 1 patient (0.5%); normal to Grade 4: 1 patient (0.5%); and Grade 1 to Grade 4: 1 patient (0.5%).

In the EOC population (N=682), 69 patients (10%) treated with MIRV experienced thrombocytopenia TEAEs; the majority were considered related to treatment (61 patients; 9%) (5.3.5.3 ISS, Table 4.2.1.1; 5.3.5.3 ISS, Table 4.7.1.1). There were only 2 patients (< 1%) who had SAEs (1 was a treatment related TEAE) (5.3.5.3 ISS, Table 4.11.1; 5.3.5.3 ISS, Table 4.11.2). The majority of thrombocytopenia TEAEs were of Grade 1 or 2 severity; 4

patients (< 1%) had a ≥ Grade 3 thrombocytopenia TEAE (3 were treatment related TEAEs) (5.3.5.3 ISS, Table 4.8.1.1; 5.3.5.3 ISS, Table 4.9.1).

Thrombocytopenia SAEs occurred in 2 patients (< 1%) (5.3.5.3 ISS, Table 4.11.1), and in one patient (< 1%) the SAE was considered related to MIRV treatment (5.3.5.3 ISS, Table 4.11.2).

Thrombocytopenia TEAEs led to dose reduction or delay in 18 patients (3%) treated with MIRV and led to treatment discontinuation in 9 patients (1%) (5.3.5.3 ISS, Table 4.10.2; 5.3.5.3 ISS, Table 4.10.1). No deaths occurred due to thrombocytopenia TEAEs (5.3.5.3 ISS, Table 4.10.3.1).

In the EOC population, laboratory value shifts from baseline to maximum grade for haematology parameters only identified 2 patients (0.3%) with worst post-baseline Grade 4 laboratory values for platelet count decreased (5.3.5.3 ISS, Table 5.1.1). Overall, the patients who experienced at least a 2-grade change in platelet count decreased from baseline include; normal to Grade 2: 12 patients (1.8%); normal to Grade 3: 2 patients (0.3%); normal to Grade 4: 1 patient (0.2%); Grade 1 to Grade 3: 1 patient (0.2%); and Grade 1 to Grade 4: 1 patient (0.2%).

Overall, MIRV is associated with relatively low myelosuppression compared with other cytotoxic chemotherapies as observed with Topo in Study 0416. Thrombocytopenia is not considered an important risk as it does not impact the benefit/risk balance of MIRV.

The risk of thrombocytopenia will be minimised in clinical practice through advising healthcare professionals in the ELAHERE SmPC that thrombocytopenia may occur with MIRV with similar guidance in the PL. For Grade 3 or 4 haematological adverse reactions, the dose should be withheld until Grade 1 or less and then resumed at one lower dose level.

Thrombocytopenia will continue to be monitored using routine pharmacovigilance activities.

- **Drug-drug interactions**

In vitro studies (CVG14-003 and CVG14-002) were conducted to evaluate PK drug interaction potentials (Module SII). Both DM4 and S-methyl DM4 showed no direct inhibition on CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5. However, DM4 showed time-dependent inhibition on CYP3A4 (K_i of 2.92 µM and 5.95 µM for testosterone 6β-hydroxylase, midazolam 1′-hydroxylase, respectively). S-methyl DM4 showed weak time-dependent inhibition of CYP2C8 and CYP2C9. In vitro studies also indicated no evidence for induction of CYP1A2, CYP2B6, and CYP3A4 in human hepatocytes following exposure to DM4 and S-methyl DM4.

DM4 and S-methyl DM4 are substrates of the P-gp efflux transporter (SVG28-001), however neither compound inhibited the P-gp efflux transporter.

No clinical studies evaluating the drug-drug interaction potential of MIRV have been conducted. Exposures in patients with or without concomitant medication were evaluated as part of the PopPK analysis (2.7.2 Summary of Clinical Pharmacology Studies, Section 3.3). During the 4 clinical studies (0416, 0417, 0401, and 0403), there were 49 patients treated with MIRV 6 mg/kg AIBW who were taking concomitant P-gp inhibitors at any time during the first three cycles of treatment in these studies. Exposures to MIRV, DM4, and S-methyl-DM4 in these patients were similar to the exposures in other patients receiving MIRV at 6 mg/kg AIBW.

There were also 19 and 59 patients who were taking concomitant weak or moderate CYP3A4 inhibitors, respectively, at any time during the first three cycles of treatment in the four studies. Exposures to MIRV, DM4, and S-methyl-DM4 in those patients were similar to the exposures in

other patients receiving MIRV at 6 mg/kg AIBW (2.7.2 Summary of Clinical Pharmacology Studies, Section 3.3).

Drug-drug interactions are not considered an important risk as they do not impact the benefit/risk balance of MIRV and can be managed in clinical practice through guidance in the SmPC and PL. The ELAHERE SmPC advises that clinical drug-drug interaction studies with MIRV have not been conducted. Healthcare professionals are informed that DM4 is a CYP3A4 substrate and that concomitant use of MIRV with strong CYP3A4 inhibitors may increase unconjugated DM4 exposure, which may increase the risk of MIRV adverse reactions. Healthcare professionals are advised that if concomitant use with strong CYP3A4 inhibitors (e.g., ceritinib, clarithromycin, cobicistat, idelalisib, itraconazole, ketoconazole, nefazodone, posaconazole, ritonavir, telithromycin, voriconazole) cannot be avoided, patients should be closely monitored for adverse reactions. Strong CYP3A4 inducers may decrease the exposure of unconjugated DM4. Patients are advised in the PL to inform their doctor if they are taking, have recently taken or might take any other medicines, including prescription and over-the-counter medicines, vitamins, and herbal supplements because some medicines may affect the way ELAHERE works and also, ELAHERE may affect the way other medicines work.

Drug-drug interactions will continue to be monitored using routine pharmacovigilance activities.

Other reasons for considering the risks not important:

- None

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risk 1: Ocular disorders

As MIRV is a DM4 (payload) tubulin-directed compound, ocular disorders were expected adverse reactions in the clinical development programme. Corneal effects were also observed in nonclinical studies (Module SII).

To minimise the risk to patients, patients with active or chronic corneal disorders, history of corneal transplantation, or active ocular conditions requiring ongoing treatment/monitoring such as uncontrolled glaucoma, wet age-related macular degeneration requiring intravitreal injections, active diabetic retinopathy with macular oedema, macular degeneration, presence of papilledema, and /or monocular vision were excluded from participation in Study 0416 (Module SIV.1).

The ocular safety profile of MIRV has been well characterised in patients receiving 6 mg/kg AIBW monotherapy.

Blurred vision grouped term includes the PTs vision blurred, visual impairment, vitreous floaters, visual acuity reduced, diplopia, presbyopia, accommodation disorder, refraction disorder, and hypermetropia.

Keratopathy grouped term includes the PTs corneal cyst, corneal deposits, corneal disorder, corneal epithelial microcysts, corneal epithelium defect, corneal erosion, corneal opacity, corneal pigmentation, keratitis, keratitis interstitial, keratopathy, limbal stem cell deficiency, and punctate keratitis.

Dry eye grouped term includes the PTs dry eye and lacrimation decreased.

Best corrected visual acuity (BCVA) was assessed for every patient at baseline and with the onset of any ocular symptom.

In Study 0416, 904 ocular TEAEs occurred in 122 of 218 patients (56%) treated with MIRV and 33 ocular TEAEs occurred in 18 of 207 patients (9%) treated with IC Chemo (5.3.5.3 ISS, Table 4.12.1). The majority of ocular TEAEs in the MIRV arm were of Grade 1 (31 patients; 14%) or Grade 2 (61 patients; 28%) severity; 30 patients (14%) had a ≥ Grade 3 ocular TEAE including 1 patient (< 1%) who experienced a Grade 4 TEAE (cataract). All ocular TEAEs in the IC Chemo arm were of Grade 1 (16 patients; 8%) or Grade 2 (2 patients; < 1%) severity. The most common (≥ 3%) ≥ Grade 3 ocular TEAEs in the MIRV arm were keratopathy (20 patients; 9%), vision blurred (17 patients; 8%), cataract, visual acuity reduced, and dry eye (all 7 patients; 3%).

The median time to first onset of an ocular TEAE in the MIRV and IC Chemo arms was 5.36 weeks (range: 0.1 to 68.6 weeks) and 12.21 weeks (range: 0.1 to 32.4 weeks), respectively (5.3.5.3 ISS, Table 4.12.2). The reported worst outcomes in the MIRV arm were dose reduced (39 patients; 18%), dose delayed or not given (30 patients; 14%), and drug permanently discontinued (4 patients; 2%). No action was taken in 49 patients (22%) with ocular TEAEs. The ocular TEAEs in the 122 patients completely resolved (62 patients; 51%) or partially improved (51 patients; 42%) in the majority of patients treated with MIRV (5.3.5.3 ISS, Table 4.12.3.1).

In the EOC population (N=682), 2601 ocular TEAEs occurred in 405 patients (59%) treated with MIRV (5.3.5.3 ISS, Table 4.12.1). The majority of ocular TEAEs were of Grade 1 or 2 severity; 75 patients (11%) treated with MIRV had ≥ Grade 3 ocular TEAEs. The most common (≥ 3%) ≥ Grade 3 ocular TEAEs were vision blurred (32 patients; 5%), keratopathy (31 patients; 5%), and cataract (28 patients; 4%).

The median time to first onset for ocular TEAEs for the EOC population was 5.14 weeks (range: 0.1 to 68.6 weeks) (5.3.5.3 ISS, Table 4.12.2). The most commonly reported worst outcomes were dose reduced (101 patients; 15%) and dose delayed or not given (74 patients; 11%). No action was taken in 221 patients (32%) and the drug was permanently discontinued in 8 patients (1%). The ocular TEAEs in the 405 patients completely resolved in 215 patients (53%) and partially improved in 154 patients (38%) (5.3.5.3 ISS, Table 4.12.3.1).

Risk-benefit impact:

Ocular disorders are an important identified risk. These can be impactful to patients as they may transiently impair vision, leading to interference with independent activities of daily living. Early recognition, evaluation, and interventions, including MIRV dose modifications and adjustment of lubricating and/or steroid eye drops, can mitigate the risk of escalation. Prompt attendance to ocular signs and/or symptoms facilitates resolution of ocular AEs and minimise the risk of needing to discontinue MIRV for ocular AEs.

The benefit of MIRV as a treatment for PROC, a life-threatening condition with short prognosis and an unmet clinical need, is considered to outweigh the risk of ocular disorders, which are most commonly low-grade and can be managed in clinical practice through ophthalmic examinations, use of lubricating eye drops, patient monitoring, use of ophthalmic topical steroids as secondary prophylaxis for ≥ Grade 2 corneal adverse reactions, and dose modifications for keratitis/keratopathy including withholding treatment, reducing the dose or permanently discontinuing treatment depending on severity grade.

Healthcare professionals are advised in the ELAHERE SmPC that MIRV has moderate influence on the ability to drive and use machines. If patients experience visual disturbances, fatigue, or

dizziness during treatment with MIRV, they should be instructed not to drive or use machines until complete resolution of symptoms is confirmed.

Ocular disorders will be further characterised using routine pharmacovigilance activities.

Missing information 1: Use in patients with moderate hepatic impairment

Patients with a history of cirrhotic liver disease (Child-Pugh Class B or C) were excluded from participation in Study 0416 (Module SIV.1). Furthermore, patients were required to have adequate liver function defined as AST and ALT ≤ 3.0 × ULN; serum bilirubin ≤ 1.5 × ULN (patients with documented diagnosis of Gilbert syndrome are eligible if TBL < 3.0 × ULN); and serum albumin ≥ 2 g/dL.

No clinical study assessing the effects of hepatic impairment on the PK of MIRV has been conducted. Intrinsic factors including demographic variables, such as hepatic impairment, were evaluated as part of the PopPK analysis (2.7.2 Summary of Clinical Pharmacology Studies, Section 3.2). The PopPK analysis showed that exposures in patients with mild hepatic impairment were similar to those in patients with normal hepatic function. However, no patients with moderate or severe hepatic impairment were included in the analysis and therefore the PK in patients with moderate or severe hepatic impairment is unknown.

In terms of metabolism, while the monoclonal antibody portion of MIRV is expected to be catabolised into small peptides; unconjugated DM4 and S-methyl-DM4 undergo metabolism by CYP3A4.

Use in patients with moderate hepatic impairment is missing information that requires further characterisation.

Risk-benefit impact:

The risk-benefit impact of administering MIRV to patients with moderate or severe hepatic impairment is currently unknown.

Use of MIRV in patients with moderate hepatic impairment will be further characterised in Study IMGN853-0425 (Part III.2). Use of MIRV in patients with severe hepatic impairment will not be further characterised. As a precautionary measure, the ELAHERE SmPC advises healthcare professionals that MIRV should be avoided in patients with moderate to severe hepatic impairment (TBL > 1.5 ULN with any AST).

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk: Ocular disorders

Potential mechanisms:

Antibody-drug conjugates containing tubulin-directed payloads have been associated with ocular AEs related to corneal keratopathy, including blurred vision. Several recently approved ADCs containing auristatin payloads, including monomethyl auristatin E (Padcev SmPC and Tivdak USPI) and monomethyl auristatin F (Blenrep SmPC), have been associated with corneal-related AEs. These ADCs are comprised of unique antibodies, linkers, and tubulin-directed payloads and each produce a distinct spectrum of effects upon the cornea. For example, the antibody component of Tivdak is directed toward the TF protein which is present on the cornea. Some of the associated toxicity is a direct effect of this ADC's antibody binding to TF. While the pathogenesis of MIRV-induced keratopathy has yet to be completely described, absence of FRα on the cornea suggests these effects are indirect. The mechanism of corneal changes is thought to be due in part to macropinocytosis of the tubulin-containing ADC into the corneal epithelial cells, resulting in corneal microcysts that arise in the periphery of the cornea and migrate centripetally (Zhao 2018). These dose dependent transient changes in refraction resulting in blurred vision resolve with corneal epithelial replacement (10 to 14 days). These effects have not resulted in the important surface AEs such as ulcers, erosions, and perforations seen in other ADCs containing tubulin-directed payloads (e.g., Blenrep, Tivdak). Essentially, each ADC is unique in its AE profile and its subsequent management.

Evidence source and strength of evidence:

As MIRV is a DM4 (payload) tubulin-directed compound and corneal effects were observed in nonclinical studies, ocular disorders were expected adverse reactions in clinical studies.

Across clinical studies, 405 of 682 patients (59%) treated with MIRV developed ocular adverse reactions. The majority were of mild or moderate severity; 75 patients (11%) had a severe (≥ Grade 3) ocular adverse reaction. The most common adverse reactions were vision blurred in 43% of patients and keratopathy in 29% of patients. The ocular adverse reactions typically occurred 6 weeks after the start of treatment and in most cases completely or partially improved. The use of lubricating and corticosteroid eye drops together with dose modifications and supportive treatment helped to minimise the severity of the adverse reactions and assisted the recovery of patients.

Clinical studies can provide an estimation of the frequency and nature of an adverse reaction that is expected to occur in clinical practice.

Characterisation of the risk:

In the nonclinical development programme, ocular changes with MIRV in the Dutch-Belted rabbit and cynomolgus monkey were observed but limited to the formation of corneal microcysts without any inflammatory response (Module SII). Punctate microcystic lesions in the cornea in the Dutch-Belted rabbit is suggestive of a close phenotypic match to the keratopathy observed in human subjects treated with MIRV. Histopathologic evaluation of the keratopathy showed marked attenuation and disorganisation of the corneal epithelium in MIRV-treated animals.

These corneal effects occurred in a dose-dependent manner with respect to onset, duration, and severity with evidence of reversibility.

In Study 0416, 904 ocular TEAEs occurred in 122 of 218 patients (56%) treated with MIRV and 33 ocular TEAEs occurred in 18 of 207 patients (9%) treated with IC Chemo (5.3.5.3 ISS, Table 4.12.1). The majority of ocular TEAEs in the MIRV arm were of Grade 1 (31 patients; 14%) or Grade 2 (61 patients; 28%) severity; 30 patients (14%) had a ≥ Grade 3 ocular TEAE (all based upon transient changes in BCVA) including 1 patient (< 1%) who experienced a Grade 4 TEAE (cataract). All ocular TEAEs in the IC Chemo arm were of Grade 1 (16 patients; 8%) or Grade 2 (2 patients; < 1%) severity.

The most common (≥ 10%) ocular TEAEs in patients treated with MIRV were vision blurred (89 patients; 41%), keratopathy (70 patients; 32%), dry eye (61 patients; 28%), photophobia (39 patients; 18%), cataract (32 patients; 15%), and visual acuity reduced (26 patients; 12%) (Table 13). The most common (≥ 3%) ≥ Grade 3 ocular TEAEs in this arm were keratopathy (20 patients; 9%), vision blurred (17 patients; 8%), and cataract, dry eye, and visual acuity reduced (all 7 patients; 3%). In the IC Chemo arm, there were no ocular TEAEs observed in ≥ 10% patients or ≥ Grade 3 ocular TEAEs.

Table 13: Ocular TEAEs (≥ 10%) by Preferred Term and Maximum Grade (All Patients, EOC population and Study 0416)

Preferred Term	All Patients (6 mg/kg AIBW Q3W) (N=706)	EOC (6 mg/kg AIBW Q3W) (N=682)	0416	
			MIRV (6 mg/kg AIBW Q3W) (N=218)	IC Chemo (N=207)
Patients with any Ocular TEAEs, n (%)				
All grades	417 (59)	405 (59)	122 (56)	18 (9)
Grade ≥ 3	76 (11)	75 (11)	30 (14)	0
Vision blurred, n (%)				
All grades	301 (43)	294 (43)	89 (41)	5 (2)
Grade ≥ 3	32 (5)	32 (5)	17 (8)	0
Keratopathy, n (%)				
All grades	201 (28)	199 (29)	70 (32)	0
Grade ≥ 3	32 (5)	31 (5)	20 (9)	0
Dry eye, n (%)				
All grades	185 (26)	181 (27)	61 (28)	5 (2)
Grade ≥ 3	12 (2)	12 (2)	7 (3)	0
Cataract, n (%)				
All grades	104 (15)	103 (15)	32 (15)	1 (< 1)
Grade ≥ 3	28 (4)	28 (4)	7 (3)	0
Photophobia, n (%)				
All grades	97 (14)	97 (14)	39 (18)	1 (< 1)
Grade ≥ 3	3 (< 1)	3 (< 1)	1 (< 1)	0
Visual acuity reduced, n (%)				
All grades	87 (12)	87 (13)	26 (12)	0
Grade ≥ 3	11 (2)	11 (2)	7 (3)	0

Preferred Term	All Patients (6 mg/kg AIBW Q3W) (N=706)	EOC (6 mg/kg AIBW Q3W) (N=682)	0416	
			MIRV (6 mg/kg AIBW Q3W) (N=218)	IC Chemo (N=207)
Eye pain, n (%)				
All grades	68 (10)	68 (10)	20 (9)	1 (< 1)
Grade ≥ 3	3 (< 1)	3 (< 1)	0	0

Abbreviations: AIBW = adjusted ideal body weight; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic case report form; EOC = epithelial ovarian cancer; IC Chemo = Investigator's choice/selected standard-of-care chemotherapy; MedDRA = Medical Dictionary for Regulatory Activities; MIRV = mirvetuximab soravtansine; Pac = paclitaxel; PLD = pegylated liposomal doxorubicin; QW = weekly; Q3W = every 3 weeks; Q4W = every 4 weeks; SOC = system organ class; TEAE = treatment-emergent adverse event; Topo = topotecan.
IC Chemo: Pac (80 mg/m^2 administered QW within a 4-week cycle); PLD (40 mg/m^2 administered Q4W); Topo (4 mg/m^2 administered either on Days 1, 8 or 15 of a 4 week cycle or for 5 consecutive days at 1.25 mg/m^2 Days 1-5 Q3W).
Coding was performed using MedDRA 24.0 and CTCAE version 5.0.
Note: Ocular TEAE are TEAE with SOC = eye disorder.
Note: TEAEs are defined as adverse events with an onset date on or after the first dose of study drug, and within 30 days of the last dose of study drug or prior to the start of a new anti-cancer treatment, whichever occurs first.
Note: When counting events, each event is counted once for each adverse event entered into the eCRF. For the remaining frequencies, each patient is counted once, with the worst grade for each preferred term.
Data cut-off dates for studies IMGN853-0401: 10 Feb 2018; IMGN853-0403: 18 Mar 2020; IMGN853-0417: 22 Dec 2022; IMGN853-0416: 06 Mar 2023
Source data: 5.3.5.3 ISS, Table 4.12.1

In Study 0416, the median time to first onset of an ocular TEAE in the MIRV arm and IC Chemo arm was 5.36 weeks (range: 0.1 to 68.6 weeks) and 12.21 weeks (range: 0.1 to 32.4 weeks), respectively (Table 14).

In the MIRV arm the actions taken for the ocular TEAEs included dose delayed (64 patients; 29%), dose reduced (43 patients; 20%), dose not given (12 patients; 6%), and drug permanently discontinued (4 patients; 2%) (Table 14). The reported worst outcomes were dose reduced (39 patients; 18%), dose delayed or not given (30 patients; 14%), and drug permanently discontinued (4 patients, 2%). No action was taken in 49 patients (22%) with ocular TEAEs. In the IC Chemo arm, no action was taken for all 18 patients with ocular TEAEs.

For blurred vision, the median time to first onset was 5.86 weeks (range: 0.3 to 47.1 weeks) in the MIRV arm (5.3.5.3 ISS, Table 4.12.2). The most common actions taken for patients were dose delayed (42 patients; 19%) and dose reduced (31 patients; 14%). The most commonly reported worst outcomes were dose reduced (28 patients; 13%) and dose delayed or not given (19 patients; 9%). No action was taken in 48 patients (22%), and the drug was permanently discontinued in 3 patients (1%). In the IC Chemo arm, no action was taken for all 6 patients (3%) with blurred vision TEAEs.

The median time to first onset of keratopathy was 6.57 weeks (range: 0.1 to 58.1 weeks) in MIRV treated patients (5.3.5.3 ISS, Table 4.12.2). The most common actions taken for patients were dose delayed (38 patients; 17%) and dose reduced (22 patients; 10%). The most commonly reported worst outcomes were dose delayed or not given (23 patients; 11%) and dose reduced (21 patients; 10%). No action was taken in 34 patients (16%), and the drug was permanently discontinued in 2 patients; < 1%). There were no keratopathy TEAEs in the IC Chemo arm.

The protocol required use of lubricating and corticosteroid eye drops together with dose modifications and supportive treatment which helped to minimise the severity of ocular adverse reactions and assisted the recovery of patients in Study 0416. Overall, ocular TEAEs in the 122 patients completely resolved (62 patients; 51%) or partially improved (51 patients; 42%, 31 of which had resolution to Grade 1) in the majority of patients treated with MIRV (5.3.5.3 ISS, Table 4.12.3.1). There was no documented improvement in 9 patients (7%); with patients reported to have Grade 1 (6 patients; 5%) or Grade 2 (3 patients; 2%) ocular TEAEs at the final assessment. In the IC Chemo arm, the ocular TEAEs in the 18 patients treated with IC Chemo completely resolved (12 patients; 67%) or partially improved (3 patients; 17%) in the majority of patients (5.3.5.3 ISS, Table 4.12.3.1). There was no documented improvement in 3 patients (17%); with all patients reported to have Grade 1 (3 patients; 17%) ocular TEAEs at the final assessment.

Table 14: Time to First Onset and Action Taken for Ocular TEAEs (All Patients, EOC Population and Study 0416)

Preferred Term	All Patients (6 mg/kg AIBW Q3W) (N=706)	EOC (6 mg/kg AIBW Q3W) (N=682)	0416	
			MIRV (6 mg/kg AIBW Q3W) (N=218)	IC Chemo (N=207)
Time to first onset of ocular TEAEs (weeks)				
N	417	405	122	18
Mean (SD)	7.66 (8.116)	7.78 (8.192)	8.58 (9.839)	12.86 (9.868)
Median	5.14	5.14	5.36	12.21
Min, Max	0.1, 68.6	0.1, 68.6	0.1, 68.6	0.1, 32.4
Action taken, n (%) [a]				
Drug permanently discontinued	8 (1)	8 (1)	4 (2)	0
Dose reduced	107 (15)	105 (15)	43 (20)	0
Infusion interrupted	1 (< 1)	1 (< 1)	0	0
Dose delayed/ not given	178 (25)	173 (25)	70 (32)	0
Dose delayed	166 (24)	161 (24)	64 (29)	0
Dose not given	27 (4)	27 (4)	12 (6)	0
Worst outcome, n (%) [b]				
Drug permanently discontinued	8 (1)	8 (1)	4 (2)	0
Dose reduced	103 (15)	101 (15)	39 (18)	0
Infusion interrupted	1 (< 1)	1 (< 1)	0	0
Dose delayed/ not given	77 (11)	74 (11)	30 (14)	0
No action taken	228 (32)	221 (32)	49 (22)	18 (9)

Abbreviations: AIBW = adjusted ideal body weight; EOC = epithelial ovarian cancer; IC Chemo = Investigator's choice/selected standard-of-care chemotherapy; max = maximum; min = minimum; MIRV = mirvetuximab soravtansine; Pac = paclitaxel; PLD = pegylated liposomal doxorubicin; QW = weekly; Q3W = every 3 weeks; Q4W = every 4 weeks; SOC = system organ class; TEAE = treatment-emergent adverse event; Topo = topotecan. IC Chemo: Pac (80 mg/m^2 administered QW within a 4-week cycle); PLD (40 mg/m^2 administered Q4W); SD = standard deviation; Topo (4 mg/m^2 administered either on Days 1, 8 or 15 of a 4 week cycle or for 5 consecutive days at 1.25 mg/m^2 Days 1-5 Q3W).

[a] A patient could have multiple actions taken.

[b] A patient was counted once based on the worst outcome. The order of the worst outcome chosen was 'Dose Permanently Discontinued', 'Dose Reduced', 'Infusion Interrupted', 'Dose Delayed/Not Given' and 'No Action Taken'.
Note: Ocular TEAE are TEAE with SOC = eye disorder.
Note: TEAEs are defined as adverse events with an onset date on or after the first dose of study drug, and within 30 days of the last dose of study drug or prior to the start of a new anti-cancer treatment, whichever occurs first.
Data cut-off dates for studies IMGN853-0401: 10 Feb 2018; IMGN853-0403: 18 Mar 2020; IMGN853-0417: 22 Dec 2022; IMGN853-0416: 06 Mar 2023
Source data: 5.3.5.3 ISS, Table 4.12.2

In the EOC population (N=682), 405 patients (59%) treated with MIRV had 2601 ocular TEAEs (5.3.5.3 ISS, Table 4.12.1). The most common (≥ 10%) ocular TEAEs by PT in patients treated with MIRV were vision blurred (294 patients; 43%), keratopathy (199 patients; 29%), dry eye (181 patients; 27%), cataract (103 patients; 15%), photophobia (97 patients; 14%), visual acuity reduced (87 patients; 13%), and eye pain (68 patients; 10%) (Table 13).

The majority of ocular TEAEs were Grade 1 or 2 severity; 75 patients (11%) treated with MIRV in the EOC population had ≥ Grade 3 ocular TEAEs (Table 13). The most common (≥ 3%) ≥ Grade 3 ocular TEAEs were vision blurred (32 patients; 5%), keratopathy (31 patients; 5%), and cataract (28 patients; 4%) (Table 13).

The median time to first onset for ocular TEAEs for the EOC population was 5.14 weeks (range: 0.1 to 68.6 weeks) (Table 14). The actions taken for the ocular TEAEs were dose delayed (161 patients; 24%), dose reduced (105 patients; 15%), dose not given (27 patients; 4%), drug permanently discontinued (8 patients; 1%), and infusion interrupted (1 patient; < 1%). The most commonly reported worst outcomes were dose reduced (101 patients; 15%) and dose delayed/not given (74 patients; 11%). No action was taken in 221 patients (32%) and the drug was permanently discontinued in 8 patients (1%).

For vision blurred, the median time to first onset was 5.86 weeks (range: 0.1 to 56.3 weeks) (5.3.5.3 ISS, Table 4.12.2). The most common actions taken for patients were dose delayed (111 patients; 16%) and dose reduced (79 patients; 12%). The most commonly reported worst outcomes were dose reduced (76 patients; 11%) and dose delayed or not given (51 patients; 7%). No action was taken in 192 patients (28%) and the dose was permanently discontinued in 6 patients (< 1%).

The median time to first onset of keratopathy was 6.71 weeks (range: 0.1 to 58.1 weeks) (5.3.5.3 ISS, Table 4.12.2). The most common actions taken for patients were dose delayed (93 patients; 14%) and dose reduced (50 patients; 7%). The most commonly reported worst outcomes were dose delayed or not given (55 patients; 8%) and dose reduced (49 patients; 7%). No action was taken in 140 patients (21%) and the drug was permanently discontinued in 4 patients (< 1%).

In the EOC population, the ocular TEAEs in the 405 patients completely resolved in 215 patients (53%) and partially improved in 154 patients (38%) (5.3.5.3 ISS, Table 4.12.3.1). While there was no documented improvement in 36 patients (9%); the majority of patients reported to have Grade 1 (28 patients; 7%) ocular TEAEs at the final assessment with only a small number of patients with Grade 2 (7 patients; 2%) or Grade 3 (1 patient; < 1%) ocular TEAEs.

Best corrected visual acuity (BCVA) was assessed for every patient at baseline and with the onset of any ocular symptom. Patients who experienced ocular TEAEs while on study were mandated to have a complete ophthalmic exam performed at the emergence of the symptoms and at every other cycle.

In Study 0416, 6 (10%) patients had end of treatment (EOT) and/or 30-day BCVA shift as noted as ≥ 3 lines (Module 2.7.4, Section 3.4.1). Of these, 3 patients had final BCVA better than 20/50. Three patients had both a reduction in BCVA (≥ 3 lines) and a final BCVA of 20/50 or worse at the EOT and/or 30-day examination (5.3.5.1 Study 0416 CSR, Section 12.5.4.1). No patient had BCVA of 20/200 or worse at the last follow-up.

In the EOC population, 496 patients (87%) treated with MIRV had a baseline BCVA and 180 patients (53%) had EOT and/or 30-day follow-up visit BCVA (5.3.5.3 ISS, Table 5.4.1.1). Of the patients with BCVA assessment at baseline and at least 1 post-baseline ophthalmic examination, 32% experienced a clinically meaningful maximal shift in BCVA (≥ 3 lines worsening from known baseline in the worse-seeing eye). Of the patients with BCVA assessment at baseline and EOT/30-day follow-up, 13% (21/162 patients) had ≥ 3 lines of worsening in BCVA at last follow-up (Module 2.7.4, Section 3.4.1).

Risk factors and risk groups:

No specific risk factors have been identified.

Preventability:

Ocular disorders are expected as MIRV is a DM4 (payload) tubulin-directed compound. The risk to patients can be minimised through increased healthcare professional awareness of the need for ophthalmic examinations, use of lubricating eye drops, patient monitoring, use of ophthalmic topical steroids as secondary prophylaxis, and dose modifications for keratitis/keratopathy depending on severity grade as detailed below. Ocular disorders will be minimised in clinical practice using routine risk minimisation measures including guidance in the SmPC and PL.

MIRV must be initiated and supervised by a physician experienced in the use of anticancer medicinal products, and its use is limited by medical prescription.

The ELAHERE SmPC advises healthcare professionals to conduct an ophthalmic exam including visual acuity and slit lamp exam before the initiation of MIRV and if a patient develops any new or worsening ocular symptoms prior to the next dose. In patients with ≥ Grade 2 ocular adverse reactions, additional ophthalmic exams should be conducted at a minimum of every other cycle and as clinically indicated until resolution or return to baseline.

It is recommended to instruct patients to use lubricating eye drops throughout treatment with MIRV.

For patients found to have signs of ≥ Grade 2 corneal adverse reactions (keratopathy) on slit lamp examination, secondary prophylaxis with ophthalmic topical steroids is recommended for subsequent cycles of MIRV, unless the patient's eye care professional determines that the risks outweigh the benefits of such therapy. These patients should be instructed to use steroid eye drops on the day of infusion and through the next 7 days of each subsequent cycle of MIRV and to wait at least 15 minutes after ophthalmic topical steroid administration before instilling lubricating eye drops. During treatment with ophthalmic topical steroids the measurement of intraocular pressure and an examination with slit lamp should be carried out regularly.

Healthcare professionals are warned that MIRV can cause severe ocular adverse reactions, including visual impairment (predominantly blurred vision), keratopathy (corneal disorders), dry eye, photophobia, and eye pain. Before the start of each cycle, the patient should be advised to report any new or worsening ocular symptoms to the treating physician or qualified individual. In patients who develop new or worsening ocular symptoms, an ophthalmic exam should be conducted before dosing. The treating physician should review the patient's ophthalmic

examination report before dosing and determine the dose of MIRV based on the severity of findings in the most severely affected eye.

Healthcare professionals are advised to monitor patients for ocular toxicity and to withhold, reduce, or permanently discontinue MIRV based on the severity and persistence of ocular adverse reactions with dose modifications for keratitis/keratopathy provided in the ELAHERE SmPC.

Patients should be advised to avoid use of contact lenses during treatment with MIRV unless directed by a healthcare professional.

Healthcare professionals are advised that MIRV has moderate influence on the ability to drive and use machines. If patients experience visual disturbances, fatigue, or dizziness during treatment with MIRV, they should be instructed not to drive or use machines until complete resolution of symptoms is confirmed.

Impact on the risk-benefit balance of the product:

Ocular disorders are an important identified risk. These can be impactful to patients as they may transiently impair vision, leading to interference with independent activities of daily living including driving and using machines. Early recognition, evaluation, and interventions, including ophthalmic examinations, use of lubricating eye drops, ophthalmic topical steroids for ≥ Grade 2 corneal adverse reactions, and dose modifications for keratitis/keratopathy can mitigate the risk of escalation. Prompt attendance to ocular signs and/or symptoms facilitates resolution of ocular AEs and minimise the risk of needing to discontinue MIRV for ocular AEs.

The benefit of MIRV as a treatment for PROC, a life-threatening condition with short prognosis and an unmet clinical need, is considered to outweigh the risk of ocular disorders, which are most commonly low-grade and can be managed in clinical practice through ophthalmic examinations, use of lubricating eye drops, patient monitoring, use of ophthalmic topical steroids as secondary prophylaxis, and dose modifications for keratitis/keratopathy depending on severity grade.

Ocular disorders will be further characterised using routine pharmacovigilance activities.

Public health impact:

The potential impact on public health is expected to be low since ocular disorders can be adequately managed through ophthalmic examinations, use of lubricating eye drops, patient monitoring, use of ophthalmic topical steroids as secondary prophylaxis, and dose modifications for keratitis/keratopathy depending on severity grade.

SVII.3.2 Presentation of the Missing Information

Missing information: Use in patients with moderate hepatic impairment

Evidence source:

The monoclonal antibody portion of MIRV is expected to be catabolised into small peptides. 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 MIRV area under the concentration-time curves (AUCs), respectively.

In vitro and nonclinical in vivo studies indicate that DM4 and S-methyl-DM4 are primarily metabolised by CYP3A4 and eliminated via biliary excretion in the faeces.

Patients with a history of cirrhotic liver disease (Child-Pugh Class B or C) were excluded from participation in Study 0416 (Module SIV.1). Furthermore, patients were required to have adequate liver function defined as AST and ALT ≤ 3.0 × ULN; serum bilirubin ≤ 1.5 × ULN (patients with documented diagnosis of Gilbert syndrome are eligible if TBL < 3.0 × ULN); and serum albumin ≥ 2 g/dL.

No clinical study assessing the effects of hepatic impairment on the PK of MIRV has been conducted. The PopPK analysis showed that exposures in patients with mild hepatic impairment were similar to those in patients with normal hepatic function (2.7.2 Summary of Clinical Pharmacology Studies, Section 3.2). The PK in patients with moderate or severe hepatic impairment is unknown as no patients with moderate or severe hepatic impairment were included in the clinical studies.

The ELAHERE SmPC informs healthcare professionals that no clinically significant difference in the PK of MIRV was observed based on mild hepatic impairment (TBL ≤ ULN and any AST > ULN or TBL > 1 to 1.5 times ULN and any AST) and that the PK of MIRV in patients with moderate to severe hepatic impairment (TBL > 1.5 ULN with any AST) is unknown. Healthcare professionals are advised that MIRV should be avoided in patients with moderate to severe hepatic impairment (TBL > 1.5 ULN with any AST) and that no dose adjustment of MIRV is recommended for patients with mild hepatic impairment (TBL ≤ ULN and AST > ULN or TBL > 1 to 1.5 times ULN and any AST).

Population in need of further characterisation:

To further characterise this population, Study IMGN853-0425 will determine an appropriate starting dose of MIRV in patients with moderate hepatic impairment using safety and PK data for MIRV, unconjugated DM4, and S-methyl DM4 in this open-label, non-randomised, dose escalation study (Part III.2).

As a precautionary measure, the ELAHERE SmPC advises healthcare professionals that MIRV should be avoided in patients with moderate to severe hepatic impairment (TBL > 1.5 ULN with any AST).

PART II: MODULE SVIIISUMMARY OF THE SAFETY CONCERNS

Table 15: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	Ocular disorders
Important potential risks	None
Missing information	Use in patients with moderate hepatic impairment

PART III PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires:

None.

Other forms of routine pharmacovigilance activities:

None.

III.2 Additional Pharmacovigilance Activities

A synopsis for Study IMGN853-0425 is provided in Annex 3.

Study IMGN853-0425 Summary

Study short name and title:

Study IMGN853-0425

A randomized Phase 2, open-label study of mirvetuximab soravtansine in patients with platinum-resistant advanced high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancers with high folate receptor-alpha expression testing 2 schedules of administration for dose optimization, with a separate cohort to determine starting dose in patients with moderate hepatic impairment

Rationale and study objectives:

To evaluate the safety and pharmacokinetics (PK) of mirvetuximab soravtansine, unconjugated DM4, and S-methyl DM4 in patients with moderate hepatic impairment, according to National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) (NCI-ODWG) criteria.

Study design:

Open-label, non-randomised, dose escalation PK and safety two-cohort study.

The first cohort study is an open-label, non-randomised, dose escalation study to determine an appropriate starting dose of MIRV in patients with moderate hepatic impairment, according to NCI-ODWG criteria. Safety and PK data for MIRV, unconjugated DM4, and S-methyl DM4 will be used to determine the appropriate starting dose of MIRV for this population.

The second cohort study is an open-label, randomised study comparing two dosing schedules, one of which (the every-other-week schedule) is designed to maximise efficacy and reduce the potential frequency of ocular AEs (per PK analysis and exposure-response [ER] modelling).

Study population:

Randomised Phase 2 cohort:

Approximately 100 patients ≥ 19 years of age with platinum-resistant high-grade serous EOC, primary peritoneal cancer, or fallopian tube cancer previously treated with 1, 2, or 3 prior systemic lines of anticancer therapy as defined in the study inclusion criteria.

Hepatic impairment cohort:

Approximately 10 patients ≥ 19 years of age with platinum-resistant high-grade serous EOC, primary peritoneal cancer, or fallopian tube cancer previously treated with 1, 2, or 3 prior systemic lines of anticancer therapy as defined in the study inclusion criteria plus with moderate hepatic impairment as defined by the NCI-ODWG (TBL > 1.5-3 × ULN).

Milestones:

Protocol finalisation: 21 Jul 2023

Study initiation: Second half of the year (H2) 2024

Study completion: 08/2026

Final study report: 02/2027

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 16: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 – Required additional pharmacovigilance activities				
Study IMGN853-0425 A randomized Phase 2, open-label study of mirvetuximab soravtansine in patients with platinum-resistant advanced high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancers with high folate receptor-alpha expression testing 2 schedules of administration for dose optimization, with a separate cohort to determine starting dose in patients with moderate hepatic impairment Planned	To evaluate the safety and PK of mirvetuximab soravtansine, unconjugated DM4, and S-methyl DM4 in patients with moderate hepatic impairment, according to NCI-ODWG criteria.	Use in patients with moderate hepatic impairment	Protocol finalisation:	21 Jul 2023
			Study initiation:	H2 2024
			Study completion:	08/2026
			Final study report:	02/2027

Abbreviations: H2 = second half of the year; NCI-ODWG = National Cancer Institute Organ Dysfunction Working Group; PK = pharmacokinetics

Part IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There are no planned or ongoing post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

PART V RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table 17: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Ocular disorders (Important identified risk)	Routine risk communication: • Adverse reactions in SmPC section 4.8 • Side effects in PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Warning that ELAHERE can cause severe ocular adverse reactions, including visual impairment (predominantly blurred vision), keratopathy (corneal disorders), dry eye, photophobia, and eye pain, that patients should be promptly referred to an eye care professional for an ophthalmic exam before initiation of mirvetuximab soravtansine, and that they should be advised to report any new or worsening ocular symptoms to the treating physician or qualified individual before the start of each cycle in SmPC section 4.4 • Recommendation to conduct an ophthalmic exam including visual acuity and slit lamp exam before the initiation of ELAHERE and if a patient develops any new or worsening ocular symptoms prior to the next dose, and that for patients with ≥ Grade 2 ocular adverse reactions, additional ophthalmic exams should be conducted at a minimum of every other cycle and as clinically indicated until resolution or return to baseline in SmPC section 4.2 • Recommendation to instruct patients to use lubricating eye drops throughout treatment with ELAHERE in SmPC sections 4.2 and 4.4 • Recommendation for patients who develop ≥ Grade 2 corneal adverse reactions to use ophthalmic topical steroids as secondary prophylaxis for subsequent cycles of mirvetuximab soravtansine in SmPC sections 4.2 and 4.4; guidance on use of ophthalmic topical steroids including waiting at least 15 minutes after ophthalmic topical steroid administration before instilling lubricating eye drops and the need for an intraocular pressure check and slit lamp examination in SmPC section 4.2 • Guidance on dose modifications for keratitis/keratopathy including monitoring, withholding or reducing the dose, or permanently discontinuing treatment based on the severity of the adverse reaction in SmPC section 4.2 • Recommendation for patients to avoid use of contact lenses during treatment with mirvetuximab soravtansine unless directed by a healthcare professional in SmPC section 4.4 • Recommendation for patients not to drive or use machines until complete resolution of symptoms is confirmed if they experience visual

1.8.2 Risk Management Plan

Safety concern	Routine risk minimisation activities
	disturbances, fatigue, or dizziness during treatment with mirvetuximab soravtansine in SmPC section 4.7 • Warning for the patient to talk to their doctor or nurse before they are given ELAHERE if they have vision or eye problems requiring active treatment or monitoring in PL section 2 • Warning for the patient to seek urgent medical attention if they experience loss of vision, damage to the cornea (the transparent layer in the front of the eye; keratopathy), dry eyes, abnormal sensitivity of the eyes to light (photophobia) or eye pain as ELAHERE can cause severe eye problems in PL section 2 • Warning that the patient will see an eye specialist before starting treatment and that it is important for them to report any new or worsening eye problems before the start of each treatment cycle; it is recommended that the patient use drops to moisturise the eyes during treatment; they are advised that if they develop certain side effects affecting the eyes, their doctor may recommend additional eye drops containing corticosteroids. Patients are advised not use contact lenses during treatment with ELAHERE unless advised by a healthcare professional, in PL section 2 • Guidance that an eye care specialist will examine the patient's eyes prior to starting treatment with ELAHERE, that it is important for the patient to tell their doctor or eye care specialist if they have any new or worsening eye problems before each treatment cycle, that if they develop moderate or severe eye problems during treatment their doctor may reduce the dose of their treatment until their problems improve, and that their doctor may adjust, withdraw or permanently stop ELAHERE treatment if signs and symptoms reveal any worsening problems in their eyes in PL section 3 • Guidance that patients are recommended to use lubricating eye drops when needed throughout ELAHERE treatment in PL section 3 • Guidance that if the patient experiences moderate or severe eye side effects that their doctor may recommend that they use topical steroid eye drops and that it is important to follow their doctor's instruction for when to take steroid eye drops, including waiting at least 15 minutes after using the topical steroid eye drops before using lubricating eye drops in PL section 3 • Warning for the patient not to wear contact lenses during treatment with ELAHERE unless they are told to do so by their doctor or eye care specialist in PL sections 2 and 3 • Warning that ELAHERE may affect the patient's ability to drive and use machines and not to drive, use tools or operate machines if they experience blurred vision, fatigue, or dizziness until their symptoms are completely better in PL section 2 Other routine risk minimisation measures beyond the Product Information: • Restricted medical prescription
Use in patients with moderate hepatic impairment	Routine risk communication: • Information that the pharmacokinetics of mirvetuximab soravtansine in patients with moderate to severe hepatic impairment (TBL > 1.5 ULN with any AST) is unknown in SmPC section 5.2

Safety concern	Routine risk minimisation activities
(Missing information)	Routine risk minimisation activities recommending specific clinical measures to address the risk: • Guidance that ELAHERE should be avoided in patients with moderate to severe hepatic impairment (TBL > 1.5 ULN with any AST) in SmPC section 4.2 Other routine risk minimisation measures beyond the Product Information: • Restricted medical prescription

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

Table 18: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Ocular disorders (Important identified risk)	Routine risk minimisation measures: • *Warning for severe ocular adverse reactions and to monitor patients in SmPC section 4.4* • *Recommendation for ophthalmic exams in SmPC sections 4.2 and 4.4, and PL section 3* • *Guidance for the patient to report any new or worsening eye problems before the start of each treatment cycle in PL sections 2 and 3* • *Recommendation to use lubricating eye drops during treatment in SmPC sections 4.2 and 4.4, and PL sections 2 and 3* • *Recommendation to use ophthalmic topical steroids for moderate or severe corneal adverse reactions in SmPC sections 4.2 and 4.4, and PL sections 2 and 3* • *Warning for the patient to talk to their doctor or nurse before they are given ELAHERE if they have*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *None*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	vision or eye problems in PL section 2 • *Dose modifications for keratitis/keratopathy by severity grade in SmPC section 4.2* • *Warning for the patient to seek urgent medical attention if they experience severe eye problems in PL section 2* • *Recommendation to avoid use of contact lenses during treatment unless directed by a healthcare professional in SmPC section 4.4 and PL sections 2 and 3* • *Guidance for driving and using machinery in SmPC section 4.7 and PL section 2* • *Adverse reactions in SmPC section 4.8 and PL section 4* • *Restricted medical prescription* Additional risk minimisation measures: • *None*	
Use in patients with moderate hepatic impairment (Missing information)	Routine risk minimisation measures: • *Guidance that ELAHERE should be avoided in patients with moderate to severe hepatic impairment in SmPC section 4.2* • *Information that the pharmacokinetics of mirvetuximab soravtansine in patients with moderate to severe hepatic impairment is unknown in SmPC section 5.2* • *Restricted medical prescription* Additional risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *Study IMGN853-0425*

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR ELAHERE (MIRVETUXIMAB SORAVTANSINE)

This is a summary of the risk management plan (RMP) for ELAHERE. The RMP details important risks of ELAHERE, how these risks can be minimised, and how more information will be obtained about ELAHERE's risks and uncertainties (missing information).

ELAHERE's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how ELAHERE should be used.

This summary of the RMP for ELAHERE should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of ELAHERE's RMP.

I THE MEDICINE AND WHAT IT IS USED FOR

ELAHERE is authorised as monotherapy for the treatment of adult patients with folate receptor-alpha (FRα) positive, platinum-resistant high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received one to three prior systemic treatment regimens (see SmPC for the full indication). It contains mirvetuximab soravtansine as the active substance and it is given intravenously.

Further information about the evaluation of ELAHERE's benefits can be found in ELAHERE's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage < link to the EPAR summary landing page >

II RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of ELAHERE, together with measures to minimise such risks and the proposed studies for learning more about ELAHERE's risks, are outlined below.

- Measures to minimise the risks identified for medicinal products can be:
- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety updated report (PSUR) assessment –so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of ELAHERE is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of ELAHERE are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of ELAHERE. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Table 19: Lists of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	Ocular disorders
Important potential risks	None
Missing information	Use in patients with moderate hepatic impairment

II.B Summary of Important Risks

Important identified risk: Ocular disorders	
Evidence for linking the risk to the medicine	As mirvetuximab soravtansine is a DM4 (payload) tubulin-directed compound and corneal effects were observed in nonclinical studies, ocular disorders were expected adverse reactions in clinical studies. Across clinical studies, 405 of 682 patients (59%) treated with mirvetuximab soravtansine developed ocular adverse reactions. The majority were of mild or moderate severity; 75 patients (11%) had a severe (≥ Grade 3) ocular adverse reaction. The most common adverse reactions were vision blurred in 43% of patients and keratopathy in 29% of patients. The ocular adverse reactions typically occurred 6 weeks after the start of treatment and in most cases completely or partially improved. The use of lubricating and corticosteroid eye drops together with dose modifications and supportive treatment helped to minimise the severity of the adverse reactions and assisted the recovery of patients. Clinical studies can provide an estimation of the frequency and nature of an adverse reaction that is expected to occur in clinical practice.

Important identified risk: Ocular disorders	
Risk factors and risk groups	No specific risk factors have been identified.
Risk minimisation measures	Routine risk minimisation measures: • Warning for severe ocular adverse reactions and to monitor patients in SmPC section 4.4 • Recommendation for ophthalmic exams in SmPC sections 4.2 and 4.4, and PL section 3 • Guidance for the patient to report any new or worsening eye problems before the start of each treatment cycle in PL sections 2 and 3 • Recommendation to use lubricating eye drops during treatment in SmPC sections 4.2 and 4.4, and PL sections 2 and 3 • Recommendation to use ophthalmic topical steroids for moderate or severe corneal adverse reactions in SmPC sections 4.2 and 4.4, and PL sections 2 and 3 • Warning for the patient to talk to their doctor or nurse before they are given ELAHERE if they have vision or eye problems in PL section 2 • Dose modifications for keratitis/keratopathy by severity grade in SmPC section 4.2 • Warning for the patient to seek urgent medical attention if they experience severe eye problems in PL section 2 • Recommendation to avoid use of contact lenses during treatment unless directed by a healthcare professional in SmPC section 4.4 and PL sections 2 and 3 • Guidance for driving and using machinery in SmPC section 4.7 and PL section 2 • Adverse reactions in SmPC section 4.8 and PL section 4 • Restricted medical prescription Additional risk minimisation measures: • None

Missing information: Use in patients with moderate hepatic impairment	
Risk minimisation measures	Routine risk minimisation measures: • Guidance that ELAHERE should be avoided in patients with moderate to severe hepatic impairment in SmPC section 4.2 • Information that the pharmacokinetics of mirvetuximab soravtansine in patients with moderate to severe hepatic impairment is unknown in SmPC section 5.2 • Restricted medical prescription Additional risk minimisation measures:

Missing information: Use in patients with moderate hepatic impairment	
	• None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study IMGN853-0425 See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-Authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of ELAHERE.

II.C.2 Other Studies in Post-Authorisation Development Plan

Study IMGN853-0425

A randomized Phase 2, open-label study of mirvetuximab soravtansine in patients with platinum-resistant advanced high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancers with high folate receptor-alpha expression testing 2 schedules of administration for dose optimization, with a separate cohort to determine starting dose in patients with moderate hepatic impairment

Purpose of the study: To evaluate the safety and pharmacokinetics (PK) of mirvetuximab soravtansine, unconjugated DM4, and S-methyl DM4 in patients with moderate hepatic impairment, according to National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria.

PART VII ANNEXES

LIST OF ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable.

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable.

ANNEX 7 OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL)

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