19 September 2024
EMA/473768/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Elahere

International non-proprietary name: mirvetuximab soravtansine

Procedure No. EMEA/H/C/005036/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ABC	ATP-binding cassette
ADA	anti-drug antibodies
ADC	antibody-drug conjugate
ADCC	antibody-dependent cell-mediated cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
ASCO	American Society of Clinical Oncology
AESI	adverse event of special interest
AIBW	adjusted ideal body weight given
AUC	area under the curve
AUC∞	area under the curve extrapolated to infinity
AUC0-t	area under the curve to the last detectable timepoint
B-IMGN853	biotinylated mirvetuximab soravtansine
BEV	bevacizumab
BICR	blinded independent central review
BID	twice a day
BR	benefit-risk
BSA	bovine serum albumin
C1D1	Cycle 1 Day 1
CA-125	cancer antigen 125
CL	clearance
CMA	conditional marketing authorisation
Cmax	maximum plasma concentration
CR	complete response/remission
CRC	cohort review committee
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
CYP	cytochrome P450
Dex	dexamethasone
DLT	dose limiting toxicity
DM4	maytansinoid Ravtansine, chemical name N2'-Deacetyl-N2'-(4-mercapto-4-methyl-1-oxopentyl)-maytansine
S-methyl-DM4	methylated N2'-[4-[(3-carboxypropyl)dithio]-4-methyl-1-oxo-2-sulfopentyl]-N2'-deacetylmaytansine
D	day
DOR	duration of response
ECHO	echocardiography
ECL	electrochemiluminescent
ECOG	Eastern Cooperative Oncology Group
ELISA	enzyme-linked immunosorbent assays
ECOG	Eastern Cooperative Oncology Group
EOC	epithelial ovarian cancer and used also as an umbrella term for epithelial

	ovarian cancer, primary peritoneal cancer and fallopian tube cancer
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-5L	European Quality of Life Five Dimension
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FIH	first in human
FOLR1	folate receptor 1
F-U	follow-up
GCIG	Gynecologic Cancer Intergroup
GI	gastrointestinal
GLP	good laboratory practice
HPLC	high performance liquid chromatography
HGSC	high-grade serous carcinoma
hr	hours
HRD	homologous recombination deficiency
HRP	horseradish peroxidase
HuFOLR1-Fc	human folate receptor 1-Fc
IC50	concentration of test article that inhibits 50% of enzyme activity
IC	investigator's choice
ICC	investigator's choice chemotherapy
ICF	informed consent form
IDMC	Independent Data Monitoring Committee
IgG	immunoglobulin G
IHC	immunohistochemistry
ILD	interstitial lung disease
IM	intramuscular
IMGN	ImmunoGen
INV	investigator
IRR	infusion-related reaction
ISS	Integrated Summary of Safety
ITT	intent-to-treat
IV	intravenous
kg	kilogram
ki	inhibition constant
kinact	maximal rate of inactivation
kI	inhibitor concentration that supports half of maximal rate of inactivation
km	Michaelis-Menton constant
KM	Kaplan Meier
LC/MS/MS	liquid chromatography with tandem mass spectrometry
LLOQ	lower limit of quantitation
LVEF	left ventricular ejection fraction
MA	marketing authorisation
MAA	marketing authorisation application
MARG	microautoradiography

MDCKII cells	Madin-Darby canine kidney cells
MDR1	multi-drug resistance protein 1
M9346A-Sulfo-SPDB-3H-DM4	3H- mirvetuximab soravtansine, tritium-labeled
M9346A	mirvetuximab antibody
MIRV	mirvetuximab soravtansine
MRI	magnetic resonance imaging
M&S	modelling and simulation
MT	mutation/mutated
MTD	maximum tolerated dose
MUGA scan	multigated acquisition scan
mL	milliliter
MOA	mechanism of action
MRD	minimum required dilution
NA	not applicable
n	number
NADPH	nicotinamide adenine dinucleotide phosphate
	NCA non-compartmental analyses
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ND	not determined
ng	nanogram
nm	nanometer
NOAEL	no-observed-adverse-effect-level
NSCLC	non-small cell lung cancer
OD	optical density
ORR	objective response rate
OS	overall survival
Pac	paclitaxel
PARP	poly (ADP-ribose) polymerase
PCE	polychromatic erythrocyte
PD	pharmacodynamic(s)
PFI	platinum free interval
PFS	progression-free survival
PFS2	time to second disease progression
PGIS	Patient global impression of severity
PLD	pegylated liposomal doxorubicin
PK	pharmacokinetic(s)
PO	orally
PPK	population pharmacokinetic(s)
PR	partial response/remission
PRO	patient-reported outcomes
PROC	platinum-resistant ovarian cancer

PS	performance status
PS2+	IHC percent staining 2+ or 3+
PO	orally
QC	quality control
Q3W	once every three weeks
Q4W	every 4 weeks
QLQ-C30	Quality-of-life Questionnaire Core 30
QoL	quality of life
QoLP	primary endpoint for quality of life
QTc	corrected QT interval
QTcB	QT Interval Corrected by the Bazett Correction Formula
QTcF	QT Interval Corrected by the Fridericia Correction Formula
QW	once weekly
RA	radioactivity
RECIST	Response Evaluation Criteria in Solid Tumors
RMP	risk management plan
ROW	rest of the world
R2PD	recommended Phase 2 dose
RR	response rate
RT-PCR	reverse transcription polymerase chain reaction
Ru-IMGN853	ruthenium labeled mirvetuximab soravtansine
SAE	serious adverse event
SA-HRP	streptavidin-conjugated horseradish peroxidase
SAT	single arm trial
SCS	summary of clinical safety
SD	standard deviation
S-methyl-DM4, DM4ME	S-methyl-N2'-[4-[(3-carboxypropyl)dithio]-4-methyl-1-oxo-2-sulfopentyl]-N2'-deacetylmaytansine
sSPDB, Sulfo-SPDB	N-Succinimidyl-4-(2-pyridyldithio)-2-sulfobutanoate
TAb	total antibody
TBA	thiobutyric acid
TBL	total bilirubin levels
TBW	total body weight
TFI	treatment free interval
TK	toxicokinetics
tmax	time at which Cmax occurs
TMB	3,3',5,5'-tetramethylbenzidine
t½	elimination half-life
Topo	topotecan
US	United States
V1	central volume of distribution
Vss	volume of distribution at steady state
WCBP	woman of childbearing potential
WT	wildtype

µg	micrograms
µM	micromolar

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Immunogen Biopharma (Ireland) Limited submitted on 29 September 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Elahere, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The applicant has changed to AbbVie Deutschland GmbH & Co. during the procedure at Day 181.

Elahere was designated as an orphan medicinal product EU/3/15/1458 on 19 March 2015 in the following condition: treatment of ovarian cancer.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Elahere as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/elahere.

The applicant applied for the following indication:

Elahere as monotherapy is indicated for the treatment of adult patients with folate receptor-alpha (FRα) positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer.

1.2. Legal basis, dossier content

The legal basis for this application refers to: Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0032/2017 on the granting of a (product-specific) waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Applicant's request for consideration

1.5.1. New active substance status

The applicant requested the active substance mirvetuximab soravtansine contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Protocol assistance

The applicant received the following protocol assistance on the development relevant for the indication subject to the present application:

Date	**Reference**
13 October 2016	EMEA/H/SA/3384/2/2016/PA/I
13 October 2016	EMEA/H/SA/3384/1/2016/PA/III
28 February 2019	EMEA/H/SA/3384/3/2019/PA/II
14 November 2019	EMEA/H/SA/3384/1/FU/1/2019/PA/II

The protocol assistance pertained to the following quality, non-clinical, and clinical aspects:

- Changes to the manufacturing process
- Starting materials
- Self-life
- Introduction of working cell bank post approval
- Specifications
- Shipping validation studies
- Chronic toxicity study, toxicology studies of the toxin DM4 and non-clinical safety studies overall development plan
- Genotoxic impurities
- Need for a QT/QTc Study
- Human pharmacokinetic data and pharmacometrics program and proposed evaluation of pharmacokinetic (ADME) factors
- Inclusion of FRα positive patients
- Primary efficacy endpoint and its proposed analysis
- Establishment of overall type I error rate in the presence of an interim futility analysis
- Crossover of patients from comparator arm and choice of comparator
- Inclusion and exclusion criteria
- Safety database

- Conditional marketing authorisation and confirmatory phase 3 study including statistical analysis plan.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johanna Lähteenvuo Co-Rapporteur: Alexandre Moreau

The application was received by the EMA on	29 September 2023
The procedure started on	26 October 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	15 January 2024
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	30 January 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	26 January 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 February 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	24 April 2024
The following GCP inspection was requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GCP inspection at 3 sites in total: one clinical investigator site in Italy from 05/02 until 09/02/2024, one clinical investigator site in South Korea from 15/02 until 21/02/2024, the sponsor in the USA from 22/04 until 26/04/2024. The outcome of the inspection carried out was issued on	7 June 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	3 June 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 June 2024
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	27 June 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	19 August 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	4 September 2024

The CHMP Rapporteurs circulated the CHMP and PRAC Updated Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	12 September 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Elahere on	19 September 2024
The CHMP adopted a report on similarity of Elahere with Zejula on (see Appendix on similarity)	19 September 2024
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	19 September 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The applicant seeks a marketing authorisation for the medicinal product Elahere (mirvetuximab soravtansine) with the following therapeutic indication:

"Elahere as monotherapy is indicated for the treatment of adult patients with folate receptor-alpha (FRα) positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer."

2.1.2. Epidemiology and risk factors

Ovarian cancer is a lethal disease with 313,959 new cases and 207,252 deaths reported worldwide in 2020 (GLOBOCAN 2023). The incidence of ovarian cancer is increasing globally with a projected 450,000 cases by 2040. Ovarian cancer is the fifth leading cause of cancer death in women in the United States (Siegel et al. 2022); in 2022, 19,880 new cases and 12,810 deaths were anticipated. In the European Union, ovarian cancer is estimated to account for 26,500 deaths annually (Dalmartello et al. 2022).

Following recent advances in primary therapy, including the adoption of maintenance treatment, the 5-year relative survival rate for ovarian cancer in the US has increased slightly over the last decade from 44% to 49% (SEER Cancer Statistics Factsheet 2019). Similarly, the ovarian cancer death rate per 100,000 persons decreased slightly in the EU (from 4.63 to 4.32) during the period 2017 to 2022 (Dalmartello et al. 2022).

According to current ESMO guidelines, epithelial ovarian cancer (EOC) represents a heterogeneous spectrum of disease entities at a clinical, pathological and molecular level. Ovarian cancer is the second most lethal gynaecological malignancy worldwide behind cervical cancer and the first in developed countries. There is currently no reliable screening method for ovarian cancer (A. González-Martín et al. 2023, Newly diagnosed and relapsed epithelial ovarian cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up).

2.1.3. Biologic features and pathogenesis

Epithelial ovarian, primary peritoneal, and fallopian tube cancers are not distinct entities but rather represent a spectrum of diagnoses that originate in the Mullerian tissue. Fallopian tube and primary peritoneal carcinomas are included in the ovarian cancer staging classification (Grant 2010, Naumann 2011, O'Shannessy 2013, Cobb 2015) and are considered to be part of epithelial ovarian cancer with the same treatment and outcomes. Epithelial ovarian, fallopian tube, and primary peritoneal cancer are collectively referenced as epithelial ovarian cancer (EOC). High-grade serous carcinoma (HGSC) represents 70% of EOC cases (A. González-Martín et al. 2023, Newly diagnosed and relapsed epithelial ovarian cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up).

In HGSC, mutational analysis confirms almost ubiquitous TP53 mutations (96%), frequent (germline and somatic) BRCA1/2 mutations (≤30%) and other molecular characteristics including CCNE1 amplification and somatic copy-number alterations, which correlate with genomic instability.

Homologous recombination deficiency (HRD) can be observed in ~50% of HGSCs due to genetic or epigenetic inactivation of DNA damage repair genes including BRCA1/2, ATM, RAD51C and RAD51D. HRD-positive cancers exhibit genomic instability manifested by abnormal copy-number profiles and thousands of somatic mutations.

Folate Receptor (FR) alpha has limited normal tissue expression. Published studies have demonstrated FRα overexpression by immunohistochemistry (IHC) in various epithelial tumours, particularly serous and endometrioid ovarian cancers and serous and endometrioid endometrial cancers (Scorer et al. 2010, Garin-Chesa et al. 1993, Kalli et al. 2008, Crane et al. 2012, Dainty et al. 2007, Jones et al. 2008, Ab et al. 2015, and Allard et al. 2007). Results in IMGN853-0401 and IMGN853-0403 are consistent with literature. Approximately 40% of patients in platinum resistant ovarian cancer expansion cohort of IMGN853-0401 had high FR alpha expression.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Early-stage ovarian cancer is often asymptomatic and therefore difficult to detect. For women who do experience symptoms in the early stages, ovarian cancer is sometimes misdiagnosed because the majority of symptoms are nonspecific. These symptoms may overlap those of gastrointestinal and other diseases, and as a result, many patients may be treated incorrectly for months or years. Thus, ovarian cancer is often first detected in advanced stages when prognosis is poor.

The advanced stage at which ovarian cancer is generally detected is reflected in the 5-year survival rates; 46% across all stages and 29% for advanced stages (Siegel et al 2017).

Ovarian cancer is often asymptomatic in the early stages and is, therefore, first detected in advanced stages, when prognosis is poor. For women who do experience symptoms in the early stages, ovarian cancer is sometimes misdiagnosed because the majority of symptoms are nonspecific. These symptoms may overlap those of gastrointestinal and other diseases, and as a result, many patients may be treated incorrectly for months or years.

The 5-year overall survival (OS) rate in advanced ovarian cancer patients decreases from 42% for Stage IIIA, 32% for Stage IIIC, and 19% for Stage IV.

Most women are diagnosed based on symptoms, with the majority presenting at an advanced stage.

2.1.5. Management

Maintenance therapy with poly adenosine diphosphate-ribose polymerase (PARP) inhibitors has been incorporated into first-line treatment for EOC, with multiple randomized studies showing a benefit in progression-free survival (PFS) over placebo (SOLO1 [Moore et al. 2018], ATHENA-mono [Monk et al. 2022], PRIMA [González-Martín et al. 2019]). For patients with homologous recombination deficiency, including BRCA mutation, outcomes have improved considerably with the use of PARP inhibitors as first-line maintenance therapy.

Despite the incorporation of maintenance therapy into the treatment paradigm, most patients with advanced EOC relapse during or after treatment with platinum-containing regimens (Armstrong et al. 2019). Disease recurring within 6 months of platinum-based chemotherapy is classified as platinum resistant whereas recurrence more than 6 months after completion of platinum is classified as platinum-sensitive. Patients with recurrent platinum-sensitive disease typically receive platinum-based combination therapy, often followed by continuation of bevacizumab or initiation of PARP inhibitor maintenance, particularly if they are BRCA positive and have not received a PARP inhibitor as first-line maintenance therapy.

Once patients develop platinum-resistant ovarian cancer, their prognosis is poor. Available therapies yield limited positive outcomes, with almost all platinum-resistant ovarian cancer (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.

According to current ESMO guidelines, the definition of platinum-sensitivity based on a 6-month cut-off of treatment-free interval from last platinum has been changed. Instead, various factors should be considered (see figure below).

Figure 1: Management of recurrent EOC (ESMO guidelines 2023, DOI: *https://doi.org/10.1016/j.annonc.2023.07.011*

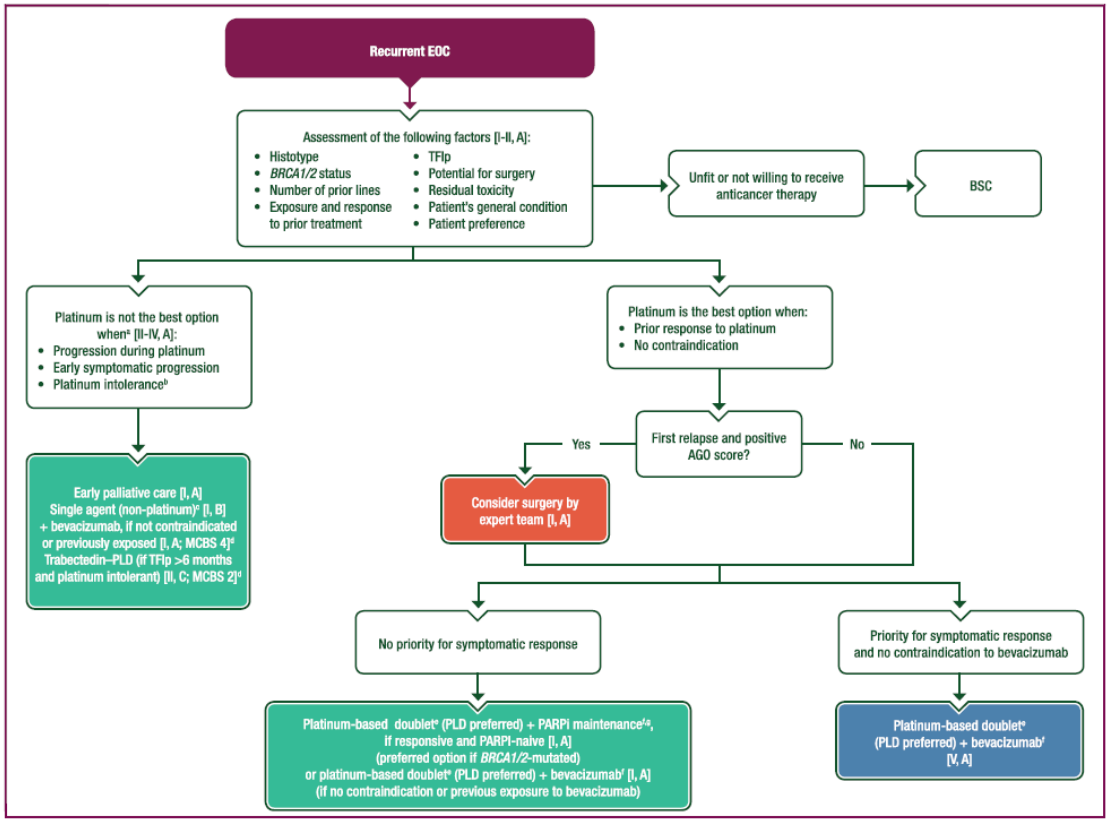


Figure 3. Management of recurrent EOC.
Purple: general categories or stratification; red: surgery; blue: systemic anticancer therapy; turquoise: combination of treatments or other systemic treatments; white: other aspects of management.
AGO, Arbeitsgemeinschaft Gynaekologische Onkologie; BSC, best supportive care; EMA, European Medicines Agency; EOC, epithelial ovarian cancer; FDA, Food and Drug Administration; MCBS, ESMO-Magnitude of Clinical Benefit Scale; mut, muation; PARPi, poly (ADP-ribose) polymerase inhibitor; PLD, pegylated liposomal doxorubicin; TFIp, treatment-free interval from last platinum.
[a]Patient choice and quality-of-life issues may also suggest that platinum is not the best option.
[b]In patients with platinum intolerance who have relapsed >6 months from previous platinum, the combination of trabectedin and PLD may be recommended [II, C; ESMO-MCBS v1.1 score: 2 for patients with platinum-sensitive disease; EMA approved, not FDA approved].
[c]Weekly paclitaxel, PLD, topotecan or gemcitabine.
[d]ESMO-MCBS v1.1[104] was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).
[e]Paclitaxel, PLD or gemcitabine (carboplatin—gemcitabine—bevacizumab: ESMO-MCBS v1.1 score: 3).[d]
[f]Until disease progression or next line of treatment is started [I, A].
[g]Olaparib for *BRCA1/2*-mutated: ESMO-MCBS v1.1 score: 2;[d] niraparib regardless of *BRCA1/2*-mut status: ESMO-MCBS v1.1 score: 3;[d] rucaparib regardless of *BRCA1/2*-mut status: ESMO-MCBS v1.1 score: 3.[d]

According to current ESMO guidelines, patients with relapsed EOC for whom platinum is not an option should be defined by [II-IV, A]:

- Proven resistance (progression during platinum)
- Expected resistance (early symptomatic progression post-platinum, response to rechallenge unlikely)
- Platinum intolerance

- Patient choice
- QoL issues.

For patients not candidates to receive platinum, integrating palliative care early in the treatment pathway is strongly recommended [I, A].

Single-agent non-platinum options that can be recommended include weekly paclitaxel, pegylated liposomal doxorubicin (PLD), topotecan and gemcitabine [I, B].

Bevacizumab should be recommended in combination with weekly paclitaxel, PLD or topotecan in patients without contraindications to bevacizumab and not previously exposed to bevacizumab [I, A; ESMO-MCBS v1.1 score: 4].

Furthermore, initial approval of paclitaxel in the US in 1992 was based on an ORR of 15% to 22% in taxane-naïve patients in the recurrent setting, prior to incorporation of paclitaxel in the frontline setting, and an ORR of 14% in PROC (Paclitaxel US PI). Paclitaxel was also approved in the EU at a dose of 175 mg/mg² (Apealea SmPC (Marketing authorisation since then withdrawn). Two early Phase 2 trials (n = 41, n = 102, respectively) of paclitaxel monotherapy given every 3 weeks in mixed platinum-sensitive ovarian cancer (PSOC) and PROC demonstrated an ORR of 17.1% (Pectasides 1998) and 20% (du Bois 1997), though median OS was 13.2 months and less than 1 year (45.9 weeks), respectively. The largest study of paclitaxel in PROC (n = 652 evaluable) in the US reported an ORR of 22% and median OS of 9 months, complicated by 78% of ≥ Grade 3 leukopenia (Trimble et al. 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 et al. 2002).

Topotecan was approved in 1996 in the US based on 2 trials in PROC with an ORR of 14% to 21%; 1 trial had a paclitaxel arm with an ORR of 14% (Hycamtin US PI). Topotecan subsequently was approved in the EU in mixed PSOC and PROC 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 et al. 1997). In a PROC population, ORR was lower at 13.7%, with median OS less than 1 year (47 weeks). Notably, this regimen is associated with significant myelotoxicity, with Grade 4 neutropenia in 82%, and Grade 4 thrombocytopenia in 30% of patients with recurrent ovarian cancer (Bookman et al. 1998). While the approved regimen for topotecan is daily for 5 days every 3 weeks, a weekly regimen is more commonly used with similar activity and improved tolerability (Abushahin et al. 2008, Sehouli et al. 2011).

PLD was approved in 1999 in the US based on 3 single-arm studies (n = 27 to 82) in PROC, which demonstrated a pooled ORR of 13.8% (Doxil US PI), and subsequent approval in the EU based on a 2001 study in second-line treatment of mixed platinum-sensitive and platinum refractory (defined as recurrence with platinum-free interval < 6 months) ovarian cancer (n = 474) compared with topotecan (Caelyx SmPC). For the platinum-refractory subgroup (n = 255), OS at 1 year was 13.8% with PLD and 9.5% with topotecan (Caelyx SmPC, Gordon et al. 2001, Gordon et al. 2004).

The last regulatory approval in PROC was in 2014 for the use of bevacizumab in combination with chemotherapy (Pujade-Lauraine et al. 2014). AURELIA was the randomized study that supported the approval of bevacizumab in combination with chemotherapy in PROC patients with 1 (60%) to 2 (40%) prior lines of therapy. In this study, the control arm, consisting of standard of care single-agent chemotherapy (paclitaxel, PLD, or topotecan), was associated with an investigator assessed ORR of 11.8% to 13%, a median PFS of 3.4 months, and an OS of 13.3 months. In the bevacizumab combination arm, the ORR was 27.3% with a median PFS of 6.7 months and OS of 16.6 months (Pujade-Lauraine et al. 2014, Avastin US PI).

Of note, most of the above compiled data is from the era prior the development of current diagnostic and treatment paradigms, most notably in advanced EOC with platinum-based doublet +/- bevacizumab followed by maintenance therapy with bevacizumab and/or PARPi.

2.2. About the product

Mirvetuximab soravtansine is an antibody-drug conjugate (ADC). The antibody is an engineered IgG1 directed against folate receptor alpha (FRα). The function of the antibody portion is to bind to FRα expressed on the surface of ovarian 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.

The final indication for Elahere is:

"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 (see section 4.2)."

Elahere must be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

Eligible patients should have FR*α* tumour status defined as ≥75% viable tumour cells demonstrating moderate (2+) and/or strong (3+) membrane staining by immunohistochemistry (IHC), assessed by a CE-marked *in vitro* diagnostic (IVD) with the corresponding intended purpose. If a CE-marked IVD is not available, an alternative validated test should be used.

Posology:

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

First, calculate IBW:	IBW = 0.9 * 165 – 92 = 56.5 kg
Then calculate AIBW:	AIBW = 56.5 + 0.4 * (80 – 56.5) = 65.9 kg

2.3. Type of application and aspects on development

This application under an article 8(3) legal basis of Directive 2001/83/EC (as a complete and independent application) is based on data from the MIRASOL study (IMGN853-0416, study 0416), together with supportive data from other studies in the mirvetuximab soravtansine (MIRV also known as IMGN853) clinical development programme.

Specific CHMP guidelines relevant for the current application: Guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95 Rev.6, 18 November 2023).

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as concentrate for solution for infusion containing 5 mg/mL of mirvetuximab soravtansine as active substance.

Other ingredients are: glacial acetic acid (E260), sodium acetate (E262), sucrose, polysorbate 20 (E432) and water for injections.

The product is available in type I glass vial with a butyl rubber stopper and an aluminum seal with a royal blue polypropylene flip cap.

The mirvetuximab soravtansine active substance, also referred to as drug substance (DS) is an antibody-drug conjugate (ADC) manufactured from 3 DS intermediates (DSI):

- DM4 toxic payload
- sulfo-SPDB linker
- M9346A monoclonal antibody

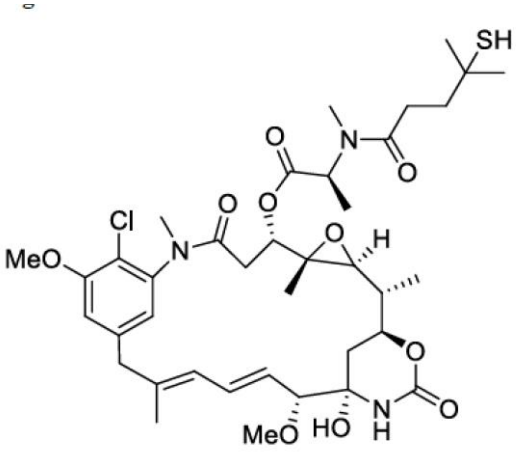
As such, the Module 3 of the MAA is organised with four DS nodes so that full quality information is presented for each of the DSIs as well as for the mirvetuximab soravtansine DS.

2.4.2. DSI DM4

2.4.2.1. General information DM4

Full information for the DSI DM4 is provided in the dossier. No international nonproprietary name (INN) has been assigned, the chemical name of maytansine is (1*S*,2*R*,3*S*,5*S*,6*S*,16*E*,18*E*,20*R*,21*S*)-11-chloro-21-hydroxy-12,20-dimethoxy-2,5,9,16- tetramethyl-8,23-dioxo-4,24-dioxa-9,22-diazatetracyclo[19.3.1.$1^{10,14}$.$0^{3,5}$]hexacosa- 10,12,14(26),16,18-pentaen-6-yl (2*S*)-2-(methyl(4-methyl-4-sulfanylpentanoyl)amino)propanoate -) corresponding to the molecular formula $C_{38}H_{54}ClN_3O_{10}S$. It has a relative molecular mass of 780.4 and the following structure, depicted in Figure 2.

Figure 2: Structure of DSI DM4



General information was provided for solubility, optical rotation and polymorphic form. Structure elucidation for DM4 was performed by mass spectrometry, 1H-, 13C-, COSY and HSQC NMR techniques, elemental analysis, XRPD, single crystal X-ray, optical rotation, FTIR and UV/VIS spectroscopy, confirming the DM4 structure. DM4 contains 7 stereogenic centres and stereochemistry is adequately controlled during the manufacture. DM4 reacts with the intermediate sulfo-SPDB, which acts as a linker for binding DM4 to the antibody M9346A to form antibody-drug conjugate mirvetuximab soravtansine.

2.4.2.2. Manufacture, process controls and characterisation

DM4 DSI synthesis is a linear three chemical conversion step synthesis route from multiple starting materials. Analytical methods for controlling the starting materials and impurities are validated and validation summaries are acceptable. Specifications are acceptable. The batch data complied with the specifications indicating that all starting materials are of consistent quality. The proposed starting materials are in-line with ICH Q11 and are sufficiently justified and acceptable.

The final DM4 DSI is purified, stored under nitrogen and shipped frozen. Maytansinol process input, typical yield range and material inputs for each step are given. Relevant process parameters, reaction times and temperatures are included in the synthesis narrative. The points of in-process control (IPCs) and critical process parameters (CPPS) are indicated in the process block flow diagram.

CPPs and IPCs are evaluated and justified under manufacturing process development and are acceptable.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Validation data is provided for three DM4 batches, all manufactured using different starting material batches. All CPP and key process parameters batches were within predefined normal operating ranges and batches comply with DM4 specifications.

Development of manufacturing process, from A (early clinical batches) to B (proposed manufacturing process) is described in detail, process understanding is considered adequate. Process B has been used to manufacture DM4 for the pivotal clinical studies and proposed for commercial production. Proven acceptable ranges (PAR) are investigated as part of the process understanding and development and proposed for reaction steps 1-3. The applicant does not claim a design space. The DM4 process has been evaluated through (FMEA) risk assessment. Quality attributes (QAs) and critical QAs (CQAs) are defined for the overall control strategy of the DM4 intermediate.

A list of observed and potential impurities was provided. Potential and actual impurities were well discussed with regards to their origin and characterised. The origin and fate of the related impurities was thoroughly discussed.

The primary packaging materials are glass bottle and cap with PTFE-coated silicone liner, which are compliant with the Ph. Eur. requirements and considered adequate for the storage of DM4 ASI, as supported by the long-term stability studies.

2.4.2.3. Specification, analytical methods, reference standards, batch analysis, and container closure DM4

The proposed DM4 specification, includes tests for identification (FT-IR 1 and by HPLC), assay (HPLC), impurities (HPLC), DL-dithiothreitol content (HPLC), DL-dithiothreitol-oxidised content (HPLC), residual solvents (GC), appearance (visual), water content (KF titration), specific optical rotation (polarimeter).

The proposed DM4 specification is acceptable. Due to the DM4 complexity and several stereogenic centres, the CHMP requested additional more sensitive identification technique (e.g., NMR) to detect possible changes in the molecular structure, however, the present identification methods were adequately justified. Tests for process related impurities are in included in the specification, it is demonstrated that the purification process can reduce these impurities. Each of the specification attributes are justified and considered acceptable for DM4 specification and aligned with ICH Q6A. The limits of the impurities are considered acceptable for the intermediate as the impurities have more opportunities to be purged during the down-stream process. The absence of a control test of benzene in the DM4 specification has been satisfactorily justified. Analytical methods have been described in sufficient detail. Method validation was conducted on the analytical methods included in the specification in accordance with ICH guidelines. Method verification was performed on the methods for identification by infrared spectroscopy and water content. Validation of analytical methods is acceptable.

Comprehensive batch analysis data is provided ranging from one early clinical batch manufactured using Process A) to process validation batches manufactured using the current Process B. Impurities and solvents levels are well below the specification limits in all latest PPQ and commercial batches. Overall, the batch analysis results show that the manufacturing process can produce DM4 DSI batches with consistent quality.

The current reference standard was taken from DM4 production batch using a manufacturing process representative of the commercial process and is sufficiently characterised. Information on the impurity standards is acceptable.

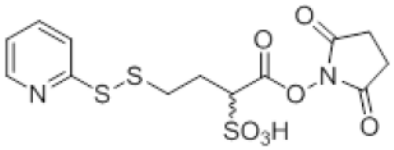
2.4.2.4. Stability DM4

Stability studies were conducted in accordance with the ICH guidance. Stability data from three process performance qualification batches (process B), manufactured by the proposed DSI DM4 manufacturer, stored in the proposed container closure system, have been provided. Data for three process performance qualification batches (process B) under stress stability conditions are available. No apparent degradation or clear trends were observed under long term stability conditions. The proposed retest period is supported by the stability data.

2.4.3. DSI sulfo-SPDB 4

Full information for the DSI sulfo-SPDB is provided in the dossier. Sulfo-SPDB is the linker binding DM4 to the antibody M9346A to form antibody-drug conjugate mirvetuximab soravtansine. No INN has been assigned, the chemical name is butanoic acid, 4-(2-pyridinyldithio)-2-sulfo-1-(2,5-dioxo-1-pyrrolidinyl) ester, its structure is depicted in **Figure 3**. General information for sulfo-SPDB racemic mixture was provided for solid state form, hygroscopicity, solubility, and polymorphism. Structure elucidation was performed by mass spectrometry., 1H-, 13C-, COSY and HSQC NMR techniques, elemental analysis, IR and UV/VIS spectroscopy. Data conforms to the sulfo-SPDB structure. Sulfo-SPDB is a crystalline material from which multiple polymorphs have been isolated. Control of polymorphism, including its stability during storage, is considered irrelevant, as sulfo-SPDB is dissolved later in the manufacturing process and it is highly soluble in the process conditions.

Figure 3: Structure of DSI sulfo-SPDB 4



2.4.3.1. Manufacture, process controls and characterisation sulfo-SPDB

Analytical methods for controlling the starting material and impurities are validated and validation summaries are acceptable. Specifications are acceptable and the batch data complied with the specifications indicating that all starting material is of consistent quality.

Process validation studies were provided although sulfo-SPDB is not sterile intermediate. The manufacturing process was described in sufficient detail, including all reagents, reaction temperatures and solvents. No reprocessing is proposed.

CPPs and IPCs are evaluated and justified under manufacturing process development and are acceptable.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Development of manufacturing process is described and process understanding shown. The synthetic route has remained the same since the beginning of the development with process A. Only a few minor modifications have been made to improve the current process B, which has been used to manufacture the majority of batches (including pivotal clinical batches).

Proven acceptable ranges (PAR) and normal operating ranges (NOR) are investigated as part of the process understanding and development. PARs are proposed for steps 1-3. The applicant does not claim a design space. The experiments to characterise the commercial process are sufficient., including OVaT experiments and few multivariate interaction experiments. QAs and CQAs are defined for the overall control strategy for sulfo-SPDB.

Formation, fate and control of organic and inorganic impurities is shortly discussed. Potential and actual impurities were well discussed with regards to their origin and characterised. Identified organic impurities are controlled in sulfo-SPDB intermediate specification.

The immediate packaging materials are 100 mL type I clear borosilicate glass bottle that are closed withscrew cap, made of Thermoplast with a polytetrafluoroethylene (PTFE)-coated silicone liner, which are considered sufficient for the intermediate packaging and the suitability of the container closure system to withstand the intended storage conditions has been demonstrated in the long-term stability studies. Packaging material is compliant with the Ph. Eur. requirements.

2.4.3.2. Specification, analytical methods, reference standards, batch analysis, and container closure sulfo-SPDB

The specification of sulfo-SPDB DSI includes tests for identification (1H NMR -Ph. Eur.- and HPLC), assay (HPLC), impurities (HPLC and UHPLC), residual solvents (GC), impurities and composition content (IC and GC), residual metals (ICP - Ph. Eur.), appearance (visual), water content (KF, Ph. Eur.). The specification of sulfo-SPDB is acceptable. The assay limit has been aligned with the latest batch data. Several specified impurities are controlled in the specification and the limits are acceptable

considering that the impurities have opportunities to be purged in the downstream manufacturing process.

All residual solvents which are used in the synthesis are limited in the intermediate specification are in line with the ICH Q3C. The absence of a control test of benzene in the sulfo-SPDB specification has been satisfactorily justified.

Analytical methods have been described in sufficient detail. Method validation was conducted on the analytical methods included in the specification in accordance with ICH Q2. Method verification was performed on the methods for identification. Validation of analytical methods is acceptable.

Comprehensive batch analysis data is provided ranging from early clinical batches manufactured using Process A to process validation batch manufactured using the current Process B. The impurities are well below specification limits in all latest PPQ and commercial batches. Overall, the batch analysis results show that the manufacturing process can produce sulfo-SPDB intermediate with consistent quality.

Reference standard is from production batch and is suitable for the intended qualitative and quantitative use. Information on the impurity standards is acceptable.

2.4.3.3. Stability sulfo-SPDB

Stability studies were conducted in accordance with the ICH guidance for production size batches. Stability data from three process performance qualification batches (process B), manufactured by the proposed DSI sulfo-SPDB manufacturer, stored in the proposed container closure system, for up to 48 months at long term stability data and for up to 6 months under accelerated stability data. Data for three process performance qualification batches (process B) under stress stability conditions is available up to 1 month. No apparent degradation or clear trends were observed, and the sulfo-SPDB intermediate appears to be stable under these conditions. The proposed retest period is supported by the stability data.

2.4.4. DSI M9346A antibody

2.4.4.1. General information M9346A

M9346A is a chimeric, recombinant, monoclonal IgG1 antibody with humanised variable regions, which is produced in CHO cells and specifically binds to folate receptor alpha (FRα). The mature antibody is composed of two identical IgG1 heavy chains each covalently linked to one kappa light chain) via a total of four inter-chain disulfide bonds, with 12 intra-chain disulfide bonds. The M9346A has one N-linked glycosylation site on each of the heavy chains.

2.4.4.2. Manufacture, process controls and characterisation M9346A

M9346A antibody is manufactured, tested, and stored. Sufficient information on EU-GMP compliance has been provided for all sites.

Description of manufacturing process and process controls

The manufacturing process has been adequately described. It is a straightforward monoclonal antibody production process that consists of 5 sequential USP and 7 sequential DSP steps. The manufacturing process starts with thawing of a single-cell bank vial followed by serial cell culture expansion in shake flasks, wave motion bioreactors, and stirred-tank bioreactors. Culture from the bioreactor is used to

inoculate the production bioreactor. The production bioreactor is operated in fed-batch mode. The material from the production bioreactor is harvested and clarified with depth filtration.

The downstream process for the M9346A antibody consists of seven steps; protein A chromatography, virus inactivation, anion exchange chromatography (AEX), cation exchange chromatography (CEX), virus filtration, and tangential flow filtration (TFF) followed by a final formulation, filtration and filling step. It is stated that bottles of M9346A DSI are stored and shipped frozen.

The manufacturing process for M9346A antibody DSI has been clearly defined and the purpose of each manufacturing step has been discussed in sufficient detail. The overall manufacturing process has been outlined in a high-level flow-diagram and separate tables indicating inputs (process materials as well as key and critical process parameters with operational ranges) and performance indicators (PIs) (key PIs and CQAs) are presented for each respective manufacturing step. The ranges of critical process parameters and the routine in-process controls (including controls for microbial purity and endotoxin), together with the related acceptance criteria, are described for each step. The active substance manufacturing process is considered acceptable.

M9346A antibody DS intermediate batch is defined as the formulated M9346A antibody. Each discrete batch of antibody intermediate is identified by a unique batch number, which is maintained throughout antibody intermediate production.

Control of materials

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. Materials used in the manufacture of the M9346A antibody DSI have been listed together with information on the quality and control of these materials. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented. CoA have been provided for materials of biological origin used early in cell line development. No materials of human or animal origin are used in the manufacture of M9346A antibody. In general, sufficient information on the history of the production cell line and establishment of the gene expression system is provided.

The presented cell bank system consists only of Master Cell Bank (MCB) derived from Research Cell Bank (RCB). The MCB was established and characterised according to the principles in ICH Q5D guideline, and it has been tested to be free from adventitious agents. A post-production cell bank (PPCB) was generated, and genetic stability was determined by comparing the DNA and RNA hybridisation patterns from the MCB and PPCB. Overall, the characterisation of the cell bank is acceptable. Overall, sufficient information is provided regarding testing of MCB.

Control of critical steps

A comprehensive overview of the control of critical steps is provided. Listed summaries of critical process parameters (CPPs, inputs to the process that impact CQAs), critical quality attributes (CQAs) measured in-process, and the critical outputs (CPIs, critical performance indicators, and hold times) that impact CQAs, with their acceptance criteria for each step of the antibody manufacturing process have been provided. In addition, short descriptions of the analytical methods used for in-process testing were provided. As the In Vitro Adventitious Virus methods are not compendial, detailed description of the methods and the results of the validation were provided.

The criticality of controls was determined using a risk-based approach based on process understanding gained throughout process development. The ranges for process parameters were defined based on process characterisation data generated by altering the normal process conditions at small-scale. The ranges for the performance indicators were defined based on process characterisation, safety, and microbial controls. Hold times were based on a combination of small-scale physico-chemical stability

studies and at-scale microbial hold studies. There are no isolated or critical process intermediates identified for antibody DSI.

Overall, the presented process controls for M9346A manufacturing are considered appropriate.

Process validation and/or evaluation

The validation of the M9346A Antibody DSI manufacturing process was performed at the commercial scale using 3 consecutive batches. Data from a 4th consecutive but terminated batch is also included to support the validation of this process. Analytical methods used for in-process testing were verified/validated before the start of the PPQ. The predefined limits for the PPQ campaign were based on the normal operating ranges (NOR) and proven acceptable ranges (PAR) established through process development and process characterisation for the process parameters. Process validation limits (PVLs) and process validation acceptance criteria (PVAC) were used to evaluate process performance during the PPQ campaign. The PPQ protocols also included the requirement for the antibody DSI quality attributes to meet the release specifications. In addition to the routine controls, specific in-process measurements were designated as performance indicators and were included in the PPQ campaign.

All process parameters met the required ranges, and performance indicators and CQAs showed consistent performance. Deviations or out of expectation events that occurred during PPQ were assessed as not having an impact on product quality or the validation and CAPAs were implemented. In conclusion, the presented process validation studies are considered to be appropriately addressed and in line with current guidance, and the studies demonstrate that the M9346 DSI manufacturing process performs effectively and reproducibly to produce M9346A antibody DSI that meets specifications

The shipping validation for M9346A antibody has been summarised. This is considered sufficient as transport validation is covered by EU GMP.

The company has also a continued process verification (CPV).

Manufacturing process development

The commercial antibody DSI manufacturing process was developed in parallel with the clinical development program. A risk-based approach to manufacturing process development was followed in accordance with ICH Q11. According to the applicant, the commercial M9436A manufacturing process was defined based on experience and knowledge gained from early phase process development, late phase process characterisation studies, technical transfer, and engineering runs. Further process knowledge was gained through closely monitoring the cGMP manufacturing of clinical trial material. Additional knowledge was gained through the evaluation of process robustness and reproducibility and process performance qualification.

The applicant has conducted comparability assessments to evaluate the analytical comparability of M9346A manufactured across the three manufacturing sites by Process A and of M9346A manufactured by Process A and B. Analytical comparability assessment included an assessment of release data, characterisation tests, as well as an assessment of M9346A on stability at long-term storage conditions and at an accelerated stability condition. In the Process A comparability assessment variation in basic species was observed with no impact to biological activity as measured by release and characterisation tests. Additionally, there were no trends on long term storage or under accelerated conditions. For the comparability assessment between Process A and Process B, the release testing result for M9346A Process B batches were assessed against pre-defined comparability target ranges derived from the release data from eight clinical Process A batches. It can be agreed that product quality attributes of

M9346A manufactured by Process A and Process B can be considered comparable and overall, no concerns regarding comparability of the processes are raised.

A failure mode effect analysis (FMEA) was performed to define critical, key, and non-key parameters for the M9346A manufacturing process. Parameters were evaluated for their potential impact on the process performance and product quality. High-risk and potential high-risk parameters were evaluated for inclusion in the studies along with other parameters for which improved process understanding was sought. Parameters with a higher probability of interaction were studied using a design of experiment (DoE) approach while others were evaluated in univariate studies. Scale-down models (SDMs) were developed for many of the unit operations. Outputs of those models were verified against large-scale runs, to ensure that the data generated at small scale were representative. After PC studies, the criticality of parameters was revisited, and normal operating ranges and proven acceptable ranges were defined. The control of each unit operation and the overall process is comprised of material controls, control of process parameters for each unit operation, and testing controls including in-process testing and release testing. The control of critical and non-critical quality attributes (CQAs and non-CQAs) was developed using both data-and risk-based approaches.

The descriptions of the SDMs have been provided in sufficient detail. SDMs were used for process development and process characterisation as well as for viral clearance studies. An in-depth risk assessment for leachable and extractable materials was performed, focusing exclusively on potential extractables and leachables that originate from materials having direct product-contact and therefore that might be present in the antibody DSI.

Overall, the process characterisation studies have been appropriately addressed and the rationale for control strategy is clearly presented.

Characterisation

The characterisation of M9346A antibody included determination of primary structure, secondary structure, high order structure, charge profiles, glycosylation, and in vitro biological activity. The primary sequence of M9346A was confirmed by state-of-the-art methods. Overall, the studies included in the characterisation are considered relevant and comprehensive. The structure of M9346A was confirmed and in vitro biological properties are as expected; the characterisation is considered appropriate.

Forced degradation studies of M9346A were conducted to elucidate the major degradation pathways using various stressed conditions. Four different conditions were used in accordance with ICH Q1A (R2) and Q1B.A risk assessment was performed to evaluate the potential process-related impurities derived from the cell substrates, cell culture and downstream processing. Reduction of process -related impurities throughout the manufacturing process has been verified. Impurities are constantly reduced to levels below specification limits. A risk assessment was performed to evaluate the potential molecular variants arising during manufacture and/or storage, which do not have properties comparable to those of the desired product with respect to activity, efficacy, and safety. No concern is raised as these product related impurities are controlled by release specification.

2.4.4.3. Specification, analytical methods, reference standards, batch analysis, and container closure M9346A

The proposed M9346A antibody DS intermediate specification includes physico-chemical tests (clarity, color, pH, and osmolality), an identity test (ELISA), tests for potency and protein content (ELISA binding assay and UV spectrophotometry), tests for purity, impurities and variants (ELISA for residual Protein A and HCP, qPCR for Residual DNA, SE-UHPLC for purity, reduced and non-reduced CGE for molecular integrity, and CEX for charge heterogeneity), and microbiological tests (Bioburden and

Bacterial endotoxins).Overall, the test parameters proposed to be included in the M9346A antibody specification are considered relevant and in line with current guidance. The parameters proposed to be included in the M9346A antibody specification have been discussed separately and very brief high-level justification for the proposed acceptance criteria has been provided. The proposed specification acceptance criteria for M9346A antibody DSI were established based on established guidance, clinical experience with mirvetuximab soravtansine generated from M9346A, and process and product knowledge. Analytical methods

M9346A antibody DSI is tested using a combination of compendial (colour, clarity, pH, osmolality, bioburden, and bacterial endotoxins) and non-compendial methods (ELISA, UV Spectroscopy, qPCR, size-exclusion ultra-high-performance liquid chromatography, capillary gel electrophoresis (reducing and non-reducing), and cation-exchange chromatography). Overall, very brief but appropriate method descriptions that include information on critical reagents and equipment as well as method details and operational parameters have been provided for all methods. Compendial methods that require suitability testing have been verified and results meet the requirements set in the Ph.Eur.In general, the validation for all non-compendial analytical methods follows ICHQ2 (R2). All predetermined validation acceptance criteria were met, and all methods are considered validated for their intended use.

Historical analytical methods for M9346A antibody have been described. Methods for charge heterogeneity, molecular integrity, purity and detection of residual HCP and Protein A have been changed during product development. Appropriate comparability studies have been performed to ensure comparability of the analytical results between the historical methods and the methods validated for commercial use.

Batch analyses

Batch data was provided for twelve batches of M9346A antibody (including 8 Process A batches and 13 Process B batches).

Reference materials

A two-tiered reference material system comprising a primary reference material (PRM) and a working reference material (WRM) was established in accordance with ICH Q6B for commercial manufacturing in 2017. Over the course of prior product development also 2 other working reference material batches have been established. Relevant information on the 2 historical reference standards including release and characterization test results has been provided. The protocol and acceptance criteria for the qualification of future WRS has been provided. A strategy for assignment of potency, to prevent a drift in potency when bridging reference materials, has been presented and is considered appropriate. Overall, the reference standards used throughout the product development have been adequately described.

2.4.4.4. Stability of M9346A DSI

Real time, real condition stability data on process B commercial scale batches from the commercial manufacturing process and under accelerated conditions according to the ICH guidelines were provided. The stability samples have been stored in the same materials as those for M9346A antibody. The use of containers is representative of the commercial scale containers in the stability studies is acceptable.

Additional stability data from process A development batches, considered representative of commercial product, stored under real time, real condition have been provided.

The stability data showed no change or adverse trends in the data. For process B batches stability data from long term conditions showed fluctuations but no adverse trending. Overall the stability of M9346A antibody has been adequately addressed in line with current guidance. The provided data support the claimed shelf-life at long term storage conditions.

The analytical methods used in stability studies have been validated and the stability-indicating properties of the analytical methods for Direct Binding by ELISA, Charge heterogeneity by Cation-Exchange HPLC, Purity by SE-UHPLC, and Molecular integrity by non-reduced and reduced CGE methods have been confirmed during assay validation through analysis of a forced degradation sample.

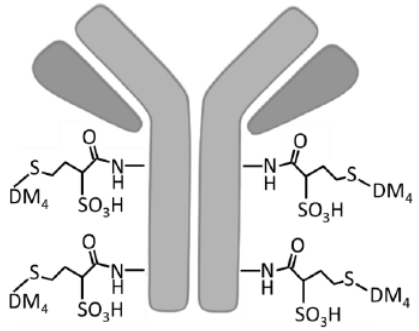
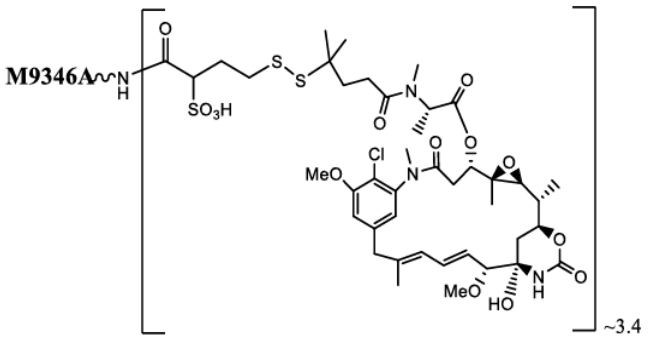
According to the applicant, the ongoing stability studies for the M9346A antibody process performance qualification (PPQ) batches will continue post-approval in accordance with the established stability protocol. Post-approval, at least one M9346A antibody batch per year will be added to the stability program under the post-approval protocol, provided a M9346A antibody batch is manufactured during that year. Any batch confirmed to fall outside of approved stability specification will be reported to health authorities in accordance with applicable regulations. The post-approval stability protocol has been provided and is considered acceptable.

2.4.5. Active substance: mirvetuximab soravtansine

2.4.5.1. General Information DS

Mirvetuximab soravtansine is an antibody-drug conjugate (ADC) manufactured by conjugating the monoclonal antibody M9346A to the maytansinoid payload DM4 via the sulfo-SPDB linker. The DM4 and sulfo-SPDB molecules are linked through a disulfide bond. This payload-linker moiety is covalently linked to the antibody through lysine residues via the NHS ester group on sulfo-SPDB. A schematic diagram of mirvetuximab soravtansine is provided in Figure 4. The ADC contains an average of 3.4 DM4 payload molecules bound to each M9346A antibody.

Figure 4: Structure of mirvetuximab soravtansine

Schematic Diagram of the Mirvetuximab Soravtansine Structure		 Note: For illustration purposes only – not intended to represent precise conjugation sites.
Chemical Structure of the Payload-Linker Moiety		 Note: Nitrogen near M9346A is derived from the ε-amino group on the lysine of the antibody.
Molecular Formula		M9346A - $[C_{42}H_{59}ClN_3O_{14}S_3]_{\sim 3.4}$
Molecular Weight		M9346A is approximately 145,678 Da Each payload-linker moiety increases molecular weight by 960 g/mol

2.4.5.2. Manufacture, process controls and characterisation DS

Description of manufacturing process and process controls

The DS manufacturing process has been adequately described.

In general, the manufacturing process for Mirvetuximab soravtansine DS has been clearly defined and the purpose of each manufacturing step has been discussed in sufficient detail. The overall manufacturing process has been outlined in a high-level flow-diagram and separate tables indicating critical and key process parameters (inputs), as well as performance indicators and in-process controls (outputs) are provided. Non-key process parameters are also assigned. The hold times applied in the DS manufacturing process are listed.

The Container Closure system

The container closure system used for mirvetuximab soravtansine DS is 10 L polycarbonate (PC) bottle closed with a white polypropylene (PP) closure (cap) containing a silicone liner. A schematic diagram of the container as well as specifications for the 10 L PC bottle, PP cap, and silicone liner were provided in the dossier. The container is accepted based on a visual inspection and a check of the supplier CoA. The name and the address of the sites of sterilisation of the drug substance container closure system have been provided, in accordance with "Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container" (EMA/CHMP/CVMP/QWP/850374/2015).

To ensure the selected container closure system was appropriate for storage of the DS, an extraction simulation study was performed. Based on these results, no chemical species or trace metals were identified for monitoring as potential leachable substances in the DS solution. Compatibility of DS with the container closure system materials was demonstrated by placing the DS on long-term stability study in reduced size containers (5 mL) from the same type and material of construction as the 10 L closure system used to store the DS. Compatibility was confirmed by performing the complete panel of release tests on stability samples. No significant changes in product quality attributes were observed when the DS was stored at the intended storage condition.

Control of materials

Raw materials used in the manufacture of the DS have been listed together with information on the quality and control of these materials. Most materials are of compendial grade (USP/NF, Ph. Eur.). Compendial raw materials are tested in accordance with the corresponding monograph. Specification, including test methods, is provided for the non-compendial material (DMA). No animal derived materials are used in the manufacturing of the DS. Polysorbate (Tween) 20 is of biological (vegetable) origin. Polysorbate 20 does not pose a significant viral or TSE/BSE risk. In addition, the filters used in the DS manufacturing process are listed.

Overall, sufficient information on the raw materials used for DS manufacturing has been provided.

The incoming DSIs (DM4, sulfo-SPDB, and M9346A antibody) for DS manufacturing are accepted based on supplier CoA, confirmation of transport conditions and identification testing.

Control of critical steps and intermediates

Listed summaries of critical process parameters (CPPs, inputs to the process that impact CQAs), critical quality attributes (CQAs) measured in-process, and the critical outputs (CPIs, critical performance indicators, and hold times) that impact CQAs, with their acceptance criteria for each step of the antibody manufacturing process have been provided. In addition, short descriptions of the analytical methods used for in-process testing were provided. The criticality of controls was determined using a risk-based approach based on process understanding gained throughout process development. The ranges for process parameters were defined based on process characterisation data generated by altering the normal process conditions at small-scale. The ranges for the performance indicators were defined based on process characterisation, safety, and microbial controls. Hold times were based on a

combination of small-scale physico-chemical stability studies and at-scale microbial hold studies. There are no isolated or critical process intermediates identified for DS. Overall, acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests. Actions taken if limits are exceeded are specified. The presented process controls for DS manufacturing are considered appropriate.

Process Validation and/or Evaluation

The validation of the DS manufacturing process was performed at the commercial scale using 3 consecutive batches. Analytical methods used for in-process testing were verified/validated before the start of the PPQ. During manufacture of the PPQ batches, the process was executed with process parameters (PP) at target operating conditions or within normal operating ranges (NORs) based on platform knowledge and manufacturing experiences with engineering and clinical trial batches. Critical and key process parameters were confirmed as remaining within NORs. The performance indicators and critical quality attributes (CQAs) were evaluated throughout the manufacturing process. Each PPQ batch was required to meet predetermined limits and acceptance criteria. Critical and key process parameters complied with the predetermined NORs, and in-process controls met pre-determined acceptance ranges/limits. Release testing for the DS PPQ batches were consistent and all results met the specifications. No deviations were reported that had an impact on product quality or the manufacturing process validation. In conclusion, the presented process validation studies are considered to be appropriately addressed and in line with current guidance and the conducted PPQ studies demonstrate that the manufacturing process consistently produces active substance of reproducible quality that complies with the pre-determined specification and in-process acceptance criteria.

Continued process verification will be started to monitor, analyze for trends (shifts, drifts, outliers), and to evaluate the trends to ensure that the validated process remains in a state of control.

The DS is manufactured at the same site as the DP and therefore shipping validation was not required.

Manufacturing process development

The commercial DS manufacturing process was defined based on experience and knowledge gained from early phase process development, late phase process characterisation studies, technical transfer, and engineering runs. Further process knowledge was gained through closely monitoring the cGMP manufacturing of clinical trial material. Additional knowledge was gained through the evaluation of process robustness and reproducibility and PPQ. A risk-based approach to process development was followed in accordance with ICH Q11.

Two comparability assessments have been conducted to evaluate the analytical comparability of DS manufactured with Process A and B, and with B and C. For each change, it has been demonstrated that the change did not have a significant influence on the quality of the product. The analytical comparability was executed based on a risk assessment of the process changes being made to ensure any product quality attributes that may be impacted were examined. Analytical comparability included an assessment of release data, characterisation tests, as well as an assessment of the DS on stability at the long-term stability condition and at a stress stability condition. In the comparability assessment between Process A and Process B slightly reduced levels of fragments were observed in Process B batches compared to Process A batches in release testing. Overall, however, the characterisation testing indicated comparability of the expected maytansinoid distribution profile, unconjugated antibody levels, and the number of conjugation sides for the Process A and Process B batches. In the

stability assessment DS was stable with no trends at long term stability condition or at the stress condition. In conclusion, the comparability between Process A and Process B can be considered confirmed. A second comparability assessment was performed to demonstrate comparability between Process B and Process C batches. All attributes from release tests from the three Process C batches met pre-defined comparability target ranges. To further evaluate the comparability between the Process B and Process C batches, additional attributes such as unconjugated antibody, conjugation sites, and maytansinoid distribution profiles were assessed. No differences were observed between the material from the two processes. Additional forced degradation studies were performed to confirm that the degradation kinetics were comparable between the Process B and Process C batches. The results from the release tests, characterisation tests, forced degradation study, and stability studies confirm that the DS manufactured by Process C and Process B are comparable and that the changes made to Process C do not impact product quality.

To define the appropriate process control strategy, a failure mode effect analysis (FMEA) was performed for Process C to define parameter risk levels and to identify parameters that required additional evaluation during process characterisation (PC) studies. Finally, normal operating ranges (NORs) and proven acceptable ranges (PARs) were defined for PPs, and acceptable ranges were defined for PIs. The final process risk assessment evaluated the role of each process parameter and performance indicator in determining the consistent performance of the process and the quality of the DS. The control of critical and non-critical quality attributes (CQAs and non-CQAs) was developed using both data- and risk-based approaches. The DS control strategy comprises material controls, control of process parameters for each unit operation, and testing controls including in-process testing and release testing to ensure process consistency, reproducibility, and desired product quality. Overall the process characterisation studies have been appropriately addressed and the rationale for control strategy is clearly presented.

Characterisation

The active substance has been sufficiently characterised. The characterisation included determination of drug loading distribution, conjugation sites, charge profiles, secondary structure, higher order structure, and biological activity. The structure of mirvetuximab soravtansine was confirmed and in vitro biological properties are as expected. Overall, the studies included in the DS characterisation are considered relevant and comprehensive.

Impurities from DSIs, unreacted DSIs, process-related impurities, and product-related impurities as potential impurities in the mirvetuximab soravtansine DS have been considered. Potential and actual impurities were well discussed with regards to their origin and characterised.

A comprehensive extractables and leachables risk assessment was performed for the DS manufacturing process and an extractables and leachables study was performed on the DS container closure materials. No trace metals were observed above the analytical evaluation threshold. No volatile compounds, or semi-volatile compounds from the process equipment and processing aids were observed above the analytical evaluation threshold (AET). No chemical species were identified for monitoring as potential leachable substances in the DS solution from the DS container closure.

Since the DM4 payload is classified as genotoxic, impurities were not assessed for genotoxicity, in accordance with ICH S9.

2.4.5.3. Specification

The specifications for the mirvetuximab soravtansine drug includes tests physico-chemical tests (color, clarity, pH, and osmolality), an identity test (ELISA), tests for potency (ELISA binding assay and a cell-based specific cytotoxicity assay), tests for content (UV spectrophotometry for protein and DM4 concentration, and maytansinoid-antibody ratio), tests for purity and impurities (SE-UHPLC for purity, reduced and non-reduced CGE for molecular integrity, SE-RP-HPLC for free maytansinoids, and RP-HPLC for residual DMA) and microbiological tests (bioburden and bacterial endotoxins).

Overall, the test parameters proposed to be included in the DS specification are considered relevant and in line with current guidance.

Analytical methods

Mirvetuximab Soravtansine DS is tested using a combination of compendial (colour, clarity, pH, osmolality, bioburden, and bacterial endotoxins) and non-compendial methods (ELISA for identity and potency, cell based cytotoxicity assay for potency, UV Spectroscopy for protein content, DM4 concentration and maytansinoid-antibody-ratio, SE-HPLC for purity, reducing and non-reducing CGE for molecular integrity, SE-RP-HPLC for free maytansinoids, and RP-HPLC for residual DMA).

Overall, brief but appropriate method descriptions that include information on critical materials and equipment as well as method details and operational parameters have been provided for all methods. Compendial methods that require suitability testing have been verified and the results are presented for bioburden and endotoxin. The results meet the requirements set in the Ph.Eur.

In general, the validation for all non-compendial analytical methods follow ICHQ2 (R1). All predetermined validation acceptance criteria were met, and all methods are considered validated for their intended use

Historical analytical methods for DS have been described. During product development changes have been made to methods for bacterial endotoxins (compendial method) and free maytansinoids (non-compendial method). For the free maytansinoids method, appropriate comparability studies have been performed to ensure comparability of the analytical results between the historical method and the method validated for commercial use. The validated method showed greater sensitivity for the detection of unspecified impurities.

Batch analysis

Batch data was provided for non-clinical, clinical, and commercial DS batches. The results are within the specifications and confirm consistency of the manufacturing process.

2.4.5.4. Reference materials

A two-tiered reference material system comprising a primary reference material (PRM) and a working reference material (WRM) was established in accordance with ICH Q6B.

2.4.5.5. Stability DS

Real time, real condition stability data on three PPQ batches (full scale primary stability batches) manufactured using the proposed commercial C process, and stored at the long-term condition up to 36 months, and at the accelerated condition up to 6 months and at the stressed condition for up to 6 months has been provided. Additional supportive stability data generated using material from manufacturing processes A, B and C is also provided. The stability samples have been stored in

reduced size containers that simulates the container closure system for the DS. The use of reduced size containers representative of the commercial scale containers in the stability studies is acceptable. The packaging for stability studies simulates the container closure system for the DS.

At the long-term conditions no changes and no adverse trending of data for up to 36 months was observed. The provided data support the claimed shelf-life of 36 months at long term storage conditions.

The analytical methods used in stability studies have been validated. The stability-indicating properties of the analytical methodshave been confirmed during assay validation through analysis of a forced degradation sample.

DS Forced degradation studies were conducted to elucidate the major degradation pathways using various stressed conditions. Four different conditions were used in accordance with ICH Q1A (R2) and Q1B.

Post-approval, any batch confirmed to fall outside of approved stability specifications will be reported to health authorities in accordance with applicable regulations. The post-approval stability protocol has been provided and is considered acceptable.

Overall, the DS stability has been adequately addressed in line with current guidance.

2.4.6. Finished medicinal product

2.4.6.1. Description of the product and pharmaceutical development

The finished medicinal product, also referred to as drug product (DP) of mirvetuximab soravtansine is a sterile and preservative-free, clear to slightly opalescent, colorless concentrate for solution for infusion in 20 mL single-dose vials intended for intravenous use.

Each vial contains 100 mg of deliverable mirvetuximab soravtansine at pH 5.0. No formula overages are included. The container closure system consists of type I glass vial with a butyl rubber stopper and an aluminum seal with a royal blue polypropylene flip cap, containing 20 mL concentrate for solution.

The qualitative and quantitative composition of DP is presented.

Excipients and their function are presented in appropriate manner and the DP formulation does not contain any novel excipients. All the excipients used in the DP comply with Ph. Eur requirements and are commonly used in the manufacturing of parenteral pharmaceutical preparations and are thus considered acceptable.

Comprehensive and systematic pharmaceutical development studies were performed in accordance with ICH Q8 guideline. These studies demonstrated the robustness of the formulation. The rationale for excipient selection is adequately described and justified. The intended commercial formulation is the same as that used during clinical studies.

The manufacturing process development of mirvetuximab soravtansine DP was performed according to ICHQ8 guideline and contained following elements: identification of potential critical quality attributes (CQA), process development and associated comparability evaluation, additional process development studies, risk assessment based on failure mode and effects analysis (FMEA), process characterisation studies.

The identification of CQAs concentrated on attributes having potential effect on biological activity, pharmacology, immunogenicity or safety and was in addition based on ICH Q3C and ICH Q6B

guidelines and risk assessment. CQAs were associated with the drug substance and antibody-DSI. The approach for identifying the CQAs is considered appropriate.

The process development history of DP includes four process versions (from process A through D). In general, the changes in the manufacturing processes with the emphasis on processes B, C and D are minor mainly relating to suite change (same facility) and scale-up. The changes in the manufacturing processes are described with sufficient details in the dossier and the rationale for each step has been provided. Analytical comparability of the manufacturing processes was demonstrated by utilizing two approaches: the comparison of DP manufacturing processes A, B and C and the comparison of DP manufacturing processes C and D. No extended characterisation or forced degradation data was provided but this is considered acceptable due to relatively minor changes between the manufacturing processes and also taking into consideration that the manufacturing process comparability studies of drug substance included characterization and force degradation data in addition to release and stability data all of which confirmed the comparability of drug substance manufacturing processes. Overall, the comparability data provided is adequate and confirms the analytical comparability between the manufacturing processes of the DP.

Several *additional studies* were conducted to support the development of the DP manufacturing processes. Extractables and leachables relating to manufacturing equipments in contact with DP were evaluated. The transport evaluation was conducted by shipping simulation study. Overall, transport arrangements are relevant and have been justified and/or validated in acceptable manner

The process characterisation studies were performed at lab scale experiments, machinability/ qualification runs and engineering run at full scale. The testing ranges were based on manufacturing suite limitations (instruments, environment), worst case process parameters, or set up beyond the normal operating ranges to evaluate the impact of variation on product/process. Overall, process characterisation demonstrated that the DP manufacturing process is robust and can deliver the required product quality and process consistency when operated within acceptable ranges.

The primary container closure systems (CCS) of the finished DP consists of type I clear borosilicate 20 mL glass vial closed with butyl rubber stoppers coated with ethylene tetrafluoroethylene and capped with an aluminum seal with a royal blue polypropylene flip cap. The vials meet Ph.Eur. 3.2.1 requirements for type I glass containers. Vial stopper meet the Ph.Eur 3.2.9. requirements and does not contain any latex. Certificate of analysis was provided for each CCS component and are considered acceptable. The same CCS has been used throughout the DP development.

Appropriate extractables and leachables studies were performed with the stopper. These studies indicated that the observed extractables and leachables were clearly below the permitted daily exposure. The applicant provided leachable data covering 48-month (upright and inverted configuration) and 60-month (upright configuration) showing that the amount of all detected organic compounds was below the permitted daily exposures. The data of 60-month at upright position was missing but the applicant commits to notify the health authority in case of unexpected results. This is acceptable. Compatibility of the primary container closure components with the DP and suitability of the CCS was addressed during pharmaceutical development and confirmed by container closure integrity and stability tests. The provided data clearly indicates that the selected CCS is appropriate and enables adequate protection from microbial contamination.

2.4.6.2. Manufacture of the product and process controls

Mirvetuximab soravtansine DP is manufactured and tested at various sites. Valid proof of GMP compliance has been provided for all sites involved in DP manufacturing.

The standard manufacturing process comprises of drug substance thawing and pooling, pre-filtration, sterile filtration, aseptic filling, stoppering, oversealing and crimping. Then, the vials are externally washed, visually inspected and stored 2-8°C at the manufacturing site. The labelling and secondary packaging is done at the different site than manufacturing. A narrative description of the full manufacturing process was provided, accompanied by a flow chart describing each step of the process including in-process controls with acceptance criteria.

Hold times during the manufacturing process are clearly summarised, justified and validated. The claimed hold times are considered acceptable and are in line with the relevant guideline.

Process controls - Critical process parameters (CPPs) and performance indicators (CPIs) with their associated acceptable ranges (CPPs) and acceptance criteria or limit (CPIs) have been presented in the tables for all relevant manufacturing steps. Also applied test methods are presented for CPIs. CPPs and CPIs were presented for drug substance pooling, sterile filtration, aseptic filling and visual inspection. In general, the acceptance criteria for the CPPs and CPIs can be agreed and are appropriately validated during manufacturing process validation. The limits for bioburden are in accordance with the relevant guideline.

The overall control strategy including identification of controlled process parameters and performance indicators with associated target values/ranges/limits has been described in appropriate manner. All process parameters are controlled to setpoints within normal operating ranges (NORs) which are mainly aligned with proven acceptable ranges (PARs). Rationale and justification for the classification of process controls applied in DP manufacture as critical or non-critical (=key) was provided. Overall, the presented process controls seem appropriate and the proposed control strategy for the DP manufacturing process can be agreed.

The DP manufacturing process was validated by producing three consecutive commercial scale PPQ batches at the commercial manufacturing site, BSP Pharmaceutical. Manufacturing process validation included steps for drug substance thawing, DP pooling/mixing, DP transfer and filtration, aseptic filling, stoppering/crimping, external washing and visual inspection. Overall, all PPQ batches were successfully validated, the presented data met acceptance criteria, demonstrating consistency and reliability of the DP manufacturing processes. All batches met the release results of the proposed commercial specification acceptance criteria. The batch numbering system is provided for the DP batches

Filter absorption, solution and chemical compatibility as well as extractable/leachable studies were tested during manufacturing process development in appropriate manner.

The aseptic process validation (media fills) was carried out for three media fill batches representing the commercial configuration. The media fill validation data was provided in the MAA but is not assessed since it is considered to be covered by GMP. Materials and equipment that will be in contact with the sterile DP are sterilised by autoclavation /depyrogenated prior to introduction into the manufacturing process. The components (stoppers and overseals) and process equipment (solution preparation and filling) are sterilised via autoclavation. The validation data of the sterilisation process demonstrated a SAL of $\geq 1x10^6$. Vials are depyrogenated after washing and rinsing. Validation data for depyrogenation is provided and criterion of reduction in recoverable endotoxin was met.

2.4.6.3. Product specification, analytical methods, batch analysis

Release and shelf-life specifications for the finished DP of mirvetuximab soravtansine cover all relevant characteristics and are set in accordance with ICH Q6B principles and according to Ph.Eur. requirements. The comprehensive panel of specifications includes tests for identity (ELISA based method), potency (assays for direct target binding and cell based cytotoxicity), purity and impurities

(monomer/HMW by SE-UHPLC, reduced and non-reduced molecular integrity by CGE, free maytansinoids, unconjugated antibody and elemental impurities), microbiological quality (sterility, bacterial endotoxins, pyrogens and container closure integrity), content (protein, total DM4 and polysorbate 20 concentration, maytansinoid-antibody ratio and gross content) appearance (appearance, color and clarity), and general physicochemical properties (pH, osmolality, subvisible particles, and extractable volume). Overall, a sufficient panel of quality attributes is proposed for release and shelf-life specifications of the finished DP and although sparse the provided justifications for specifications are considered adequate.

The presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on three batches using a validated ICP-MS method was provided. Based on the risk assessment and the presented batch data it is agreed that the elemental impurities are controlled in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Analytical methods utilised in the specification determination of the finished DP include both compendial and non-compendial methods and are described, discussed and assessed both in the drug substance and drug product sections. Compendial methods including appearance, color, clarity, bacterial endotoxins, sterility, pH, osmolality, subvisible particles and extractable volume are based on respective Ph.Eur. or USP monographs. Compendial methods that require suitability testing have been verified and the results are presentedfor endotoxin, sterility and elemental impurities. The results for sterility and elemental impurities met the requirements set in the Ph.Eur. The current endotoxin method presents a low endotoxin recovery. The applicant is recommended to demonstrate compliance with the revised Ph.Eur texts omitting the RPT and Pyrogenicity (5.1.13) that will be published in Supplement 11.8 of the Ph. Eur., with an implementation date of 1 July 2025, post-approval (REC 1). Since the in-house method for the container closure integrity is based on visual inspection of colour, the applicant is recommended to establish a method for container closure integrity with quantitative limit of detection based on spectrophotometric determination to be utilised in stability program and submit updated versions of the method by January 31, 2025 (REC 2)**.** In-house methods for polysorbate 20 concentration and unconjugated antibody have been appropriately validated according to the principles of ICH Q2 (R2) guideline and are confirmed to be suitable for their intended use.

Batch analytical data was provided for non-clinical, clinical and commercial DP batches (including 1 Process A batch, 8 Process B batches, 10 Process C batches and 8 Process D batches). Overall, all batches met the acceptance criteria of release in place at the time indicating adequate batch-to-batch consistency and controlled manufacturing process.

Reference materials

Please see reference standards of the active substance.

2.4.6.4. Stability of the product

Real time/real condition stability data on three primary batches (PPQ batches) manufactured at a pilot scale representative of the commercial process, using the same formulation and identical CCS, have been placed under long term storage conditions (5°C ± 3°C) for up to 48 months for upright and 36 months for inverted position as well as under accelerated (25°C ± 2°C/60% RH ± 5% RH) conditions for up to 6 months (both upright and inverted), in line with ICH Q1A and ICH Q5C. Supportive data from six batches is presented. The CCS used for supporting lots is identical to that for primary lots. Furthermore, 9 months data was provided for one production lot. Samples stored at the recommended storage conditions met the stability acceptance criteria. Slight increasing trend was observed in HMW of SE-UHPLC data and in total free maytansinoid corresponding to free DM4-sulfo TBA. High variation in the number of particles was observed with no clear trend. No statistical analyses of the stability data were performed.

Photostability studies were performed in appropriate manner according to ICH Q1B guideline including white light and UV light exposures. This supports the conclusion that the DP should not be exposed to direct white light for an extended period of time.

The data support the proposed shelf-life of 60 months is proposed for the finished DP stored at the recommended storage conditions: "Store upright in a refrigerator (2 °C - 8 °C). Do not freeze. Keep the vial in the outer carton in order to protect from light".

A post-approval stability protocol has been provided. The provided protocol is considered acceptable.

In-use stability studies – The finished DP of mirvetuximab soravtansine is a concentration for solution for infusion and must be diluted before IV administration. The applicant performed compatibility studies with two diluents: 0.9% NaCl and 5% dextrose. The study demonstrated that mirvetuximab soravtansine is compatible with 5% dextrose but incompatible with 0.9% NaCl. Thus, only 5% dextrose solution can be used for the dilution of the finished DP.

The following shelf life for the diluted solution is given in the SmPC: "After dilution, the chemical and physical stability has been demonstrated between 1 mg/mL and 2 mg/mL for 8 hours at 15 °C - 25 °C or for 24 hours at 2 °C - 8 °C followed by 8 hours at 15 °C - 25 °C." In-use stability studies including four separate studies were conducted to assess compatibility with a wide range of commonly used IV bags, infusion sets, and catheters used to prepare, store, and administer diluted DP. Studies 1, 2 and 4 were performed at ambient temperature for 8 hours and in study 3 the diluted DP was held first at 2-8°C for 24 hours and then at ambient temperature for 24 hours. The proposed in use shelf life is acceptable, however the applicant is recommended to perform in-use stability study with one of the PPQ batches at 75% of the shelf-life The EMA should be notified in case of unexpected results. According to the SmPC (section 6.6) 0.2 or 0.22 µm polyethersulfone inline filter should be used during IV infusion. The applicant has justified the usage of inline filter.

2.4.7. Adventitious agents

Non-viral and prion adventitious agents

No animal derived materials were used in the generation and establishment of the MCB or during the manufacturing of the M9346A antibody and the manufacturing process of mirvetuximab soravtansine does not contain any material of human or animal origin. Therefore, the risk of adventitious agents entering the DP is in general considered low. Cell banks (MCB and PPCB) have been tested for sterility and mycoplasma, and testing is performed during the antibody, DS, and DP manufacturing process to monitor any possible contamination by bacteria, or fungi. The risk of microbial and mycoplasma contamination has overall been adequately addressed.

Viral adventitious agents and viral clearance studies

Materials of biological origin were used early in cell line development prior to the creation of the research cell bank (RCB). Viral risk assessment concluded materials derived from human blood were tested and shown to be non-reactive for anti-HIV1&2, Anti-HCV, and HBsAg. All materials from bovine origin were derived from cattle born, raised, and slaughtered in countries where BSE was not known to exist at the time these materials were made. Sheep plasma was collected from live animals that were healthy with no sign of disease. The results of RCB viral testing confirm the RCB is negative for the presence of viral contaminants tested and the viral risk assessment concluded the materials of biological origin utilised early in development of the CLD238 cell line demonstrate acceptable low viral safety risk.

The MCB was manufactured from the cell line CLD238 using no materials of animal origin. MCB testing included bovine and porcine viruses in accordance with ICH Q5A. In addition, the PPCB was tested using both in vitro and in vivo assays for the absence of viral adventitious agents. The full data on MCB and LIVCA characterisations has been provided. Testing is performed routinely during the antibody manufacturing process to monitor any possible viral adventitious agent contamination at the production bioreactor step. Viral safety testing has been performed for unclarified harvest generated from the M9346A Antibody Manufacturing Process in accordance with Q5A and Q6B. The method used for viral control at the different stages of the manufacturing process development and control has been described with enough details in order to be able to evaluate their suitability. Unprocessed bulk of DSI mirvetuximab is tested for absence adventitious virus and the methods are sufficiently described.

Scale-down models of the commercial purification process were employed to evaluate the ability of specific processing steps to remove and/or inactivate potential viral contaminants in accordance with requirements in ICH Q5A(R1). The process steps evaluated were protein A affinity chromatography, low pH viral inactivation, FT anion exchange chromatography, and viral retentive filtration. The choice of model viruses tested (Xenotropic Murine Leukemia virus (XMuLV), Mouse Minute Virus (MMV), Pseudorabies virus (PRV), and Reo virus Type 3 (Reo-3)) is considered acceptable. Viral clearance studies for the chromatography steps were performed using both new and aged resin to assess any significant difference in the capability of aged resins in removing viruses. The chromatography columns were run under worst-case conditions. Scale-down models were used in the evaluation. The full reports of viral clearance studies were provided.

Viral load data over time for the low pH inactivation step shows there is no active PRV detected in the T= 0 min sample suggesting rapid kinetics of inactivation under the tested conditions. The results for the XMuLV virus show that this virus is resistant to the pH treatment at the worst-case condition tested during this study. Both chromatographic steps (protein A affinity chromatography and anion exchange chromatography) contribute to the virus removal. The lowest overall clearance was at least 13.76 log10 (MMV) and the highest was at least 19.34 log10 (PRV). It was also demonstrated that resin use for up to 100 cycles for protein A chromatography resins and up to 40 cycles for anion exchange chromatography resins does not negatively affect virus reduction. Overall, the inactivation/removal of different types of viruses is sufficiently demonstrated. At least two orthogonal steps are demonstrated to achieve a LRF of over 4 log and therefore the overall cumulative reduction is considered safe and acceptable.

To estimate the potential number of retrovirus-like particles present in a dose of finished product, the applicant has tested a sample of unpurified harvest material. Using the test data along with values for process yield, log viral clearance, product dosing level, and average weight of a patient, the applicant calculated an estimate that less than 1 endogenous virus-like particle in 106 doses of finished product is expected, which represents low risk.

2.4.8. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Overall, no major objections related to Module 3 were identified during the procedure; a number of other concerns were raised. These issues have been appropriately addressed during the procedure. Two recommendations related to the container closure integrity test of the finished product and the pyrogen test of the finished product have been raised for the applicant's consideration.

2.4.9. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.10. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

Area	Number	Description	Classification	Due date
Quality	1	The applicant is recommended to establish a method for container closure integrity for the finished product with quantitative limit of detection to be utilised in stability program and submit updated versions of the method.	REC	January 31, 2025
Quality	2	In view of the 3R principles and the overhaul of the Ph. Eur. pyrogen testing strategy, the rabbit pyrogen test (RPT) should be replaced with suitable alternative in vitro tests. The EDQM has announced the adoption of 57 Ph. Eur. texts omitting the RPT, together with the new general chapter on Pyrogenicity (5.1.13). The revised texts omitting the RPT and Pyrogenicity (5.1.13) will be published in Supplement 11.8 of the Ph. Eur., with an implementation date of 1 July 2025. It is the applicant's responsibility to ensure compliance with the Ph. Eur. As a consequence, the applicant is recommended to submit, after the granting of the MAA and without undue delay, a variation to replace RPT with a suitable in vitro test to control the pyrogenicity of the product (e.g. methods described in general chapters 2.6.14.	REC	

		Bacterial endotoxins, 2.6.30. Monocyte-activation test or 2.6.32. Test for bacterial endotoxins, or other suitable alternative method, demonstrating compliance with the Ph. Eur)".		

2.5. Non-clinical aspects

2.5.1. Introduction

The non-clinical development of mirvetuximab soravtansine was conducted as per International Conference for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) S9 Guidelines and Q&As: Nonclinical Evaluation for Anticancer Pharmaceuticals.

The expression of FRα in normal and tumour tissues was evaluated by immunohistochemical (IHC) and microarrays analyses of formalin-fixed, paraffin-embedded (FFPE) normal tissue and ovarian cancer tissues using an anti-human FRα mouse monoclonal antibody (M9246A). Pharmacokinetic (PK) and metabolic disposition studies were conducted with MIRV in animal species used in the evaluation of the toxicological properties of the drug, ie, Dutch Belted rabbits and cynomolgus monkeys. The toxicity and toxicokinetic profile of mirvetuximab soravtansine was assessed in a single dose administration and a 10-week GLP repeat dose GLP toxicity studies in cynomolgus monkey. Ocular evaluations with MIRV were performed in pigmented male Dutch Belted rabbits in repeat intravenous (IV) administrations GLP study. The toxicity of DM4 payload was assessed in non GLP single dose toxicity studies in the mouse and cynomolgus monkey. DM4 and the active metabolite S-methyl DM4 were assessed *in vitro* for the genotoxic potential in a bacterial reverse mutation assay and *in vivo* in Sprague Dawley rats for the clastogenicity.

EMA Scientific Advice for non-clinical development was received on 13 October 2016 on the chronic toxicity study, toxicology studies of the toxin DM4, Non-clinical Safety Studies Plan and QT/QTc Study.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

The primary pharmacodynamic studies included characterisation of the FRα expression in normal and tumor tissues, the binding to the target cell surface FRα and specificity including tissue-cross reactivity studies, intracellular processing and cytotoxicity resulted from the release of DM4-containing cytotoxic catabolites (primarily S-methyl-DM4), induction of cell cycle arrest, bystander effect, immune effector activity (ADCC, ADCP and CDC) and anti-tumour activity in ovarian cancer xenograft models).

FRα expression in human tissues

FRα is overexpressed in non-mucinous tumors of epithelial origin, including ovarian, endometrial, renal, and lung cancers, and has limited expression in normal human tissues. FRα expression in tissues were in line with published data and demonstrated that 72% of ovarian cancers and 52% of endometrial cancers were FRα positive. 83% of the serous ovarian cancer subtypes were positive, followed by endometrioid and clear cell subtypes (68% and 67% respectively). These data support the

proposed therapeutic use of the MIRV. Ocular expression of FRα was noted in ciliary bodies, in the pigmented epithelial cells.

The levels and patterns of FRα expression in the human and monkey kidneys were similar showing strong staining of proximal tubules, but differences were seen in the lung. Lower than human expression of FRα in pneumocytes and no staining in bronchial epithelium was noted in the monkey lung.

MIRV binding to FRα, specificity and tissue cross-reactivity

M9346A bound to cells expressing FRα with high affinity Kd of 0.05 -0.1 nM. Binding was specific. The conjugation to DM4 maytansinoid moiety did not impact the binding affinity. M9346A did not block or compete binding of a natural FRα ligand, folate, to the FRα.

MIRV (and M9346A) cross-reacts only with rhesus and cynomolgus monkey FRα, out of toxicological species. The binding affinity of M9346A to cynomolgus monkey FRα (from cells and kidney lysate) was similar to that of human FRα. M9346A does not bind to other folate receptor family members FRβ, FRγ or FRδ.

The immunoreactivity of MIRV with human and monkey tissues was similar in 8 frozen tissues including choroid plexus (epithelial cells), fallopian tube (surface epithelium), kidney (ducts and tubules), lung (respiratory epithelium and bronchial glands), pancreas (ducts), salivary gland (acinar cells and ducts), parathyroid (epithelium), pituitary (pituitary cells). Epithelial cells of the spinal cord and surface epithelium of the stomach showed similar intensities but differed in staining pattern (membrane staining noted in human and cytoplasmic staining in monkey). Significant staining discrepancies were noted in bronchial epithelium of the lung (strongly stained in human, minimal staining in monkey), the duct of human breast and eccrine sweat glands of the skin which were positive in human and weak or negative in monkey.

MIRV MoA and *in vitro* potency

Activation of MIRV occurs *via* internalization and lysosomal processing. MIRV is internalized by the target cancer cells via antigen-mediated endocytosis, delivered to lysosomes by the vesicular trafficking, and degraded into lysine-Nε-Sulfo-SPDB-DM4. Lysine-Nε-Sulfo-SPDB-DM4 undergoes further intracellular reduction and S-methylation, leading to the formation of DM4 and the active metabolite S-methyl DM4. All cancer cell lines tested had similar sensitivity to unconjugated cell-permeable S-methyl DM4.

Maytansinoid DM4 induces metaphase G2-M phase arrest of dividing cells and inhibits the polymerization of tubulin resulting in cell death. S-methyl DM4 was highly cytotoxic with IC_{50} values from 1.1 to 32 pM.

MIRV has bystander effect. It was demonstrated that in mixed culture of FRα-negative and FRα-positive cells exposed to 5 nM MIRV, the degree of cytotoxicity was similar to that upon incubation of MIRV with FRα-positive cells alone.

Sensitivity for cytotoxicity of cervical, ovarian and placental cancer cell lines correlated with FRα membrane expression levels (Table 1, Figure 5). The amount of catabolites generated was directly proportional to the level of FRα expression (Table 1). The threshold of antigen mediated sensitivity of cells to MIRV was between 20,000 to 150,000 antibody-drug-conjugate. The lysosomal degradation ranged from 24% on OVCAR-3 cells to 57% for JEG-3 cells. The ABC (Antibody Binding site per Cell) values ranged from 58,000 for the resistant OVCAR-3 to 4500,000 for the highly sensitive KB cells.

Table 1: Summary of the in vitro cytotoxic activity of MIRV

Cell Line	FRα Expression, Ab Binding Sites per Cell[a]		MIRV IC_{50}, nM	MIRV + Excess (0.5 mM) M9346A, Control IC_{50}, nM	Fold Decrease in Cytotoxicity with Unmodified Antibody (Control IC_{50}/ IC_{50})
	FACS	3H-M9346A Binding Assay			
KB cervical carcinoma	4,000,000	2,400,000	**0.1**	2	20
IGROV-1 ovarian carcinoma	400,000	990,000	**0.5**	10	20
JEG-3 placental choriocarcinoma	150,000	140,000	1.0	12	12
SKOV-3 ovarian carcinoma	20,000	30,000	10	10	1
OVCAR-3 ovarian carcinoma	7,000	13,000	**2**	2	1

a):ABC values are reported for two different methods: a flow cytometry (FACS) assay using phycoerythrin labelled antibody and radioactivity-based assay using ^{3}H-M9346A. The difference in the values reported may be due in part to differences in the two methods, and to day to day variability of FRα expression.

Figure 5: The sensitivity of FRα positive cell lines to MIRV versus the level of RFα expression.

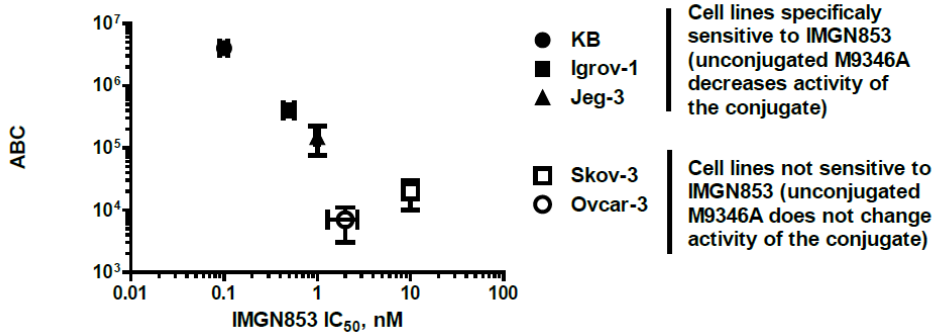
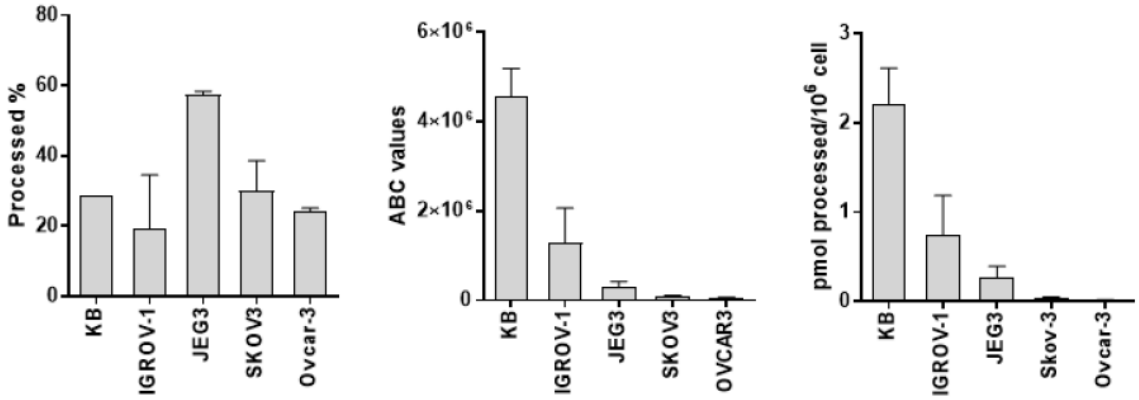
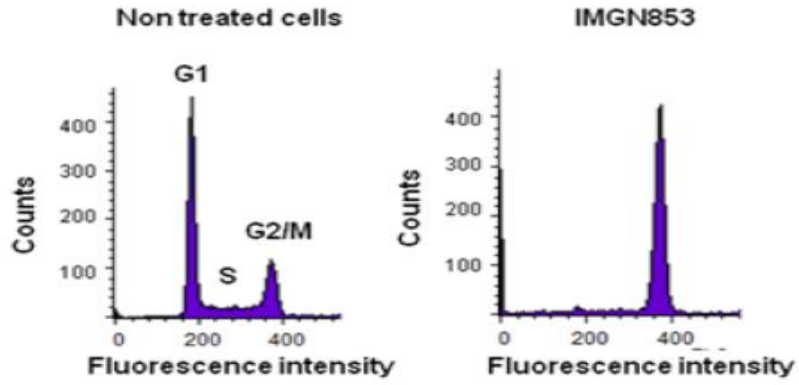


Figure 6: M9346A binding and processing in cancer cells



MIRV induced cell-cycle arrest. 2 nM MIRV increased cells in G2/M phase from 25% to 90% (Figure 7).

Figure 7: Induction of cell cycle arrest



Effector functions

MIRV had ADCC activity in NK effector cells and FRα-positive IGROV-1 target cells and resulted in 30% cell lysis with an EC_{50} of 20 pM. M9346A and MIRV inducted modest ADCP activity that was concentration dependent with EC_{50} values of $1.4x10^{-11}$ M and $4.2x10^{-11}$ M, respectively. The maximal phagocytosis-% was higher in KB cells than in IGROV-1 cells (50% versus 35%). M9346A and MIRV had negligible CDC activity.

In vivo potency

Efficacy of MIRV was assessed in three FRα-positive human ovarian carcinoma models (IGROV-1, OVCAR-3, OV-90) in SCID mice xenografts. To assess anti-tumor efficacy, the tumor growth inhibition value T/C (%) and total log cell kill value (LCK) was calculated. T/C% was calculated from median tumor volume of the treated vs median tumor volume of the control and LCK from the T-C tumor growth delay value in days divided by 3.32 x Td, where Td is the tumor volume doubling time in days. 5, 2.5 and 1.2 mg/kg MIRV IP doses was used in all studies.

IGROV-1 xenograft model: MIRV delayed the tumor growth and extended survival (by 60 days in 5 mg/kg group). %T/C was 9% (for both 5 and 2.5 mg/kg) and LCK 1.6 and 1% for 5 and 2.5 mg/kg (100 and 50 µg/kg of DM4). 1.2 mg/kg dose was ineffective. *OVCAR-3 xenograft model:* MIRV delayed the tumor growth and extended survival (by120 days in 5 mg/kg group). %T/C was 0% and LCK 3.9 and 2.4 for 5 and 2.5 mg/kg (100 and 50 µg/kg of DM4), which according to NCI standards and SRI criteria, are considered indication of a high anti-tumor activity. *OV-90 xenograft model:* MIRV delayed the tumor growth and extended survival (by 40 days in 5 mg/kg group). %T/C was 18% and 33% and LCK 1.9 and 1.2 for 5 mg/kg and 2.5 (100 and 50 µg/kg of DM4), which according to NCI standards and SRI criteria, are considered indication of a moderate anti-tumor activity. Partial regressions in 2/6 animals were noted in 5 mg/kg MIVR treatment group only. Dose 1.2 mg/kg was inefficient.

Xenograft model ***Dose***	**tumor growth inhibition %T/C**	**total log cell kill LCK**	**extended survival (days)**
IGROV-1			
5 mg/kg	9%	1.6	60
2.5 mg/kg	9%	1.0	
1.2 mg/kg	ineffective		

Xenograft model ***Dose***	**tumor growth inhibition %T/C**	**total log cell kill LCK**	**extended survival (days)**
OVCAR-3			
5 mg/kg	0 *	3.9 *	120
2.5 mg/kg	0 *	2.4 *	
1.2 mg/kg	ineffective		
OV-90			
5 mg/kg	18 **	1.9 **	40
2.5 mg/kg	33 **	1.2 **	
1.2 mg/kg	ineffective		

* considered indication of a high anti-tumour activity according to NCI standards and SRI criteria

** considered indication of a high anti-tumour activity according to NCI standards and SRI criteria

In general, MIRV at IV dose of 5 and 2.5 mg/kg (with 100 and 50 µg/kg maytansinoid concentration) delayed the tumor growth but did not result in complete clearance of the tumors. Highest anti-tumor activities were seen in OVCAR-3 xenografts.

2.5.2.2. Secondary pharmacodynamic studies

No secondary pharmacology studies have been conducted with MIRV.

2.5.2.3. Safety pharmacology programme

In a GLP study on HEK293 cells, DM4 inhibited hERG current by 3.1 ± 0.4% at 10 µM and 16.6 ± 0.7% at 60 µM ($P < 0.05$) versus 2.2 ± 0.5% in control cells. S-methyl DM4 increased the hERG current by 6.7 ± 0.7% at 10 µM and inhibited the current by 4.4 ± 0.3% at 60 µM versus 1.5 ± 0.8% in control cells, at both concentrations the changes to current were statistically significant ($P < 0.05$). The IC_{50} for the inhibitory effect of DM4 and S-methyl DM4 on hERG potassium current could not be calculated but was estimated be > 60 µM.

Safety pharmacology parameters were assessed in the GLP 10-week repeat dose toxicity study in male and female cynomolgus monkeys.

Electrocardiograms using jacketed external telemetry procedures were collected once during the predose phase for each sex; on Days 10 and 52 of the dosing phase; and on Day 10 (males) or 12 (females) and Day 31 (males) or 33 (females) of the recovery phase. Blood pressure and vital signs (respiration rates, pulse oximetry, and body temperature) were also assessed. No cardiac, CNS or respiratory effects were identified in cynomolgus monkeys after IV administration of MIRV up to 8 mg/kg for 4 doses on a Q3W schedule.

2.5.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interactions studies have been conducted with MIRV.

2.5.3. Pharmacokinetics

Methods of analysis

PK and metabolic disposition studies were conducted with MIRV in animal species used in the evaluation of the toxicological properties of the drug, i.e., Dutch Belted rabbits and cynomolgus monkeys. The analytical methods included ELISA and LC/MS/MS to quantitate the amount of MIRV, total antibody (TAb), N2′ -deacetyl-N2′ -(4-mercapto 4-methyl-1-oxopentyl) maytansine (DM4), the metabolite S-methyl DM4, and anti-drug antibodies (ADA) in various sample matrices.

All bioanalytical methods used to support the GLP-compliant toxicology study of MIRV with a TK component were fully validated according to applicable FDA/EMA guidance and demonstrated acceptable precision, accuracy, and reproducibility. The validation also demonstrated adequate stability of samples stored at -70 ºC (or -80±10 ºC), at room temperature, and after freeze/thaw cycles. For GLP studies, sample analyses after the method validation were completed within the duration of storage stability demonstrated for each individual analyte. Procedures established during validation were followed. For non-GLP studies, acceptable accuracy and precision were required and achieved.

Absorption

In both monkeys and rabbits, maximal concentrations for ADC and total antibody (Tab) were observed following immediately post infusion, and both C_{max} and AUC_{∞} generally increased proportionally with dose. In both species and as expected, the observed $t_{½}$ for TAb was approximately 1.5 to 2- fold longer than that observed for ADC, which ranged from 97.4 to 103 hours following single doses and from 105 to 121 hours with repeated administrations in monkeys and 60 to 75 hours with single and repeated administrations, respectively, in rabbits. Maximum DM4 concentrations increased with dose in monkeys, and maximum concentrations of both DM4 and S-methyl DM4 generally increased with dose in rabbits. Peak DM4 concentrations in rabbits were observed immediately following infusions, where T_{max} values for S-methyl DM4 averaged 20 hours. Additionally, in humans median T_{max} of DM4 was ~5-6 h, and that of S-methyl DM4 ~24-48 hours, however there was remarkable variation between the subjects.

A Single-Dose Toxicology Study of Mirvetuximab Soravtansine in Cynomolgus Monkeys (Study Number WRT28-001)

Table 2: Mean ADC PK parameters following single IV administration of MIRV to cynomolgus monkeys.

Parameter	1 mg/kg	3 mg/kg	5 mg/kg	10 mg/kg
C_{max} (µg/mL)	35.6	87.8	135.1	280.6
$t_{½}$ (hr)	86.0	94.7	96.5	98.2
AUC_{∞} (hr*µg/mL)	2142	7015	12716	25583
CL (mL/hr/kg)	0.5	0.4	0.4	0.4
V_{ss} (mL/kg)	45.0	45.3	44.8	42.2

Note: Male and female monkeys were combined for PK parameters.

Table 3: Mean TAb PK parameters following single IV administration of MIRV to cynomolgus monkeys.

Parameter	1 mg/kg	3 mg/kg	5 mg/kg	10 mg/kg
C_{max} (µg/mL)	31.5	75.4	120.2	249.3
$t_{½}$ (hr)	113.1	138.3	167.8	168.9
$AUC_{∞}$ (hr*µg/mL)	2724	9225	15208	30287
CL (mL/hr/kg)	0.4	0.3	0.3	0.3
V_{ss} (mL/kg)	51.6	57.4	74.3	74.3

Note: Male and female monkeys were combined for PK parameters.

Table 4: Mean Cmax of DM4 following a single IV administration of MIRV to cynomolgus monkeys.

Dose Level (mg/kg)	C_{max} (µg/mL)
1	0.035
3	0.062
5	0.095
10	0.129

Note: Male and female monkeys were combined.

10-Week Intravenous GLP Toxicology Study in Cynomolgus Monkeys with a 5-Week Recovery Period (Study Number CVT28-001)

Table 5: Mean (±SD) ADC PK parameters following a single intravenous administration of MIRV at 2, 4, and 8 mg/kg to cynomolgus monkeys: Day 1.

Parameter	2 mg/kg			4 mg/kg			8 mg/kg		
	Male n=6	Female n=6	Both n=12	Male n=6	Female n=6	Both n=12	Male n=6	Female n=6	Both n=12
C_{max} (µg/mL)	51.8 (4.2)	61.3 (9.9)	56.5 (8.8)	112 (11)	110 (12.4)	111 (11.2)	229 (22.4)	214 (27.7)	221 (25.1)
$t_{½}$ (hr)	94.5 (9.39)	100 (11.4)	97.4 (10.4)	96.7 (6.1)	99.4 (10.6)	98.1 (8.3)	99.7 (9.4)	106 (8.1)	103 (9.1)
$AUC_{∞}$ (hr*µg/mL)	5060 (532)	5560 (1070)	5310 (849)	11900 (885)	10600 (1350)	11200 (1280)	22500 (2350)	20800 (4020)	21600 (3270)
CL (mL/hr/kg)	0.399 (0.0451)	0.371 (0.0698)	0.385 (0.0579)	0.338 (0.0253)	0.382 (0.0435)	0.360 (0.0408)	0.359 (0.0412)	0.397 (0.0713)	0.378 (0.0589)
V_{ss} (mL/kg)	44.1 (2.36)	40.6 (5.99)	42.3 (4.69)	38.6 (3.54)	43.2 (4.51)	40.9 (4.55)	41.0 (3.19)	47.0 (7.13)	44.0 (6.14)

Table 6: Mean (±SD) ADC PK parameters following repeated IV administration of MIRV at 2, 4, and 8 mg/kg to cynomolgus monkeys: Day 64.

Parameter	2 mg/kg			4 mg/kg			8 mg/kg		
	Male n=6	Female n=6	Both n=12	Male n=6	Female n=6	Both n=12	Male n=6	Female n=6	Both n=12
C_{max} (µg/mL)	56.5 (5.23)	52.0 (9.86)	54.2 (7.88)	119 (11.8)	106 (8.16)	113 (11.9)	226 (24.0)	216 (19.9)	221 (21.6)
$t_{½}$ (hr)	102[a] (NA)	108[a] (NA)	105[b] (21.7)	129 [a] (NA)	112[a] (NA)	121[b] (11.1)	123[a] (NA)	118[a] (NA)	121[b] (4.12)
AUC_{∞} (hr*µg/mL)	5440[a] (NA)	5090 [a] (NA)	5270 [b] (1070)	12300 [a] (NA)	11300 [a] (NA)	11800 [b] (1240)	23500 [a] (NA)	24100 [a] (NA)	23800 [b] (2210)
CL (mL/hr/kg)	0.369[a] (NA)	0.418[a] (NA)	0.394[b] (0.0893)	0.325[a] (NA)	0.358 [a] (NA)	0.342[b] (0.0394)	0.346[a] (NA)	0.332[a] (NA)	0.339[b] (0.0330)
V_{ss} (mL/kg)	43.6[a] (NA)	50.6[a] (NA)	47.1[b] (9.45)	41.2[a] (NA)	40.2[a] (NA)	40.7[b] (1.62)	49.0[a] (NA)	46.5[a] (NA)	47.7[b] (4.07)

[a] n = 2.
[b] n = 4.

NA= Not applicable.

Table 7: Mean (±SD) TAb PK parameters following a single IV administration of MIRV at 2, 4, and 8 mg/kg to cynomolgus monkeys: Day 1.

Parameter	2 mg/kg			4 mg/kg			8 mg/kg		
	Male n=6	Female n=6	Both n=12	Male n=6	Female n=6	Both n=12	Male n=6	Female n=6	Both n=12
C_{max} (µg/mL)	49.3 (5.18)	53.4 (10.8)	51.3 (8.37)	101 (13.4)	93.7 (12.2)	97.4 (12.9)	193 (26.1)	191 (22.7)	192 (23.3)
$t_{½}$ (hr)	134 (18.3)	148 (19.7)	141 (19.6)	162 (14.6)	172 (29.5)	167 (22.8)	177 [a] (18.0)	210 (26.3)	195[b] (27.9)
AUC_{∞} (hr*µg/mL)	5170 (601)	6560 (1940)	5860 (1550)	12500 (901)	10700 (2350)	11600 (1940)	24500 [a] (3370)	24000 (7290)	24200[b] (5590)
CL (mL/hr/kg)	0.392 (0.0505)	0.342 (0.0809)	0.358 (0.0733)	0.322 (0.0229)	0.392 (0.0975)	0.357 (0.0769)	0.332 [a] (0.0476)	0.356 (0.0914)	0.345[b] (0.0724)
V_{ss} (mL/kg)	74.9 (7.68)	68.2 (13.9)	71.6 (11.3)	75.2 (9.32)	97.5 (33.1)	86.4 (25.9)	84.0 [a] (8.90)	106 (20.2)	95.8 [b] (19.1)

[a] n = 5.
[b] n = 11.

Table 8: Mean (±SD) TAb PK parameters following a single IV administration of MIRV at 2, 4, and 8 mg/kg to cynomolgus monkeys: Day 64.

Parameter	2 mg/kg			4 mg/kg			8 mg/kg		
	Male n=6	Female n=6	Both n=12	Male n=6	Female n=6	Both n=12	Male n=6	Female n=6	Both n=12
C_{max} (µg/mL)	52.6 (5.80)	52.1 (8.10)	52.3 (6.72)	101 (12.5)	102 (12.6)	102 (12.0)	202 (17.2)	204 (23.2)	203 (19.5)
$t_{½}$ (hr)	142[a] (NA)	156[a] (NA)	149[b] (34.8)	175[a] (NA)	148[a] (NA)	161[b] (16.7)	225[a] (NA)	187[a] (NA)	206[b] (35.5)

Parameter	2 mg/kg			4 mg/kg			8 mg/kg		
	Male n=6	Female n=6	Both n=12	Male n=6	Female n=6	Both n=12	Male n=6	Female n=6	Both n=12
AUC_{∞} (hr*µg/mL)	6920 [a] (NA)	6840 [a] (NA)	6880 [b] (1750)	16000 [a] (NA)	11500 [a] (NA)	13800 [b] (2990)	32000 [a] (NA)	31700 [a] (NA)	31900 [b] (3400)

[a] n = 2.
[b] n = 4.
NA = Not applicable.

Table 9: Mean (±SD) DM4 PK parameters following single and repeated IV administrations of MIRV at 2, 4, and 8 mg/kg to cynomolgus monkeys: Day 1 and day 64.

Parameter	2 mg/kg			4 mg/kg			8 mg/kg		
	Male n=6	Female n=6	Both n=12	Male n=6	Female n=6	Both n=12	Male n=6	Female n=6	Both n=12
Day 1									
C_{max} (ng/mL)	0.229 (0.0428)	0.26 (0.0424)	0.227 (0.0407)	0.362 (0.0696)	0.390 (0.0621)	0.376 (0.0646)	0.752 (0.115)	0.709 (0.120)	0.730 (0.114)
AUC_{0-t} (ng*hr/mL)	3.07 (1.62)	3.15 (1.55)	3.11 (1.51)	9.73 (4.05)	6.38 (0.807)	8.05 (3.29)	28.6 (6.92)	22.3 (6.64)	25.5 (7.28)
Day 64									
C_{max} (ng/mL)	0.151 (0.0775)	0.188 (0.0365)	0.185 (0.0307)	0.414 (0.0493)	0.362 (0.0478)	0.388 (0.0537)	0.784 (0.0887)	0.742 (0.148)	0.763 (0.118)

n = Number of animals.

Distribution

The cytotoxic payload, DM4, and its active metabolite, S-methyl DM4, were highly protein bound in human and rat plasma (>99%). In monkey plasma, DM4 was >99% bound, and S-methyl DM4 was 96% bound. PK of MIRV was evaluated in repeat-dose studies in pigmented Dutch Belted rabbits. This rabbit strain was also used for distribution study of MIRV in ocular tissues. Single-dose toxicity studies with DM4 and DM1 were conducted in CD-1 mice. However, *in vitro* plasma protein binding and partitioning of DM4 and the metabolite S-methyl DM4 in blood cells was determined in rat, monkey, and human plasma, but not in mouse or rabbit plasma.

A distribution study with ^{3}H-MIRV was conducted in pigmented Dutch Belted rabbits to assess distribution of MIRV in the ocular tissues. Radioactivity was detected in the plasma and all ocular tissues; the elimination was slow with half-lives ranging from 70 to 120 hours. In rats after a single ^{3}H-MIRV IV dose, the highest radioactivity was observed in the liver, lung, and kidney in addition to bone marrow and the spleen. Radioactivity was detected in the eyes, with concentrations in the eye being maintained through 336 hours postdose, indicating a slow clearance of radioactivity from this organ. It was concluded that the observed low concentrations of radioactivity in the brain may originate from residual blood in brain samples in the absence of perfusion.

Metabolism

In the study investigating the involvement of specific human cytochrome P450 (CYP) isoforms in the metabolism of both DM4 and S-methyl DM4 human hepatic microsomes, CYP-isoform-selective inhibitory chemicals, and recombinant human cytochromes P450 were used. The results indicated that only inhibition of CYP2C9, CYP2C19, and CYP3A4 let to significantly reduced (>50%) metabolism of both DM4 and S-methyl DM4, indicating these as possible CYP isoforms involved in their metabolism.

Overall, the data indicated CYP3A4 as the predominant enzyme responsible for the *in vitro* microsomal biotransformation of DM4 and S-methyl DM4.

The proposed metabolic pathway based on cumulative radio-profiling and spectrometry results in plasma, urine, or bile following a single intravenous administration of ^{3}H-MIRV to male Sprague Dawley rats includes 5 main metabolites M1, M2, M5, M6, and M10. These same metabolites were identified following incubation of maytansinoids DM4 and S-methyl DM4 with human liver microsomes. The published literature (Widdison 2015) provides supporting evidence that metabolism of DM4 and S-methyl DM4 in human liver microsomes produces 5 metabolites being identical to those identified in rat excreta *in vivo*.

The mAb component of the ADC is expected to be cleaved into small inactive peptides by catabolic pathways.

Excretion

A distribution and excretion study with ^{3}H-MIRV in rats showed that hepato-biliary excretion is the major elimination pathway of DM4-related radioactivity.

Pharmacokinetic drug interactions

The *in vitro* inhibitory potential of DM4 and the active metabolite S-methyl DM4 on the activities of the following human hepatic cytochromes (CYP) P450 enzymes: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 was investigated. DM4 and S-methyl DM4 showed no direct inhibition on the CYP enzymes tested in the study. DM4 showed time-dependent inhibition on CYP3A4 in kin_{act} (maximal inactivation) and K_I (concentration at 50% kin_{act}) assay. For testosterone 6β-hydroxylase, K_I and kin_{act} values of DM4 were 2.92 µM and 0.193 minute^{-1}, respectively. For midazolam 1′ -hydroxylase, K_I and kin_{act} values of DM4 were 5.95 µM and 0.322 minute^{-1}, respectively. S-methyl DM4 showed weak time-dependent inhibition of CYP2C8 and CYP2C9.

Treatment of the human hepatocyte cultures from three donors that were separately incubated with DM4 or S-methyl DM4, DM4 and S-methyl DM4 at concentrations of 0.3, 1, and 3 µM did not elicit mRNA induction to the level of >4-fold of solvent control and >20% of positive control for CYP1A2, CYP2B6, or CYP3A4 in any of the cultures.

In *in vitro* CYP induction study significant loss of both test articles occurred after exposure to hepatocytes for 4 or 24 hours. For DM4, only 3.46, 3.50, and 3.28 % remained at 4 hours, and 0.922, 1.24, and 1.38 % remained at 24 hours, for the 0.75, 1.5, and 3 µM treatments, respectively. The S-methyl-DM4 showed 54.2, 60.9, and 62.0 % remaining at 4 hours and 27.0, 37.4, and 43.8 % remaining at 24 hours for the 0.75, 1.5, and 3 µM treatments, respectively. For induction study 0.3, 1 and 3 µM concentrations were used while in stability assay the concentrations of 0.75, 1.5 and 3 were used.

2.5.4. Toxicology

The monkey was demonstrated to be the most appropriate animal species for toxicological evaluation of MIRV based on FOLR1 gene sequence homology assessments, in vitro binding assays, and IHC analysis of FRα protein expression on fresh frozen tissue sections using MIRV.

The toxicity and TK profile of MIRV was assessed following single and repeat IV administrations in the cynomolgus monkey. Ocular evaluations with MIRV were performed in male Dutch Belted rabbits in a single-dose and repeat-dose IV administration studies.

2.5.4.1. Single dose toxicity

The acute toxicity studies of MIRV (GLP) and DM4 (non-GLP) were conducted in cynomolgus monkey after a single IV dose followed by the recovery period (MRV: 5 days or 29 days; DM4: 29 days). The small molecule payload, DM4 was also assessed in single dose non-GLP toxicity study in the mouse (up to 4.1 mg/kg/dose).

Non-adverse MIRV-related clinical observations were limited to skin effects of monkeys. Adverse MIRV-related microscopic findings of hypocellularity in lymph nodes and bone marrow correlated with the changes in clinical pathology (lowering of WBC and lymphocyte counts). All alterations in hematology parameters had resolved by the study day 7 evaluation. The highest nonseverely toxic dose (HNSTD) was 10 mg/kg/dose, the highest dose tested, and the no observed adverse effect level (NOAEL) was 3 mg/kg/dose.

Toxicity findings associated with a single IV dose of DM4 in mice 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.

A single IV administration of DM4 in cynomolgus monkey at a dose of 0.1 mg/kg/dose was associated with clinical pathology alterations including mild leukopenia primarily due to neutropenia, which corresponded microscopically to bone marrow depletion.

2.5.4.2. Repeat dose toxicity

In a GLP compliant 10-week IV toxicity and TK study of MIRV with 2, 4, and 8 mg/kg/dose Q3W for four consecutive doses in cynomolgus monkeys there were numerous skin findings including broken skin, dry skin, discolored skin, scaly skin, sores, scabs, and/or scars; these occurred mostly in animals that received doses >4 mg/kg/dose. In addition, skin abrasions, superficial dermal erosions, and ulcerative wounds occurred in animals that received 8 mg/kg/dose, i.e., higher than the NOAEL 4 mg/kg/dose. The skin findings were not considered adverse because they did not lead to serious health concerns and were clinically manageable.

MIRV-related abnormal ophthalmic findings were noted at the scheduled ophthalmic examinations conducted during Week 9 of the dosing phase and during Week 4 of the recovery phase in animals administered 8 mg/kg/dose. Keratopathy, characterized by faint perilimbal corneal pigment migration into clear cornea (especially superiorly), occurred in half the animals during Week 9 of the dosing phase. In one male on Day 70 of the dosing phase, the ophthalmic examination revealed corneal microcystic lesions, which retained fluorescein stain in the superior perilimbal region. This suggested the corneal pigmentation likely was secondary to other corneal changes (such as corneal microcysts) that were not initially observed during regularly scheduled examinations. Corneal findings in animals administered 8 mg/kg/dose were considered adverse because corneal microcysts have been reported to be associated with visual disturbances (e.g., blurred vision) in humans.

MIRV-related clinical pathology changes were limited to animals receiving 8 mg/kg/dose. Hematology effects were consistent with decreased hematopoiesis which occurred primarily at the end of the dosing phase. All effects on clinical pathology test results exhibited evidence of reversibility by the end of the recovery phase and were considered non-adverse. MIRV-related microscopic observations at the terminal sacrifice were noted in the IV injection sites of animals given 8 mg/kg/dose, the skin/subcutis (areas other than the injection sites) of males given 8 mg/kg/dose, and in the corneal epithelium and (keratinized skin of the) eyelids of animals given ≥4 mg/kg/dose. Corneal epithelial attenuation was noted unilaterally in one male administered 8 mg/kg/dose. Attenuation was considered an adverse

finding. All other MIRV-related pathology findings except for unilateral corneal epithelial pigmentation in one male given 8 mg/kg/dose at the terminal sacrifice had reversed at the recovery sacrifice.

Anti-MIRV antibodies (ADA) were not detected in any animal throughout the study following IV administration of MIRV.

2.5.4.3. Genotoxicity

The ability of DM4 and the active metabolite S-methyl DM4 to induce reverse mutations in histidine-requiring strains of Salmonella typhimurium (S. typhi) and tryptophan-requiring strain(s) of Escherichia coli (E. coli) in the absence and presence of a rat liver metabolizing system (S9) were studied in Bacterial Reverse Mutation Assay (Ames test). DM4 and S-methyl DM4 were studied for *in vivo* clastogenic activity and/or ability to disrupt the mitotic apparatus through the detection of micronuclei (chromosome or chromosal fragments) in polychromatic erythrocytes (PCE) in rat bone marrow.

Table 10: Overview of in vitro mutagenicity tests with DM4 and S-methyl DM4

Type of test/ study ID/GLP	**Test system**	**Concentrations/ Metabolising system**	**Results positive/negative/equivocal**
Gene mutations in bacteria/CVT14-001 (DM4)/GLP	Salmonella strains TA98, TA100, TA1535, TA1537, E. Coli strain WP2uvrA	1.6, 5.0, 16.0, 50.0, 160, 500, 1600, and 5000 µg/plate +/- S9	Negative Precipitation at 1600 and 5000 µg/plate with all tester strains in the absence and presence of S9 except WP2uvrA in the presence of S9, where there was precipitation only at 5000 µg/plate. Toxicity at 5000 µg/plate with TA1535 in the absence of S9 as indicated by decreased revertant colony counts.
Gene mutations in bacteria/CVT14-002 (S-methyl DM4)/GLP	Salmonella strains TA98, TA100, TA1535, TA1537, E. Coli strain WP2uvrA	1.6, 5.0, 16.0, 50.0, 160, 500, 1600, and 5000 µg/plate +/- S9	Negative Precipitation at >1600 µg/plate with all tester strains in the absence of S9. Toxicity, as indicated by reduced bacterial background lawns, observed with all tester strains at >500 µg/plate.
In Vivo Rat Bone Marrow Micronucleus Assay/CVT13-003 (DM4)	Rat/Sprague Dawley/males	0.010, 0.020, and 0.040 mg/kg/dose	Positive Statistically significant increases in the mean percent of micronucleated polychromatic erythrocytes (PCEs) at 0.040 mg/kg/dose as

			compared to the vehicle control. DM4 was cytotoxic to the bone marrow (ie, significant decreases in the %PCE) at 0.040 mg/kg/dose.
In Vivo Rat Bone Marrow Micronucleus Assay/CVT13-004 (S-methyl DM4)	Rat/Sprague Dawley/males	0.010, 0.020, and 0.040 mg/kg/dose	Positive A dose-dependent and statistically significant increase in the mean percent of micronucleated PCEs in the 0.020 and 0.040 mg/kg/dose dose groups, compared to vehicle control. Increases in micronucleated PCEs in the 0.04 mg/kg/dose group outside the historic vehicle control range and the 95% confidence interval. S-methyl DM4 was cytotoxic to the bone marrow (ie, significant decreases in the %PCE) at 0.04 mg/kg/dose.

In *in vitro* bacterial reverse mutation assay, both DM4 and S-methyl DM4 were negative both in *Salmonella* and *E. coli* test strains. Precipitation of the test item and cell toxicity were observed at high concentrations. In *in vivo* rat bone marrow micronucleus assay using male SD rats, both DM4 and S-methyl DM4 proved to be clastogenic by inducing micronuclei in polychromatic erythrocyte (PCE) in rat bone marrow. In addition, both substances were cytotoxic to the bone marrow, which resulted in decreases in the %PCE. The genotoxicity and cytotoxicity of DM4 and the metabolite were expected and in line with the MoA of maytansinoids.

2.5.4.4. Carcinogenicity

Carcinogenicity studies have not been conducted with mirvetuximab soravtansine or DM4.

2.5.4.5. Reproductive and developmental toxicity

No reproductive or developmental studies were conducted with MIRV.

2.5.4.6. Toxicokinetic data

MIRV is an ADC, therefore TK were determined separately for ADC (MIRV), total antibody (TAb), and DM4 payload.

TK data were collected in single-dose and repeat-dose toxicity studies in cynomolgus monkeys and ocular toxicity studies in Dutch Belted rabbits.

Table 11: TK studies overview

Type of Study	Test Article	Test System	Method of Admin.	Doses (mg/kg/dose)	GLP Compliance	Study Number
Single-Dose Toxicity	MIRV	Cynomolgus Monkey	IV	1, 3, 5, and 10	GLP	IMK28-002; IMI28-001[a] (WRT28-001)
Repeat-Dose Toxicity	MIRV	Cynomolgus Monkey	IV	2, 4 and 8	GLP	CVT28-001
Other: Ocular Toxicity	MIRV	Dutch Belted Rabbits	IV	4, 8 and 12	Non-GLP	CVT28-002
	MIRV	Dutch Belted Rabbits	IV	4, 8 and 12	Non-GLP	CVT28-003

Abbreviations: Admin = Administration; GLP = Good laboratory practice; IV = Intravenous.
[a] Bioanalytical and TK analyses of the plasma samples were not included as part of the WRT28-001 toxicology report, but were reported separately under study IMK28-002 (MIRV and total antibody) and IMI28-001 (free DM4).

Table 12: Overview of TK data: antibody drug conjugate (MIRV)

Analyte: mirvetuximab soravtansine		**Overview of Toxicokinetics Data (SD)[d]**			
Daily Dose (mg/kg/dose)	**TK Parameter**	**Cynomolgus Monkey**		**Dutch Belted Rabbits**	**Study Number**
		Male	**Female**	**Male**	
1	C_{max} (µg/mL)	35.6[a,b]	35.6[a,b]	-	IMK28-002[f] (WRT28-001)[e]
	$AUC_{0-\infty}$ (µg•h/mL)	2142[a,b]	2142[a,b]	-	
2	C_{max} (µg/mL)	51.8 (4.2)	61.3 (9.9)	-	CVT28-001[e]
	$AUC_{0-\infty}$ (µg•h/mL)	5060 (532)	5560 (1070)	-	
3	C_{max} (µg/mL)	87.8[a,b]	87.8[a,b]	-	IMK28-002[f] (WRT28-001)[e]
	$AUC_{0-\infty}$ (µg•h/mL)	7015[a,b]	7015[a,b]	-	
4	C_{max} (µg/mL)	112 (11)	110 (12.3)	105.12 (25.80); 106 (22)	CVT28-001[e]; CVT28-002; CVT28-003
	$AUC_{0-\infty}$ (µg•h/mL)	11900 (885)	10600 (1350)	6140.71 (1719.87); 6167 (865)	
5	C_{max} (µg/mL)	96.5[a,b]	96.5[a,b]	-	IMK28-002[f] (WRT28-001)[e]
	$AUC_{0-\infty}$ (µg•h/mL)	12716[a,b]	12716[a,b]	-	
8	C_{max} (µg/mL)	229 (22.4)	214 (27.7)	259.29 (17.18) 220[c] (24)	CVT28-001[e]; CVT28-002; CVT28-003
	$AUC_{0-\infty}$ (µg•h/mL)	22500 (2350)	20800 (4020)	12822.46 (1960.84) 14136[c] (1402)	
10	C_{max} (µg/mL)	280.6[a,b]	280.6[a,b]	-	IMK28-002[f] (WRT28-001)[e]
	$AUC_{0-\infty}$ (µg•h/mL)	25583[a,b]	25583[a,b]	-	

Analyte: mirvetuximab soravtansine		**Overview of Toxicokinetics Data (SD)[d]**			
Daily Dose (mg/kg/dose)	**TK Parameter**	**Cynomolgus Monkey**		**Dutch Belted Rabbits**	**Study Number**
		Male	**Female**	**Male**	
12	C_{max} (µg/mL)	-	-	359.05 (99.27) 311 (37)	CVT28-002; CVT28-003
	$AUC_{0-\infty}$ (µg•h/mL)	-	-	17359.06 (4333.03) 15942[c] (3838)	

Abbreviations: AUC_{0-inf} = Area under the concentration-time curve from hour 0 to infinity; C_{max} = Maximal concentrations; SD = Standard deviation.
[a] No standard deviation calculated.
[b] Reported data is combined male and female. No apparent gender difference was noted.
[c] n=4.
[d] All data represented in this table is after a single dose of MIRV regardless of dosing schedule.
[e] GLP compliant
[f] Bioanalytical and TK analyses of the plasma samples were not included as part of the WRT28-001 toxicology report, but were reported separately under study IMK28-002 MIRV and total antibody) and IMI28-001 (free DM4).

Table 13: Overview of TK data: TAb

Analyte: Total Antibody		**Overview of Toxicokinetics Data (SD)[f]**			
Daily Dose (mg/kg/dose)	**TK Parameter**	**Cynomolgus Monkey**		**Dutch Belted Rabbits**	**Study Number**
		Male	**Female**	**Male**	
1	C_{max} (µg/mL)	31.5[a,b]	31.5[a,b]	-	IMK28-002[h] (WRT28-001)[e]
	$AUC_{0-\infty}$ (µg•h/mL)	2724[a,b]	2724[a,b]	-	
2	C_{max} (µg/mL)	49.3 (5.2)	53.4 (10.8)	-	CVT28-001[f]
	$AUC_{0-\infty}$ (µg•h/mL)	5170 (601)	6560 (1940)	-	
3	C_{max} (µg/mL)	75.4[a,b]	75.4[a,b]	-	IMK28-002[h] (WRT28-001)[e]
	$AUC_{0-\infty}$ (µg•h/mL)	9225[a,b]	9225[a,b]	-	
4	C_{max} (µg/mL)	101 (13.4)	93.7 (12.2)	108.73 (19.65) 114 (14)	CVT28-001[f]; CVT28-002; CVT28-003
	$AUC_{0-\infty}$ (µg•h/mL)	12500 (901)	10700 (2360)	8017.17 (1867.56) 10715 (2386)	
5	C_{max} (µg/mL)	120.2[a,b]	120.2[a,b]	-	IMK28-002[h] (WRT28-001)[e]
	$AUC_{0-\infty}$ (µg•h/mL)	15208[a,b]	15208[a,b]	-	
8	C_{max} (µg/mL)	193 (26.1)	191 (22.7)	194.10 (27.54) 212[c] (17)	CVT28-001[f]; CVT28-002; CVT28-003
	$AUC_{0-\infty}$ (µg•h/mL)	24500 (3370)	24000 (7290)	14667.36[c] (2253.50) 15172[a,d]	

Analyte: Total Antibody		**Overview of Toxicokinetics Data (SD)[f]**			
Daily Dose (mg/kg/dose)	**TK Parameter**	**Cynomolgus Monkey**		**Dutch Belted Rabbits**	**Study Number**
		Male	**Female**	**Male**	
10	C_{max} (µg/mL)	249.3[a,b]	249.3[a,b]	-	IMK28-002[h] (WRT28-001)[e]
	$AUC_{0-\infty}$ (µg•h/mL)	30287[a,b]	30287[a,b]	-	
12	C_{max} (µg/mL)	-	-	327.88 (47.74) 290 (29)	CVT28-002; CVT28-003
	$AUC_{0-\infty}$ (µg•h/mL)	-	-	23677.73 (4953.72) 26637[e] (4251)	

Abbreviations: AUC_{0-inf} = Area under the concentration-time curve from hour 0 to infinity; C_{max} = Maximal concentrations; SD = Standard deviation.

[a] No standard deviation calculated.

[b] Reported data is combined male and female. No apparent gender difference was noted.

[c] n=4; [d] n=2; [e] n=3

[f] All data represented in this table is after a single dose of MIRV regardless of dosing schedule.

[g] GLP compliant

[h] Bioanalytical and toxicokinetic analyses of the plasma samples were not included as part of the WRT28-001 toxicology report but were reported separately under study IMK28-002 (MIRV and total antibody) and IMI28-001 (free DM4).

Table 14: Overview of TK data: DM4 payload

Analyte: DM4		**Overview of Toxicokinetics Data (SD)[d]**			
Daily Dose (mg/kg/day)	**TK Parameter**	**Cynomolgus Monkey**		**Dutch Belted Rabbits**	**Study Number**
		Male	**Female**	**Male**	
1	C_{max} (ng/mL)	35[a,b]	35[a,b]	-	IMI28-001[f] (WRT28-001)[e]
	$AUC_{0-\infty}$ (ng•h/mL)	NC	NC	-	
2	C_{max} (ng/mL)	0.229 (0.043)	0.226 (0.042)	-	CVT28-001[e]
	$AUC_{0-\infty}$ (ng•h/mL)	NC	NC	-	
3	C_{max} (ng/mL)	62[a,b]	62[a,b]	-	IMI28-001[f] (WRT28-001)[e]
	$AUC_{0-\infty}$ (ng•h/mL)	NC	NC	-	
4	C_{max} (ng/mL)	0.362 (0.070)	0.390 (0.062)	0.642 (0.135) 1.38 (0.24)	CVT28-001[e]; CVT28-002; CVT28-003
	$AUC_{0-\infty}$ (ng•h/mL)	20.0[a]	7.83[a]	8.973[c] (2.129) 19.4(4.4)	
5	C_{max} (ng/mL)	95	95	-	IMI28-001[f] (WRT28-001)[e]
	$AUC_{0-\infty}$ (ng•h/mL)	NC	NC	-	
8	C_{max} (ng/mL)	0.752 (0.115)	0.709 (0.120)	1.105 (0.194) 2.30[c] (0.30)	CVT28-001[e]; CVT28-002; CVT28-003
	$AUC_{0-\infty}$ (ng•h/mL)	36.8 (6.70)	31.8 (4.36)	27.187[c] (13.224) 36.5[c](4.7)	
10	C_{max} (ng/mL)	129[a,b]	129[a,b]	-	IMI28-001[f] (WRT28-001)[e]

Analyte: DM4		**Overview of Toxicokinetics Data (SD)[d]**			
Daily Dose (mg/kg/day)	**TK Parameter**	**Cynomolgus Monkey**		**Dutch Belted Rabbits**	**Study Number**
		Male	**Female**	**Male**	
	$AUC_{0-\infty}$ (ng•h/mL)	NC	NC	-	
12	C_{max} (ng/mL)	-	-	1.986[c] (0.320) 3.30 (0.37)	CVT28-002; CVT28-003
	$AUC_{0-\infty}$ (ng•h/mL)	-	-	39.870 (3.304) 62.4 (21.7)	

Abbreviations: - = No data available for designated dose; AUC_{0-inf} = Area under the concentration-time curve from hour 0 to infinity; C_{max} = Maximal concentrations; NC = Not calculated; SD = Standard deviation.
[a] No standard deviation calculated.
[b] Reported data is combined male and female. No apparent gender difference was noted.
[c] n=4
[d] All data represented in this table is after a single dose of MIRV regardless of dosing schedule.
[e] GLP compliant.
[f] bioanalytical and TK analyses of the plasma samples were not included as part of the WRT28-001 toxicology report but were reported separately under study IMK28-002 (MIRV and total antibody) and IMI28-001 (free DM4).

In a 10-week toxicity study in monkeys a mid-dose of 4 mg/kg/dose Q3W of MIRV was selected to characterize potential toxicity at an exposure metric which was predicted to be similar to that of the IV dose (6 mg/kg, AIBW) utilized for the registrational studies. This dose was considered as NOAEL. This dose level 4 mg/kg/dose corresponded to mean C_{max} of 113 µg/mL and AUC_{0-24} of 1960 µg*hr/mL for MIRV. Animal: human exposure multiple based on C_{max} was close to 1. When monkey AUC_{0-24} was compared to human AUC_{tau} (area under the concentration vs. time curve over the dosing interval 21 days) exposure margin was 0.09; however, when monkey $AUC_{0-\infty}$ was used for comparison the exposure multiple was 0.57.

2.5.4.7. Local Tolerance

Local tolerance was evaluated as part of the GLP repeat-dose study in cynomolgus monkeys and was based upon clinical observations and anatomic pathology evaluations. In 10-week repeat-dose toxicity study (4 consecutive doses Q3W) MIRV-related microscopic observations at the terminal sacrifice were noted in the IV injection sites of animals given the high 8 mg/kg/dose. The microscopic findings at the IV injection sites were epithelial ulceration/erosion, edema 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.

2.5.4.8. Other toxicity studies

Antigenicity

No stand-alone antigenicity studies were conducted with MIRV.

In a 10-week IV repeat-dose toxicity study in cynomolgus monkeys, all animals that received MIRV tested negative for the presence of anti-IMGN853 (MIRV) antibodies throughout the study. Moreover, plasma samples collected from a single-dose toxicity study in monkeys no immunogenicity response was detected against the MIRV antibody or DM4 component. In clinical studies, there was no apparent impact of ADA on MIRV clearance or exposure in patients with concurrent PK and immunogenicity data.

Immunotoxicity

No stand-alone immunotoxicity studies were conducted with MIRV.

Single IV administration up to 10 mg/kg/dose in cynomolgus monkeys resulted in cellular depletion of the bone marrow and lymphoid tissues, effects that correlated to observed changes in clinical

pathology parameters. The small molecule payload, DM4, was administered as a single IV dose at 0.1 mg/kg/dose in the cynomolgus monkey to assess the toxicity profile. DM4-related clinical pathology alterations included mild leukopenia primarily due to neutropenia, which corresponded microscopically to bone marrow depletion.

Studies on impurities

Two free maytansinoid-related impurities, maysine and DM4-sulfo-TBA were qualified in single-dose tolerability study in female CD-1 mice. The MTD for maysine administered as a single intravenous injection was ≥10 mg/kg/dose, the highest dose tested. The MTD for DM4-sulfo-TBA administered as a single intravenous injection was ≥15 mg/kg/dose, the highest dose tested., Maysine and DM4-sulfo-TBA were both qualified at specification limit of ≤ 4.0% (mol/mol). The impurities were dosed only once in mouse studies; however, this can be accepted since posology in patients is once every 3 weeks (21-day cycle).

Phototoxicity

DM4 was assessed for phototoxicity to Balb/c 3T3 fibroblast cells using the neutral red uptake (NRU) assay. DM4 was phototoxic in the NRU assay system when tested up to 100 µg/mL. For evaluation of phototoxicity, the cells were exposed to up to 5 J/cm2 of ultraviolet A light (UV-A) irradiation in total. The photo-irritation factor (PIF) was calculated for DM4 as 15.17 (IC_{50} in the absence of UV-A [8.712 µg/mL] divided by IC_{50} in the presence of UV-A [0.582 µg/mL]). The PIF value 15.17 indicates "phototoxicity" based in criteria given in OECD 432.

Ocular toxicity/Distribution

Ocular toxicity of MIRV was assessed altogether in three non-GLP ocular toxicity studies in rabbits. The ocular distribution and PK was assessed in male pigmented rabbits.

In a non-GLP 4-week IV infusion ocular toxicity and toxicokinetic study with MIRV administered once weekly to male Dutch Belted rabbits with a 3-week recovery phase, MIRV at doses of 4, 8, or 12 mg/kg/dose was associated with a dose-related keratopathy, characterized by subtle multifocal subepithelial punctate microcystic lesions in the perilimbal cornea. There was a dose dependent increase in severity, onset, and time of resolution with the observed lesions. Corneal microcysts were typically associated with slight multifocal punctate fluorescein stain retention. Some or all eyes of animals administered 8 or 12 mg/kg/dose also exhibited corneal pigmentation in the affected region. Corneal lesions tended to diminish during the recovery phase, but complete resolution was observed only in animals given 4 mg/kg/dose. MIRV-related attenuation and degeneration/necrosis (individual cell) of the corneal epithelium were noted microscopically in the eyes of animals given ≥4 mg/kg/dose of MIRV. Pigmentation was present in the cornea of animals given 12 mg/kg/dose. These microscopic observations were considered adverse and generally persisted at the end of the recovery phase without a clear change in incidence or severity.

In the second non-GLP 4-week study of MIRV following IV infusion administered weekly in Dutch Belted rabbits, corneal changes associated with MIRV were first noted on Day 15 and eventually included varying combinations of multifocal punctate corneal microcystic changes that affected the superior perilimbal cornea, slight multifocal perilimbal corneal fluorescein stain retention typically over the corneal microcystic lesions but sometimes without visible microcysts, and, later on, corneal pigmentation in the superior perilimbal region.

At all scheduled sacrifices (the first being on Day 3), one or more MIRV -related microscopic observations were noted for the eyes and eyelids; these included individual cell degeneration/necrosis, attenuation, and pigmentation in corneal epithelium; and individual cell degeneration/necrosis, cytomegaly/karyomegaly, and/or attenuation of epithelium in the eyelids. Individual corneal epithelial

cell degeneration/necrosis, the earliest MIRV-related ocular change noted, was present at interim sacrifice 1 (Day 3) for animals treated with MIRV.

In the non-GLP 12-week study of MIRV following IV infusion administered Q3 weekly in Dutch Belted rabbits with a 3-week recovery, administration of 4 mg/kg/dose MIRV was associated with corneal lesions (corneal microcysts) in only one animal on Day 15 of the dosing phase (2 weeks after the first dose). This lesion resolved by the next examination and did not recur after repeated dosing. No animals administered 8 mg/kg/dose had corneal findings. Administration of 12 mg/kg/dose was associated with MIRV related corneal lesions in all five animals. These lesions included: multifocal punctate corneal fluorescein stain retention (with or without visible corneal microcysts), multifocal perilimbal corneal microcysts, perilimbal corneal pigmentation, and sporadic instances of corneal vascularization, corneal edema, and corneal haze, which could involve much of the cornea.

At the terminal sacrifice, MIRV-related microscopic observations were noted in the corneal epithelium of animals administered 8 or 12 mg/kg/dose of MIRV. In both groups, corneal observations included minimal to slight attenuation of the corneal epithelium and minimal degeneration/necrosis of individual corneal epithelial cells. At the recovery sacrifice, MIRV-related minimal attenuation of the corneal epithelium was noted in the right eye of one animal administered 12 mg/kg/dose.

Ocular tissue distribution and PK of two test articles, MIRV (M-sulfo-SPDB-3H-DM4) and conjugate analog M9346A-SPDB-3H-DM4 were assessed after a 30-minute IV infusion in male pigmented rabbits. The preferential tissue distribution of M-SPDB-3H-DM4 with SPDB linker but same ^{3}H -label position in DM4 backbone to the corneal epithelium at levels 3- to 4-fold higher than MIRV was correlated with higher incidence of keratopathy (multifocal subepithelial punctate microcystic lesions in perilimbal cornea that generally co-localized with fluorescein staining patterns. In other corneal layers such difference in radioactivity was not measured. Generally, there was limited ocular distribution of test substance-related radioactivity above background in all examined eyes when assessed by MARG. Radioactivity was associated with most structures of the eye at 1 and 24 hours after 30-min infusion of MIRV and declined thereafter, although radioactivity was associated with the lens at all sampling times.

Following administration of an MIRV analog M-SPDB-3H-DM4 with SPDB linker, besides corneal epithelium with radioactivity at levels 3- to 4-fold higher than MIRV, radioactivity was only consistently associated with the lens of the eye. MIRV targets and binds to FRα located on the cell surface through the mAb component. Upon binding to FRα, the ADC is internalized, processed, and degraded in the lysosomes resulting in release of DM4-derived catabolites. In tissue cross reactivity studies MIRV-related cytoplasmic staining in human cornea was observed, which the applicant considered unspecific.

2.5.5. Ecotoxicity/environmental risk assessment

The environmental risk assessment for MIRV has been conducted according to the Guideline on the environmental risk assessment of medicinal products for human use, EMEA/CHMP/SWP/4447/00 corr 2, 2006, the respective Draft Guideline as agreed by the safety working party (2018) and the Questions and answers on 'Guideline on the environmental risk assessment of medicinal products for human use', EMA/CHMP/SWP/44609/2010 Rev.

Phase 1: Estimation of exposure

Screening for Persistence, Bioaccumulation and Toxicity

A Phase 1 assessment was conducted for DM4, the cytotoxic payload of MIRV. This is acceptable since proteins such as antibodies are not considered to be harmful to the environment. In a GLP compliant study (OECD 105) water solubility of DM4 was determined to be 6.2 mg/L at 20.0°C. DM4 is not a dissociating compound and therefore determination of a Dow, an ion corrected Kow, is not required.

The octanol/water partitioning coefficient (log Kow) of DM4 was determined using the high-pressure liquid chromatography (HPLC) method (OECD 117; GLP compliant). Log Kow of the test item was determined to be 3.5.

Calculation of PEC_{SW}:

The Fraction of Market Penetration (Fpen) value for calculation of PECsw was refined by both the prevalence of the disease and the treatment schedule.

In summary, based on the most recently estimated prevalence of ovarian cancer and the treatment regimen the resulting Fpen is 0.00002303.

The amount of DM4 conjugated to the antibody is approximately 2% of the total ADC (in terms of molecular weight). At a therapeutic dose of 6 mg/kg (MIRV) the dose for DM4 is approximately 0.02 * 6.0 = 0.12 mg/kg (or 12 mg for a 100 kg patient).

$$PEC_{SW} = \frac{12\ mg \times 0.00002303}{200\ L \times 10}$$

$$= 0.00000013818\ mg/L = 0.000138\ \mu g/L$$

The calculated PEC_{sw} for DM4 is approximately 70-fold below the action limit of 0.01 µg/L. Hence further investigations on the environmental fate and effects detailed in Phase II Tier A of the EMA guidance document are not required.

Conclusions on ERA:

DM4 PEC_{SW} value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5.

DM4 is not a PBT substance. The log Kow of DM4 was determined to be 3.5. This is below the trigger value which would require further screening for PBT (log Kow > 4.5).

Table 15: Summary of main study results

Substance: DM4 (Maytansinoid)			
CAS-number: 796073-69-3			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107		Potential PBT: N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	3.5	not B
PBT-statement:	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, refined (prevalence, treatment schedule)	0.000138	µg/L	< 0.01 threshold N
Other concerns (e.g. chemical class)	Maytansinoids are cytotoxic compounds, inhibiting tubulin polymerization		Y

2.5.6. Discussion on non-clinical aspects

Pharmacology:

The pharmacology data is considered in general adequate; the development program is *in line* with the regulatory guidelines.

In vitro correlation between the cell killing activity and the FRα cell-membrane expression was shown; 'sensitivity correlated with FRα expression levels and the amount of catabolites generated was directly proportional to the level of FRα expression'. According to the *in vitro* data, IGROV-1 cells had 4-10x10^5 binding sites per cell and OVCAR-3 far less *i.e.,* 7-13x10^3 (75-times less FRα target antibody binding sites per cells). *In vitro* cytotoxic IC_{50} values correlated with the binding. All cell lines had similar sensitivity to unconjugated cell-permeable S-methyl DM4 and ability to process surface-bound MIRV. In *in vivo* ovarian cancer xenograft models MIRV was more efficient (extended the survival time, T/C% and LCK) against the OVCAR-3 tumors than IGROV-1 tumors.

The different activity of MIRV against OVCAR-3 and IGROV-1 in vitro and in vivo contributing to the anti-tumour efficacy could be related to a combination of factors including i) higher expression of FRα by OVCAR-3 cells in vivo and ii) higher sensitivity to the maytansinoid S-methyl-DM4 and cell division rate of OVCAR-3 cells compared to IGROV-1 cells. It was confirmed that aside these differences *in vitro* and *in vivo* results, the totality of evidence supports the concept that MIRV requires high FRα expression for its activity, and that FRα level of expression is an important but not the only factor driving MIRV activity.

MIRV membrane-associated staining was noted in human eye conjunctiva and cytoplasmic staining in cornea, which were stated be nonspecific or negligible.

Pharmacokinetics:

PK and metabolic disposition studies were conducted with MIRV in animal species used in the evaluation of the toxicological properties of the drug, i.e., Dutch Belted rabbits and cynomolgus monkeys. Bioanalytical methods used to support the GLP-compliant toxicology study of MIRV with a TK component were fully validated according to applicable FDA/EMA guidance. For non-GLP studies, acceptable accuracy and precision were required and achieved.

The cytotoxic payload, DM4, and its active metabolite, S-methyl DM4, were highly protein bound in human and rat plasma (>99%). In monkey plasma, DM4 was >99% bound, and S-methyl DM4 was 96% bound. PK of MIRV was evaluated in repeat-dose studies in pigmented Dutch Belted rabbits. Single-dose toxicity studies with DM4 and DM1 were conducted in CD-1 mice. Plasma protein binding (PPB) and partitioning (BPP) of DM4 and S-methyl DM4 in blood cells were determined in rat, monkey, and human plasma, but not in mouse or rabbit plasma. The purpose of assessing PPB and BPP was to evaluate safety coverage from the most relevant toxicology species for patients. Monkey is an appropriate species for MIRV as an antibody-drug conjugate, and the rat is appropriate for the payload. As a non-human primate, the monkey study is more relevant and supersedes the mouse tolerability study.

DM4 and S-methyl DM4 were the primary plasma metabolites in all non-clinical species. A comparison of the metabolite profile of the ADC between rat and human indicated 13 metabolites in rat but only 4 metabolites in human, with no unique human metabolite.

An ocular distribution study with ^{3}H-MIRV was conducted in Dutch Belted rabbits. No brain tissue was collected in this study. It was concluded that radioactivity detected in the choroid-retinal pigment epithelium (RPE), which is a highly vascularized tissue, was likely due to residual blood in the tissue samples that were not perfused prior to analysis. Similarly, in the rat distribution study, low levels of

radioactivity were found in the brain. This is also likely due to residual blood in the brain tissues that were not perfused.

A distribution and excretion study with ^{3}H-MIRV in rats showed that hepato-biliary excretion is the major elimination pathway of DM4-related radioactivity; excretion into the urine was a minor contributor to the elimination. DM4 and S-methyl-DM4 were found as minor metabolites (<0.1% of total radioactivity) in the bile, thus, potential drug interactions at hepatic efflux transporters are not expected to affect systemic and hepatocellular exposure to DM4 and S-methyl-DM4. DM4 and S-methyl-DM4 must be distributed into hepatocytes before they can be metabolized and, subsequently, metabolites excreted into the bile. The applicant is recommended to investigate if DM4 and/or S-methyl-DM4 are substrates of the hepatic uptake transporters OATP1B1 and OATP1B3 and to share the results with the Agency. The product information should be updated (SmPC section 5.2 / Transporter systems; SmPC section 4.5) if clinically relevant interactions are observed (PAM, Recommendation).

Unconjugated DM4 and S-methyl DM4 are substrates of P-gp but are not inhibitors of P-gp. Adequate information about PK interactions of DM4 and S-methyl DM4 is given in section 5.2 of the SmPC. CHMP Guideline on the investigation of drug interactions (section 5.3.4.1) states: "*In vitro* inhibition studies are recommended to investigate whether the investigational drug inhibits any of the transporters known to be involved in clinically relevant *in vivo* drug interactions. Presently, these include P-glycoprotein/MDR1 (ABCB1), OATP1B1 (SLCO1B1), OATP1B3 (SLCO1B3), OCT2 (SLC22A2), OAT1 (SLC22A6), OAT3 (SLC22A8) and BCRP (ABCG2). Investigations of the inhibitory effect on OCT1 (SLC22A1), MATE1 (SLC47A1) and MATE2 (SLC47A) could also be considered. Inhibition of the transporter BSEP (ABCB11) should also preferably be investigated". In Study 0403 where MIRV was dosed at 6 mg/kg AIBW, the observed C_{max} was 0.0052 µM and 0.0085 µM for DM4 and S-methyl-DM4, respectively. This represents a 3 orders of magnitude lower concentrations than the lowest concentration typically tested in the context of a *in vitro* drug-drug-interaction (DDI) study, thus the potential of DM4 and S-methyl-DM4 to interact with the additional transporters is considered low. It would not be meaningful to evaluate their potential interactions at concentrations that greatly exceed the actual clinical exposures in patients.

The inhibitory potential of DM4 and the S-methyl DM4 on the activities of human hepatic cytochromes (CYP) P450 enzymes was studied in vitro and based on these results, no need for clinical interaction study to evaluate *in vivo* risk for time dependent inhibition was identified.

In *in vitro* CYP induction study (CYP1A2, CYP2B6, and CYP3A4) significant loss of both test articles occurred after exposure to hepatocytes for 4 or 24 hours. A high metabolic turnover of both DM4 and S-methyl-DM4 was noted in liver microsomes in the metabolic reaction phenotyping study. In the CYP induction study, the loss of DM4 and S-methyl-DM4 in the incubation with hepatocytes was due to metabolism. However, after a 24-hour incubation of the test articles at 3 µM (the highest concentration for induction), the remaining concentrations were still significantly higher than the clinical C_{max} concentrations of DM4 at only 4.11 ± 2.28 ng/mL and S-methyl-DM4 at only 6.98 ± 6.79 ng/mL when MIRV is dosed at 6 mg/mL AIBW Q3W in Study 0403. The results indicate sufficient exposure to both test articles and validity of the induction results.

At later time points (48 h or 72 h) the remaining concentrations of DM4 and S-methyl-DM4 were not assessed. However, the hepatocyte cell viability at 24, 48, and 72 h was similar, which could indicate that the concentrations of the remaining test articles are also similar since both DM4 and S-methyl-DM4 are cytotoxic. It is also worth noting that DM4 is primarily converted to S-methyl-DM4 by a hepatic thiol methyltransferase. Therefore, it is obvious that the initial metabolic loss of DM4 and S-methyl-DM4 in incubation with hepatocytes for the first 24 hours still leaves the test articles at concentrations significantly higher than the clinical exposures in patients. The induction study results

ensured that no evidence for induction of CYP1A2, CYP2B6, and CYP3A4 was observed at the clinically relevant exposures to DM4 and S-methyl-DM4.

The choice of CYP isoforms for *in vitro* inhibition and induction studies followed the guidance given in CPMP/EWP/560/95/Rev. 1 Corr. 2** Guideline on the investigation of drug interactions.

Toxicology:

The acute toxicity studies of MIRV (GLP) and DM4 (non-GLP) were conducted in cynomolgus monkey after a single IV dose followed by the recovery period (MIRV: 5 days or 29 days; DM4: 29 days). The small molecule payload, DM4 was also assessed in single dose non-GLP toxicity study in the mouse.

The toxicity profile of DM4 in both monkey and mouse was similar to that established with MIRV, indicating the toxicities identified are attributable to the DM4 payload.

In the monkey 10 weeks repeat-dose toxicity study, MIRV-related abnormal ophthalmic findings were noted at the scheduled ophthalmic examinations conducted during Week 9 of the dosing phase and during Week 4 of the recovery phase in animals administered high 8 mg/kg/dose. Corneal findings in animals administered 8 mg/kg/dose were considered adverse because corneal microcysts have been reported to be associated with visual disturbances (e.g., blurred vision) in humans (Eaton 2015 and Moore 2017).

Ocular toxicity of MIRV was assessed in three non-GLP ocular toxicity studies in Dutch Belted rabbits. In the non-GLP 12-week study of MIRV at the terminal sacrifice MIRV-related microscopic observations were noted in the corneal epithelium of animals administered 8 or 12 mg/kg/dose of MIRV. Corneal observations included minimal to slight attenuation of the corneal epithelium and minimal degeneration/necrosis of individual corneal epithelial cells.

Ocular tissue distribution and PK of two test articles, were assessed after a 30-minute IV infusion in pigmented male rabbits.

The tissue distribution of M9346A-SPDB-3H-DM4 to the corneal epithelium at levels 3- to 4-fold higher than MIRV was correlated with higher incidence of keratopathy (multifocal subepithelial punctate microcystic lesions in perilimbal cornea that generally co-localized with fluorescein staining patterns.

MIRV targets and binds to the FRα located on the cell surface through the mAb component. Upon binding to FRα, the ADC is internalized, processed, and degraded in the lysosomes resulting in release of DM4-derived catabolites. In tissue cross reactivity studies MIRV-related cytoplasmic staining in human cornea was observed, which the applicant considered unspecific.

In *in vitro* bacterial reverse mutation assay, both DM4 and S-methyl DM4 were negative both in Salmonella and E. coli test strains. A validity of the test was shown by a positive control. Precipitation of the test item and cell toxicity were observed at high concentrations. In *in vivo* rat bone marrow micronucleus assay using male SD rats, both DM4 and S-methyl DM4 proved to be genotoxic by inducing micronuclei in PCE in rat bone marrow. In addition, both substances were cytotoxic to the bone marrow, which resulted in decreases in the %PCE. The genotoxic potential for DM4 and S-methyl DM4 was expected based on their mechanism of action. As differentiation between clastogenic and aneugenic activity cannot be made based on the performed tests, the SmPC and RMP mention that DM4 and S-methyl DM4 resulted in micronuclei in polychromatic erythrocytes instead of stating that they are clastogenic.

The designs of *in vitro* and *in vivo* tests were based on appropriate OECD test guidelines.

MIRV is intended for the treatment of ovarian cancer. Preclinical development program of MIRV is within the scope of ICH S9. In the guideline carcinogenicity studies are not required for therapeutics

intended for to treat patients with advanced cancer. Therefore, the applicant's decision not to conduct carcinogenicity studies is acceptable.

No reproductive or developmental studies were conducted with MIRV.

The absence of any reproductive or developmental studies was justified by referring to ICH S9. According to the guideline these studies are not essential for the purpose of marketing applications for pharmaceuticals that are genotoxic and target rapidly dividing cells (e.g., bone marrow) in general toxicity studies or belong to a class that has been well characterized as causing developmental toxicity. The payload of MIRV, DM4 (and the active metabolite S-methyl DM4), is cytotoxic, targets rapidly dividing cells and belongs to a class of compounds (maytansinoid) for which developmental toxicity/teratogenicity has been described in the literature (Sieber 1978; Issell 1978). Findings in general toxicity studies and *in vivo* genotoxicity studies support genotoxicity and cytotoxicity of DM4 and its active metabolite. In conclusion, the absence of reproductive and developmental studies is endorsed. There are no data on the effect of Elahere on human fertility. However, given the mechanism of action of Elahere leads to microtubule disruption and death of rapidly dividing cells, there is the potential for drug-related fertility effects. Administration of Elahere to pregnant patients is not recommended, and patients should be informed of the potential risks to the foetus if they become or wish to become pregnant.

The absence of juvenile toxicity study is acceptable for this product indicated in adult patients only; it is in line with the waiver granted by the EMA for all subsets of the paediatric population for treatment of ovarian carcinoma, fallopian tube carcinoma and peritoneal carcinoma.

Two free maytansinoid-related impurities, maysine and DM4-sulfo-TBA, were both qualified at specification limit of ≤4.0% (mol/mol). The impurities were dosed only once in mouse qualification studies; however this can be accepted since posology in patients is once every 3 weeks (21-day cycle).

DM4 was assessed for phototoxicity to Balb/c 3T3 fibroblast cells using the neutral red uptake (NRU) assay. DM4 was phototoxic in the NRU assay system when tested up to 100 µg/mL. For evaluation of phototoxicity, the cells were exposed to up to 5 J/cm2 of ultraviolet A light (UV-A) irradiation in total. The photo-irritation factor (PIF) was calculated for DM4 as 15.17 (IC_{50} in the absence of UV-A [8.712 µg/mL] divided by IC_{50} in the presence of UV-A [0.582 µg/mL]). The PIF value 15.17 indicates "phototoxicity" based in criteria given in OECD 432.

ERA:

The antibody and linker moieties of Mirvetuximab soravtansine are natural substances, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, mirvetuximab is not expected to pose a risk to the environment.

DM4 (maytansinoid) PEC $_{surfacewater}$ value is below the action limit of 0.01 µg/L. and is not a PBT substance as log K_{ow} does not exceed 4.5. Therefore, DM4 is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

The review of non-clinical data available for MIRV indicates no issues for concern. From a non-clinical point of view, the application is approvable.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 16: Conducted clinical studies.

	Pivotal Study	**Supportive Studies**		
	IMGN853-0416 (Study 0416, MIRASOL)	**IMGN853-0417 (Study 0417, SORAYA)**	**IMGN853-0401 (Study 0401)**	**IMGN853-0403 (Study 0403)**
Phase and Design features	Phase 3, Open-label, randomized	Phase 3, Open-label, single-arm	First-in-human, open-label, nonrandomized, dose escalation, and dose expansion	Phase 3, Open-label, randomized
Study population	Patients with advanced, high-grade PROC with: 1-3 prior lines of therapy Tumors expressing a high level of FRαa	Patients with advanced, high-grade PROC with: 1-3 prior lines of therapy, including bevacizumab Tumors expressing a high level of FRαa	Patients with epithelial ovarian cancer and other FRα-positive tumoursa	Patients with advanced, high-grade PROC with: 1-3 prior lines of therapy Tumors expressing medium or high levels of FRαa
Treatment regimens	1:1 randomization: MIRV 6 mg/kg AIBW Q3W (N = 227) IC of select chemotherapies[b] (N = 226)	MIRV 6 mg/kg AIBW Q3W (N = 106)	MIRV: Dose escalation: 0.15 mg/kg TBW to 7.0 mg/kg TBW (n = 44 Q3W; n = 25 QW) Dose expansion: 6 mg/kg AIBW Q3W (ie, RP2D) (epithelial ovarian cancer n = 113; endometrial cancer n = 24)	2:1 randomization: MIRV[c] 6 mg AIBW Q3W (N = 248) IC of select chemotherapies (N = 118)[d]
Efficacy endpoints	Primary: PFSINV Key secondary: ORRINV, OS, PRO (EORTC QLQ-OV28)	Primary: ORRINV Key secondary: DORINV	ORRINV, DORINV, PFSINV	Primary: PFSBICRe Key secondary: ORRBICR, PRO (EORTC QLQ-OV28), OS

AIBW = adjusted ideal body weight; **BICR** = blinded independent central review; **DOR** = duration of response; **DOR_{INV}** = investigator-assessed DOR; **EORTC** = European Organisation for Research and Treatment of Cancer; **FRα** = folate receptor alpha; **IC** = investigator's choice (of select chemotherapies); **ORR** = objective response rate; **ORR_{BICR}** = BICR-assessed ORR; **ORR_{INV}** = investigator-assessed ORR; **OS** = overall survival; **PFS** = progression-free survival; **PFS_{BICR}** = BICR-assessed PFS; **PFS_{INV}** = investigator-assessed PFS; **PRO** = patient-reported outcome; **Q3W** = every 3 weeks; **Q4W** = every 4 weeks; **QLQ-OV28** = Quality of Life Questionnaire-Ovarian Cancer Module; **QW** = once weekly; **RP2D** = recommended Phase 2 dose; **TBW** = total body weight.

[a] FRα expression was based on the following:
Study 0416 and Study 0417: ≥ 75% cells stained at 2+ intensity (PS2+ scoring method).
Study 0403: ≥ 50% of cells with any FRα membrane using the 10X scoring method, including a medium level of FRα (50%-74%) and high FRα (≥ 75%).
Study 0401: ≥ 25% cells stained at 2+ intensity.

[b] The IC chemotherapies included (1) paclitaxel 80 mg/m^2 IV infusion QW; (2) topotecan, either 4 mg/m^2 QW ×3 within 4-week cycles; or 1.25 mg/m^2 ×5 within 3-week cycles; or (3) PLD 40 mg/m^2 IV infusion Q4W.

[c] In Study 0403, 4 additional patients were treated with mirvetuximab soravtansine in Stage 1: N = 2 received Schedule A at 6 mg/kg AIBW Q3W; N = 2 received Schedule B at 6 mg/kg AIBW Q4W.

[d] The IC chemotherapies included (1) paclitaxel 80 mg/m^2 IV infusion QW; (2) topotecan 4 mg/m^2 QW ×3 within 4-week cycles; (3) PLD 40 mg/m^2 IV infusion Q4W.

[e] In Study 0403, the primary efficacy endpoint was evaluated in the ITT population (FRα expression ≥ 50% of tumor cells) and in the subgroup of patients with high FRα expression (≥ 75% of tumor cells).

For most patients treated with MIRV in clinical studies, the administered dose was based on each patient's adjusted ideal body weight (AIBW) to reduce the between-subject variability in exposure to MIRV. The proposed posology is likewise based on AIBW, calculated as follows:

- **AIBW** = Ideal Body Weight (IBW [kg]) + 0.4*(Actual weight [kg] – IBW)
- Female IBW [kg] = 0.9*height [cm] – 92

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Clinical pharmacokinetic (PK) data were collected in four clinical efficacy and safety studies (see above table). Studies 0401 and 0403 provided dense PK sampling data and studies 0417 and 0416 sparse sampling data. No dedicated clinical pharmacology studies were conducted. PK of plasma MIRV, DM4, and S-methyl-DM4 were evaluated using non-compartmental analyses (NCA) in studies 0401 and 0403 and population PK (PPK) analysis; the final pooled PPK dataset included data of all four studies. In addition, PK of total antibody (TAb; representing the ADC plus antibody which has no conjugated DM4) in study 0401 and study 0403 was characterized using NCA. The PK profiles of the TAb were similar to that of the intact MIRV, except that the elimination rate for the TAb was slightly slower than that of the ADC. The recommended dose and regimen for Elahere is 6 mg/kg adjusted ideal body weight (AIBW) as an intravenous infusion administered once every 3 weeks (21-day cycle).The pharmacokinetics were characterised after patients were administered mirvetuximab soravtansine 0.161 mg/kg to 8.71 mg/kg AIBW doses (i.e., 0.0268 times to 1.45 times the approved recommended dose of 6 mg/kg AIBW), unless otherwise noted.

Bioanalytical methods

Table 17: Summary of Bioanalytical Methods for PK and Immunogenicity

Assay	Anticoagulant	Method	Assay Range	Application	Clinical Study	Method Validation Report
ADC	K2EDTA	ELISA	225 to 1500 ng/mL[a]	PK	Study 0401 Study 0403 Study 0417 Study 0416	ICD 604 and H8605MVHuPl01[b]
ADC	Sodium heparin	ELISA	75 to 2500 ng/mL	PK	Study 0401	ICD 604.2
TAb	K2EDTA	ELISA	500 to 4000 ng/mL	PK	Study 0401 Study 0403 Study 0417 Study 0416	ICD 605 and H8605MVHuPl[b]
TAb	Sodium heparin	ELISA	500 to 5000 ng/mL	PK	Study 0401	ICD 605.2
DM4 and DM4-Me	K2EDTA	LC/MS/MS	0.100 to 50 ng/mL for both DM4 and DM4-Me	PK	Study 0401 Study 0403 Study 0417 Study 0416	LCMSF 740.2 and H8605MVHuPl02[b]
ADA	K2EDTA	ECL	NA	Immunogenicity	Study 0401 Study 0403 Study 0417 Study 0416	ICDIM 212 and H8605MVHuPl03[b]
ADA	Sodium heparin	ECL	NA	Immunogenicity	Study 0401	ICDIM 212.2
NAb	K2EDTA	Cell based	NA	Immunogenicity	Study 0401 Study 0403 Study 0417 Study 0416	ICDCBA 118 and H8605MVHuPl04
Assay	**Anticoagulant**	**Method**	**Assay Range**	**Application**	**Clinical Study**	**Method Validation Report**
Soluble FRα	K2EDTA	LC/MS/MS	0.39 to 100 ng/mL	Biomarker	Study 0401 Study 0403	IML28-006
Soluble FRα	K2EDTA	LC/MS/MS	4.00 to 2000 pM	Biomarker	Study 0417 Study 0416	FLL28[c]

Abbreviations: ADA = antidrug antibody; ADC = antibody-drug conjugate; DM4 = payload; DM4-Me = S-methyl DM4; ECL = electrochemilumiscent; ELISA = enzyme-linked immunosorbent assay; FRα = folate receptor alpha; K2EDTA = dipotassium ethylenediaminetetraacetic acid; LC/MS/MS = liquid chromatography with tandem mass spectrometry; NA = not applicable; NAb = neutralizing antibody; PK = pharmacokinetics; TAb = total antibody.

[a] For H8605MVHuPl01, the assay range was 75 to 1500 ng/mL.

[b] Methods validated for Study 0416 in Chinese patients.

[c] In Study 0416, assay used to analyze samples from all countries except China.

All PK assays were validated according to ICH M10 on bioanalytical method validation and bioanalytical reports including ISR were provided.

Mirvetuximab soravtansine concentrations in potassium edetate plasma were determined by an ELISA assay using a murine monoclonal anti-maytansine antibody (α-maytansine) for capturing mirvetuximab soravtansine, a horseradish peroxidase (HRP)-conjugated donkey anti-human immunoglobulin G (IgG) (heavy and light chain) or horseradish peroxidase-labeled Goat Anti-Human IgG, Monkey ads-HRP for the detection, and 3,3',5,5'-tetramethylbenzidine (TMB) as a chromogenic substrate. Two methods were developed, one for samples in sodium heparin and one for samples in potassium edetate. The methods were developed and validated by PPD™. In addition, United-Power Pharma Tech Co., Ltd. validated the method for samples in K_2EDTA for the subset of patients in study 0416 in China. The lower limit of quantification (LLOQ) was 75.0 ng/ml and the upper limit of quantification (ULOQ) was 1500 ng/ml. Lipemia, or hemolysis did not interfere with the assay. Also, carboplatin, bevacizumab or pegylated liposomal doxorubicin did not interfere with the assay.

The assay for samples in sodium heparin plasma followed the same principle as the assay for samples in potassium edetate plasma and it was validated by PPD™. The LLOQ was 75.0 ng/ml and the ULOQ was 2500 ng/ml. Lipemia, or hemolysis did not interfere with the assay.

Total antibody was quantitatively measured from human plasma using an ELISA assay using human folate receptor 1-Fc to capture TAb, and a biotinylated anti-human IgG-Fc as a secondary antibody. HRP-conjugated streptavidin was used for the detection and TMB as a colorimetric substrate. The assay was developed and validated by PPD™. In addition, United-Power Pharma Tech Co., Ltd. (Beijing, China) validated the method for samples in K_2EDTA for the subset of patients in study 0416 in China. The assays followed the same principle but PPD™ used biotinylated monoclonal anti-human IgG-Fc, clone HP-6017 (αIgGFc:B) for detection while United-Power Pharma Tech used horse radish peroxidase-labeled detection antibody (Goat Anti-Human IgG, Monkey ads-HRP). The quantitation range for the assays is 500 - 4000 ng/ml. Lipemia, or hemolysis did not interfere with the assay. The assay performance was examined in the presence of bevacizumab, pegylated liposomal doxorubicin, carboplatin and pembrolizumab. No interference was observed. The assay for samples in sodium heparin followed the same principle and was validated by PPD.

DM4 and its metabolite DM4-Me in human plasma were quantitated by HPLC with ES-MS/MS detection using deuterated DM4-d_6 and DM4-Me-d_6 as internal standards. Analytes were isolated through protein precipitation using a Water 96 well Ostro plate, reconstituted and analyzed by HPLC with column-switching and ES-MS/MS detection. The method was validated by PPD™ and United Power Pharma. The quantitation range was 0.1-50.0 ng/ml. No interference with hemolysis or lipemia was observed.

Two liquid chromatography-MS/MS methods for the determination of sFRα in K_2EDTA human plasma were developed at ImmunoGen, Inc. (IML28-006) and at Frontage Laboratories, Inc. (FLL28-001). Only the method developed at Frontage Laboratories, Inc. was validated, while the method developed at ImmunoGen was qualified according to the recommendations of the Food and Drug Administration (FDA) Guidance for Bioanalytical Method Validations. In both methods, an isotope labeled peptide (VLNV(l3C5, 15N)PLCK) was used as the internal standard. Human FRα, His-tag FRα was used as a reference standard and analyzed as a surrogate analyte (soluble human folate receptor-α). The LLOQ of the IML28-006 method is 0.39 ng/ml for sFRα, and the dynamic range of the method is 0.39 to 100 ng/ml. The LLOQ of the FLL28-001 method is 4.00 pM for sFRα, and the dynamic range of the method is 4.00 to 2000 pM. No assay was available in the local laboratory in China; therefore, no sFRα data were available for patients enrolled in study 0416 in China.

A 3-tiered MSD-ECL assay using murine monoclonal anti-M9346A antibodies as positive control was developed for the detection of anti-mirvetuximab soravtansine antibodies in human plasma. The method was developed and validated by PPD™ in sodium heparin plasma (ICDIM 212.2) and K_2EDTA (ICDIM 212) human plasma and by United-Power Pharma in K_2EDTA human plasma (H8605MVHuPl03). The assay procedure was the same for both human plasma collection anticoagulants. The drug tolerance of the PPD™ assay was 10.2 µg/ml for 64.2 ng/ml anti-drug antibodies (ADA). The cytotoxic component DM4 and the naked antibody M9346A did not interfere with the assay. A cell-based assay was developed for the detection of NAbs to mirvetuximab soravtansine in K_2EDTA human plasma. This bioanalytical method uses a bead extraction with acid dissociation sample pretreatment to overcome high concentrations of mirvetuximab soravtansine in samples, followed by a functional cell based NAb bioassay. Proliferation of keratin-forming cells is measured using the CellTiter-Glo® Luminescent Cell Viability Assay, which is a method of determining the number of viable cells in a culture based on quantitation of the adenosine triphosphate present, an indicator of metabolically active cells. In the presence of NAbs to mirvetuximab soravtansine, cell proliferation is not inhibited, and therefore resulting in a higher luminescent signal. The method was developed and validated by PPD™ in K_2EDTA human plasma (ICDCBA 118) and by United-Power Pharma (H8605MVHuPl04). The cross validation of the assay between the ICDCBA 118 and H8605MVHuPl04 methods demonstrated comparable performance.

Absorption

MIRV is administered as an intravenous infusion and therefore bioavailability is 100%. There have been no studies performed with other routes of administration.

The formulation of MIRV has not changed over the course of clinical development and is the same as the proposed commercial formulation. Minor manufacturing process changes were made during the clinical development (see section 2.4 Quality aspects). All patients treated with MIRV in study 0417 and the pivotal study 0416 received drug product manufactured by the commercial process.

Distribution

Results of PPK analysis and non-compartmental analyses indicate that MIRV has a small volume of distribution, approximately 2.5 to 4 L, suggesting that MIRV is distributed mainly in plasma. The mean (±SD) steady state volume of distribution of mirvetuximab soravtansine was 2.63 (±2.98) L. *In vitro* human plasma protein binding of DM4 and S-methyl DM4 was >99%.

Elimination

The elimination pathways of MIRV (ADC) were not investigated.

The antibody component of MIRV is a monoclonal IgG1 molecule, which has molecular weight (MW) of ~146 kDa. Renal filtration is negligible for proteins with MW > 50 kDa. Target-mediated elimination is expected to take place but probably accounts for a small part of elimination of mirvetuximab soravtansine at the proposed dose.

The mean (±SD) total plasma clearance of mirvetuximab soravtansine was 18.9 (±9.8) mL/hour. The mean terminal phase half-life of mirvetuximab soravtansine after the first dose was 4.9 days. For the unconjugated DM4, the mean (±SD) total plasma clearance was 14.5 (±4.5) mL/hour and the mean terminal phase half-life was 2.8 days. For S-methyl-DM4, the mean (±SD) total plasma clearance was 5.3 (±3.4) L/hour and the mean terminal phase half-life was 5.1 days. 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.

Incidence of treatment-emergent and treatment-induced anti-drug antibodies (ADA) against MIRV was modest (< 10%). Graphical exploratory analysis indicated no apparent association between ADA status and exposure to MIRV. It was concluded that because of the low occurrence of ADA, the effect of these antibodies on the PK of MIRV is unknown.

Metabolism

In vivo metabolism of DM4 following IV bolus injection of tritiated MIRV (M9346A-Sulfo-SPDB-^{3}H-DM4) was investigated in male Sprague Dawley rats (study IMG28-001; see section 2.5 Non-clinical aspects).

IgG antibodies are mainly catabolized by lysosomal proteolysis and then eliminated from or re-used by the body, which is assumed to be the case for mirvetuximab soravtansine.

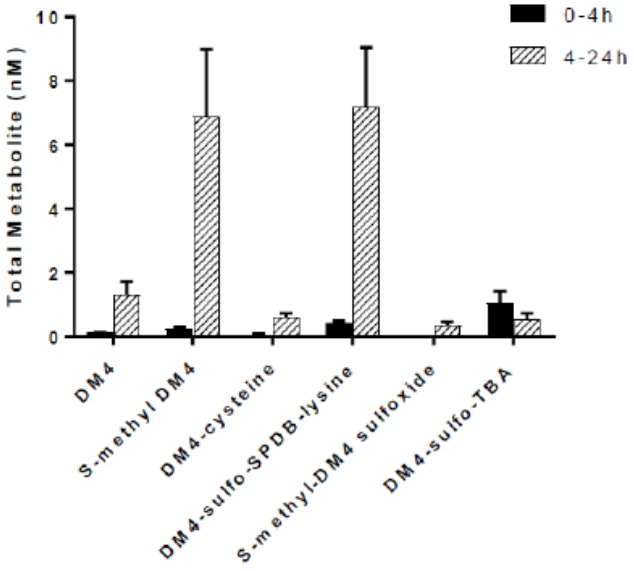
DM4 is released from the ADC either as the drug-payload complex is catabolized by lysosomal proteolysis, or extracellularly by deconjugation of the payload from the complex. DM4 is metabolized by a S-methyl transferase to S methyl-DM4. Both DM4 and S-methyl-DM4 are also metabolized by CYP3A4. Unconjugated DM4 and S-methyl-DM4 over MIRV ratios in study 0403, based on molarity, were approximately 0.4% and 1.4%, respectively. DM4-sulfo-SPDB-lysine and DM4-sulfo-TBA were also identified in human plasma in study 401 but were observed at trace levels. S-methyl-DM4 and DM4-sulfo-SPDB-lysine were the main metabolites detected in urine over 24 hours following

administration of MIRV. Human mass-balance studies were not conducted; in male Sprague Dawley rats biliary excretion was the predominant route of elimination of DM4-related material.

Results of *in vitro* studies CVG14-001 and SVG28-001 indicate that DM4 and S-methyl-DM4 are mainly metabolized by CYP3A4, and both are substrates of P-gp (see section 2.5 Non-clinical aspects).

DM4 and its metabolites in urine were characterized in six patients in study 0403 during Cycle 2, Cycle 3, or Cycle 4 (Report IMG28-003). Samples were collected prior to dosing, at 0-4 hours and 4-24 hours and analysed using high performance liquid chromatography (HPLC) coupled with high-resolution mass spectrometric (HRMS) methods. Six metabolites were identified from patient urine samples (see figure below); glucuronide conjugates were not observed. It was estimated that approximately 0.70% of all payload-related materials were excreted in urine over 24 hours post-infusion.

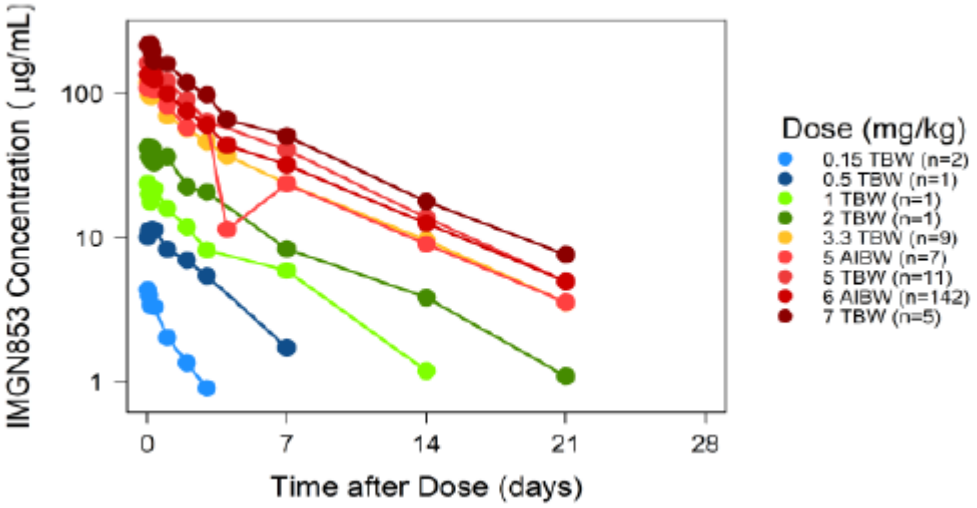
Figure 8: Metabolite Excretion in Urine Samples (IMG28-003)



Dose proportionality and time dependencies

In study 0401, exposure to MIRV increased approximately proportionally with dose over the dose range 3.3 to 7 mg/kg total body weight (TBW), which includes the proposed dose 6 mg/kg AIBW. Following very low subtherapeutic doses (0.15 to 0.5 mg/kg TBW), clearance was higher than following higher doses (see figure below).

Figure 9: Mean MIRV Plasma Concentration vs. Time following the first dose, by dose.



The tables below summarises the exposure parameters of mirvetuximab soravtansine, unconjugated DM4, and its metabolite S-methyl-DM4 following administration after the first and the third cycle (3-weeks) of mirvetuximab soravtansine 6 mg/kg AIBW to patients. Peak mirvetuximab soravtansine concentrations were observed near the end of intravenous infusion, while peak unconjugated DM4 concentrations were observed on the second day after administration of mirvetuximab soravtansine, and the peak S-methyl-DM4 concentrations were observed approximately 3 days after administration of mirvetuximab soravtansine. Steady state concentrations of mirvetuximab soravtansine, DM4, and S-methyl-DM4 were reached after 1 treatment cycle. Accumulation of the mirvetuximab soravtansine, DM4, and S-methyl-DM4 was minimal following repeat administration of mirvetuximab soravtansine.

No time dependencies were identified in PPK analysis.

Table 18: Mean (SD) Cycle 1 and Cycle 3 PK and exposure parameters in patients who received 6 mg/kg AIBW MIRV in study 0401

PK Parameter	Study 0401 - 6 mg/kg AIBW					
	Cycle 1			Cycle 3		
	MIRV	DM4	S-Methyl DM4	MIRV	DM4	S-Methyl DM4
C_{max} (µg/mL)	146.9 (30.14)	5.247[1] (2.990)	12.43[1] (12.39)	154.6 (33.08)	5.016[1] (2.389)	9.974[1] (5.485)
AUC_{last} (h*mg/mL)	16.44 (4.177)	246.0[2] (133.3)	2485[2] (2536)	18.91 (4.940)	270.1[2] (95.62)	1806[2] (1046)
T_{max} (h)	3.97 (2.87)	25.6 (64.3)	80.4 (98.0)	4.01 (5.74)	56.9 (151)	68.0 (148)
$t_{1/2}$ (h)	119.4 (22.58)	73.80 (28.99)	122.2 (25.23)	127.8 (34.11)	80.62 (26.12)	130.4 (23.47)
CL (mL/h)	22.20 (6.476)	27.13 (10.70)[3]	4.178 (2.453)[3]	19.80 (4.953)	25.56 (8.387)[3]	4.936 (3.322)[3]
V_{ss} (L)	3.198 (0.742)	2050 (738.4)[4]	793.7 (532.4)[4]	3.172 (1.022)	2183 (929.5)[4]	906.4 (770.9)[4]
Accumulation ratio[5]	.	.	.	1.11 (22.4%)	1.17 (181.3%)	1.09 (69.3%)
[1]ng/mL; [2]h*ng/mL; [3] CL/F (L/h); [4] V_{ss}/F; [5] Geometric mean (CV%)						

Table 19: Mean (SD) Cycle 1 and Cycle 3 PK and exposure parameters in patients who received 6 mg/kg AIBW MIRV in study 0403

PK Parameter	Study 0403 - 6 mg/kg AIBW					
	Cycle 1			Cycle 3		
	MIRV	DM4	S-Methyl DM4	MIRV	DM4	S-Methyl DM4
C_{max} (µg/mL)	137.3 (62.26)	4.108[1] (2.285)	6.984[1] (6.794)	137.0 (40.51)	3.870[1] (1.957)	5.742[1] (5.023)
AUC_{tau} (h*mg/mL)	20.65 (6.838)	530.1[2] (245.0)	1848[2] (1585)	22.70 (4.938)	447.9[2] (157.6)	1587[2] (1299)
AUC_{last} (h*mg/mL)	20.60 (6.960)	516.6[2] (240.7)	1858[2] (1586)	22.52 (5.126)	436.4[2] (155.9)	1585[2] (1306)
T_{max} (h)	25.8 (76.5)	21.3 (61.3)	195 (95.7)	15.5 (64.5)	16.8 (59.8)	131 (91.6)
$t_{1/2}$ (h)	117.8 (27.85)	67.16 (13.76)	122.5 (27.13)	126.2 (28.15)	79.09 (33.04)	160.4 (63.85)
CL (mL/h)	18.91 (9.812)	14.52 (4.509)[3]	5.301 (3.369)[3]	15.58 (4.771)	17.17 (7.607)[3]	5.973 (4.515)[3]
V_{ss} (L)	2.632 (2.977)	745.7 (409.3)[4]	1377 (899.5)[4]	2.218 (1.403)	1172 (1072)[4]	1584 (1488)[4]
Accumulation ratio[5]	.	.	.	1.15 (43.2%)	1.11 (97.0%)	1.01 (53.4%)
[1]ng/mL; [2]h*ng/mL; [3] CL/F (L/h); [4] V_{ss}/F; [5] Geometric mean (CV%)						

Population PK model

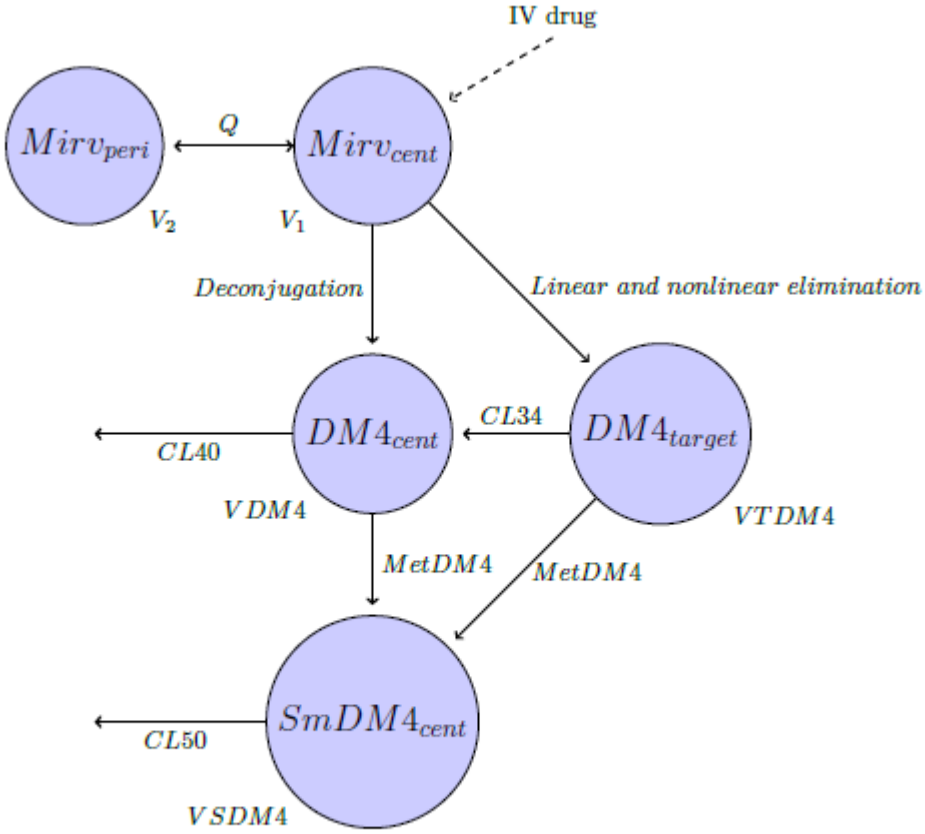
An initial PPK model was built using dense PK data from studies 0401 and 0403. It was externally validated against the sparse PK data of studies 0417 and 0416 and demonstrated overall adequate performance. The final PPK model (Report QPK28-012) was developed subsequently using data from all four studies to support the current MAA. Both models were developed using the same methods.

The analyses were based on plasma MIRV, DM4, and S-methyl-DM4 concentration data; TAb concentrations were not evaluated in the PPK models. A structural model for MIRV was developed first, followed by a covariate search to establish the covariate model for mirvetuximab soravtansine. This final MIRV PK model ("ADC model") was then expanded to fit a model ("payload model") to the unconjugated DM4 and S-methyl-DM4 concentrations in plasma by fixing the MIRV PK parameters to the estimates of the final ADC model. Covariate effects were evaluated using stepwise covariate modelling ($P<0.01$ for inclusion, $P<0.001$ for exclusion). All PPK analyses were carried out using FOCE-I method in NONMEM.

The dataset of the final PPK model included a total of 758 patients, 692 (91.3%) of whom were administered 6 mg/kg AIBW Q3W. Samples below the lower limit of quantification (BLQ) were excluded; the proportion of samples BLQ was high for DM4 (37.1%) and low for MIRV and S-methyl-DM4 (0.96% and 3.0%, respectively).

The final MIRV (ADC) PPK model was a 2-compartment distribution model with linear and non-linear elimination from the central compartment (V1). The joint model included two compartments (central and target compartment) for DM4 and one (central) compartment for S-methyl-DM4. Formation of unconjugated DM4 was described to happen as 1) deconjugation from the ADC in central compartment, and 2) release from the target compartment. Clearance of DM4 was described to happen by 1) metabolism to S-methyl-DM4 and 2) nonspecific clearance from central compartment. S-methyl-DM4 had one clearance pathway in the model. The following statistically significant covariates were identified (each measured at baseline): AIBW, serum albumin, tumour burden (size) and sFRα level on MIRV CL; AIBW and age on MIRV V1; AIBW and ALT on the formation of S-methyl-DM4 from DM4. The structure of the joint PPK model is shown in the figure below. Parameter estimates for the final ADC model and payload model are shown in the two below tables.

Figure 10: Structural diagram of the joint PPK model.



Q: Intercompartmental clearance. V1: Volume of distribution of central compartment. V2: Volume of distribution of peripheral compartment. CL34: Transfer clearance of DM4 from target to central. CL40: Clearance of DM4 from central other than conversion to S-Methyl-DM4. CL50: Clearance of S-methyl-DM4. MetDM4: Metabolism of DM4 to S-methyl-DM4. VDM4: Volume of distribution of DM4 in central compartment. VTDM4: Volume of distribution of DM4 in target compartment. VSDM4: Volume of distribution of S-methyl-DM4.

Table 20: Parameter Estimates for the final ADC PK Model (Run 22, QPK28-012)

Parameter	Description	Estimate	Relative SE (%)	95% CI	CV%
θ_1	CL ($L \cdot h^{-1}$)	0.0153	2.63*	(0.0145 - 0.0161)	
θ_2	V1 (L)	2.62	0.767*	(2.58 - 2.66)	
θ_3	Q ($L \cdot h^{-1}$)	0.00995	5.38*	(0.00895 - 0.0111)	
θ_4	V2 (L)	1.75	4.11*	(1.61 - 1.89)	
θ_5	V_{max} ($\mu mol \cdot h^{-1}$)	0.00118	12.5*	(0.000924 - 0.00150)	
θ_6	Km ($\mu mol/L$)	0.0421	17.2*	(0.0301 - 0.0589)	
θ_7	CL_{AIBW}	1.01	7.57	(0.864 - 1.16)	
θ_8	CL_{ALB}	-0.563	12.7	(-0.704 - -0.423)	
θ_9	CL_{TUMOR}	0.0403	24.4	(0.0211 - 0.0595)	
θ_{10}	$V1_{Age}$	0.178	19.6	(0.109 - 0.246)	
θ_{11}	$V1_{AIBW}$	0.817	7.83	(0.692 - 0.942)	
θ_{12}	$CL_{LOGSFOLR1}$	0.225	21.3	(0.131 - 0.319)	
$\omega_{1.1}$	ω^2_{CL} (var)	0.0479	12.3	(0.0364 - 0.0595)	22.2
$\omega_{2.1}$	$\omega^2_{V1,CL}$ (covar)	0.0249	17.0	(0.0166 - 0.0332)	
$\omega_{2.2}$	ω^2_{V1} (var)	0.0261	16.5	(0.0177 - 0.0346)	16.3
$\omega_{4.4}$	ω^2_{V2} (var)	0.0426	24.6	(0.0221 - 0.0631)	20.9
$\omega_{6.6}$	ω^2_{Km} (var)	0.337	28.9	(0.146 - 0.528)	63.3
$\sigma_{1.1}$	Σ_{Prop_1} (var)	0.0334	4.31	(0.0306 - 0.0362)	
$\sigma_{2.2}$	Σ_{Prop_2} (var)	0.0677	10.1	(0.0543 - 0.0811)	

*%RSE for parameters that were log-transformed approximated with $\sqrt{(exp(se(\theta)^2) - 1)} \cdot 100$. AIBW: Adjusted ideal body weight (kg). ALB: Serum albumin (g/dL). Age: Age (y). CI: Confidence interval. CL: Systemic clearance. CV: Coefficient of variation. Km: Michaelis-Menten constant. Q: Intercompartmental clearance. SE: Standard error. V1: Volume of distribution of central compartment. V2: Volume of distribution of peripheral compartment. V_{max}: Maximum rate. TUMOR: Baseline Tumor Burden (Sum of Longest Diameters, mm). LOGSFOLR: Log transformed soluble FRα (pmol/L). Prop1: Proportional residual error for IMGN853-0401 and IMGN853-0403. Prop2: Proportional residual error for IMGN853-0417 and IMGN853-0416. ω^2_X : Variance of the inter-individual variability of parameter X. $\omega^2_{X,Y}$: Covariance of the inter-individual variability of parameters X and Y.

Table 21: Parameter Estimates for the final payload PK Model (Run 104, QPK28-012)

Parameter	Description	Estimate	Relative SE (%)	95% CI	CV%
θ_{13}	Alpha	0.683		(NA - NA)	
θ_{14}	Beta (h^{-1})	0.0264		(NA - NA)	
θ_{15}	VTDM4 (L)	241	8.97*	(202 - 287)	
θ_{16}	CL34 ($L \cdot h^{-1}$)	2.44	10.7*	(1.98 - 3.00)	
θ_{17}	VDM4 (L)	3.66	10.5*	(2.98 - 4.50)	
θ_{18}	CL40 ($L \cdot h^{-1}$)	7.54	6.37*	(6.66 - 8.55)	
θ_{19}	MetDM4 ($L \cdot h^{-1}$)	3.92	9.06*	(3.29 - 4.68)	
θ_{20}	VSDM4 (L)	21.9	12.0*	(17.3 - 27.7)	
θ_{21}	CL50 ($L \cdot h^{-1}$)	1.98	3.55*	(1.85 - 2.12)	
θ_{22}	$MetDM4_{AIBW}$	0.616	16.1	(0.421 - 0.811)	
θ_{23}	$MetDM4_{ALT}$	-0.0909	33.4	(-0.150 - -0.0315)	
$\omega_{11.11}$	ω^2_{VDM4} (var)	0.603	17.9	(0.392 - 0.815)	91.0
$\omega_{12.12}$	ω^2_{CL40} (var)	0.324	11.0	(0.254 - 0.394)	61.9
$\omega_{13.13}$	ω^2_{MetDM4} (var)	0.0384	22.4	(0.0215 - 0.0553)	19.8
$\omega_{14.14}$	ω^2_{VSDM4} (var)	1.40	6.25	(1.23 - 1.57)	175
$\omega_{15.15}$	ω^2_{CL50} (var)	0.361	6.71	(0.314 - 0.408)	65.9
$\sigma_{3.3}$	$\sigma_{DM4\ Prop_1}$ (var)	0.0771	6.24	(0.0677 - 0.0865)	
$\sigma_{4.4}$	$\sigma_{DM4\ Prop_2}$ (var)	0.128	8.65	(0.107 - 0.150)	
$\sigma_{5.5}$	$\sigma_{SDM4\ Prop}$ (var)	0.205	2.91	(0.194 - 0.217)	

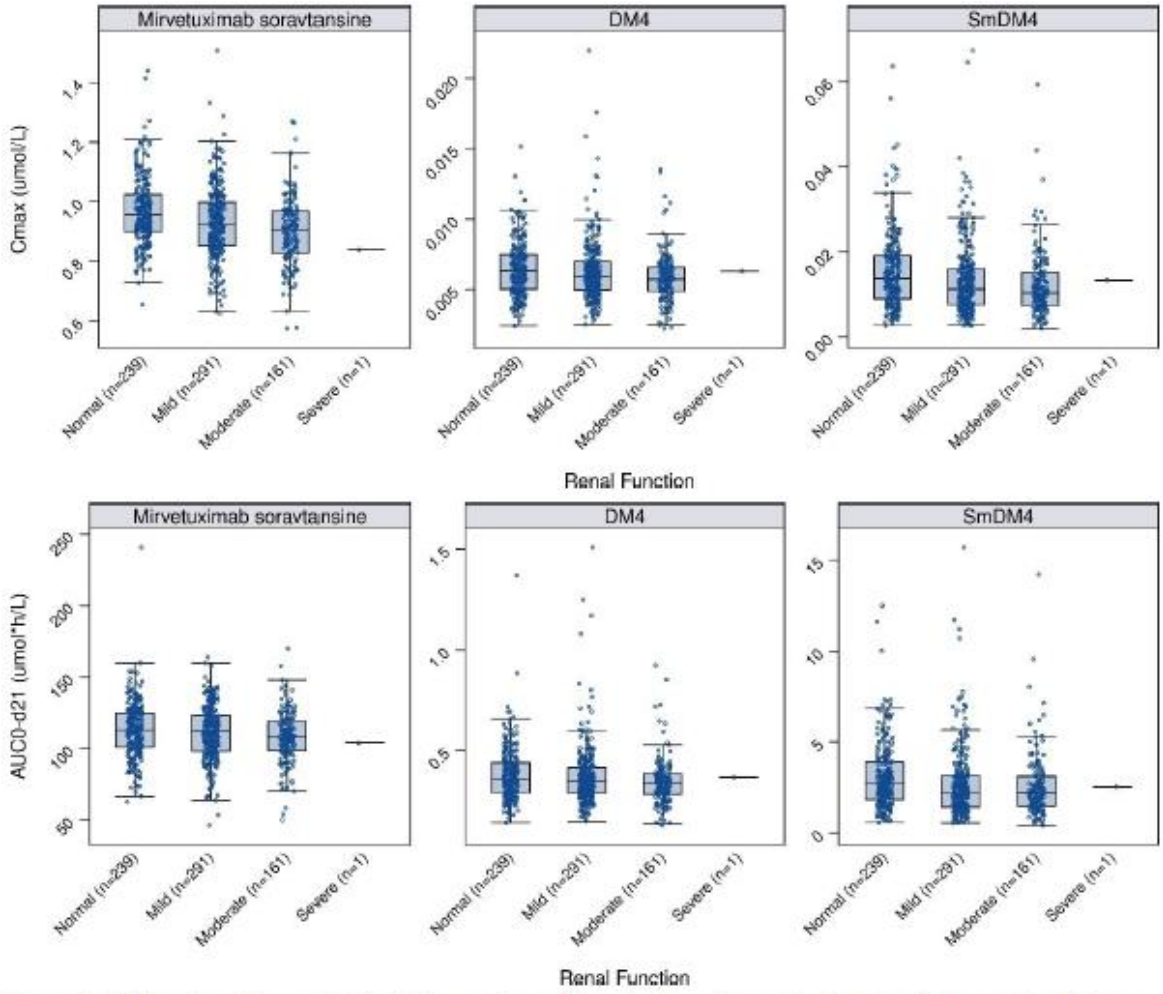
*%RSE for parameters that were log-transformed approximated with $\sqrt{(exp(se(\theta)^2)-1)}\cdot 100$. AIBW: Baseline adjusted ideal body weight. Alpha: Constant to constraint DAR(t) to physiologically plausible value. ALT: Alanine aminotransferase. Beta: Macro rate constant. CI: Confidence interval. CL34: Transfer clearance of DM4 from target to central. CL40: Clearance of DM4 from central other than conversion to S-Methyl-DM4. CL50: Clearance of S-methyl-DM4. CV: coefficient of variation. MetDM4: Metabolism of DM4 to S-methyl-DM4. SE: standard error. VDM4: Volume of distribution of DM4 in central compartment. VTDM4: Volume of distribution of DM4 in target compartment. VSDM4: Volume of distribution of S-methyl-DM4. Prop1: Proportional residual error for IMGN853-0401 and IMGN853-0403. Prop2: Proportional residual error for IMGN853-0417 and IMGN853-0416. Prop: Proportional residual error for all four studies. ω^2_X : Variance of the inter-individual variability of parameter X. $\omega^2_{X,Y}$: Covariance of the inter-individual variability of parameters X and Y.

Special populations

Predicted exposure parameters for patients treated with 6 mg/kg AIBW were compared to evaluate the exposure to MIRV, DM4, and S-methyl-DM in special populations.

Predicted exposure to MIRV, DM4, and S-methyl-DM4 was similar between patients with normal renal function (n=239) and those with mild (n=291) or moderate (n=161) renal impairment (see figure below).

Figure 11: Predicted C_{max} and $AUC_{0\text{-}d21}$ at Cycle 1 by Renal Function

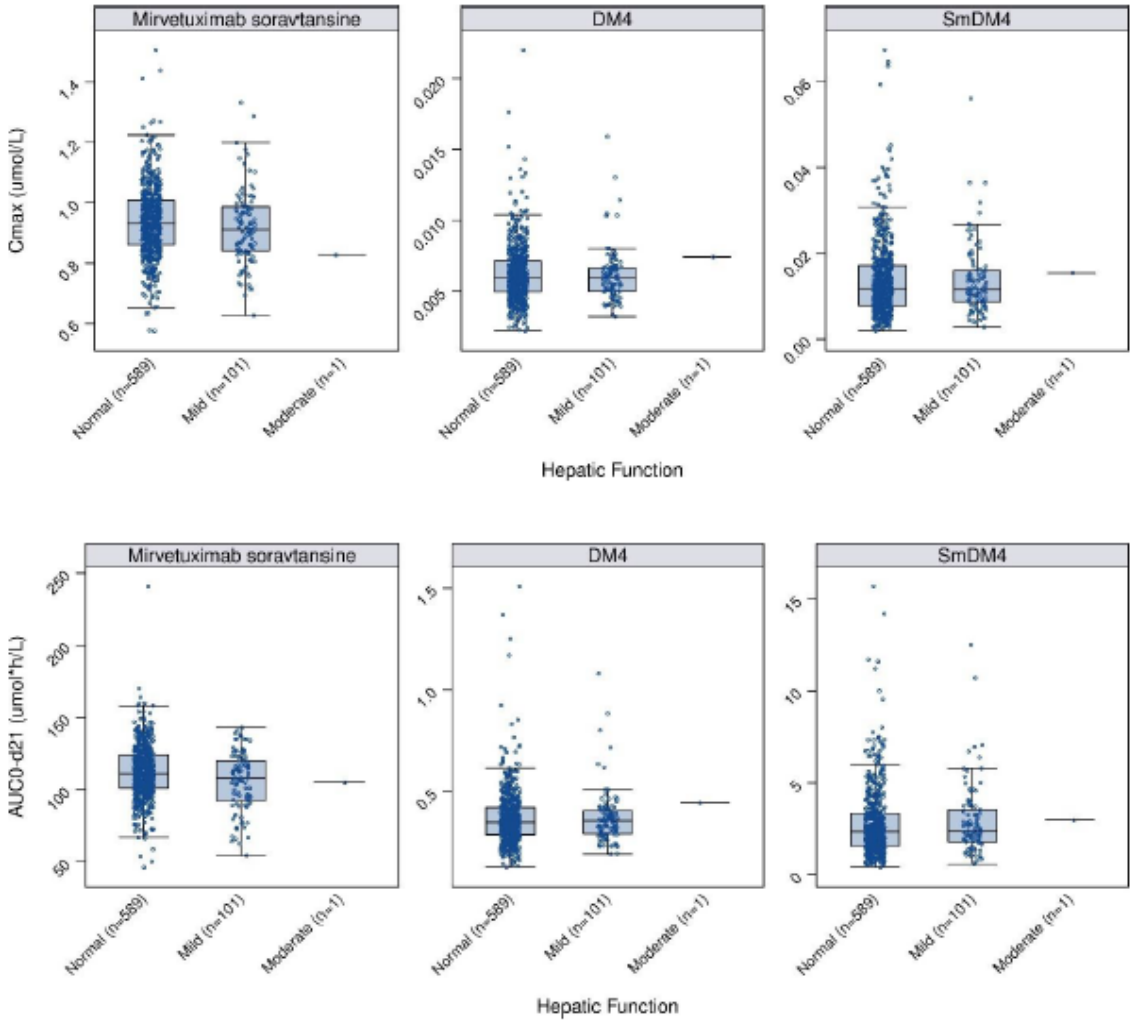


Box and whisker plot: The central line is the sample median, the boxes denote the interquartile range, the whiskers extend to 1.5 times the interquartile range. Points: Individual estimates.

Abbreviations: C_{max} = Maximum concentration; $AUC_{0\text{-}d21}$ = Area under the concentration versus time curve over the first 21-day treatment cycle.

Predicted exposure to MIRV, DM4, and S-methyl-DM4 was similar between patients with normal hepatic function (n=589) and those with mild hepatic impairment (n=101), defined according to the National Cancer Institute (NCI) classification system for hepatic dysfunction (see figure below).

Figure 12: Predicted C_{max} and $AUC_{0\text{-}d21}$ at Cycle 1 by NCI hepatic dysfunction class.



Box and whisker plot: The central line is the sample median, the boxes denote the interquartile range, the whiskers extend to 1.5 times the interquartile range. Points: Individual estimates.

Abbreviations: C_{max}: Maximum concentration. $AUC_{0\text{-}d21}$: Area under the concentration versus time curve over the first 21-day treatment cycle.

The range of body weight, ideal body weight (IBW), and adjusted ideal body weight (AIBW) in the PK population (n=758) was 36.1-136 kg, 25.5-75.0 kg, and 38.7-96.7 kg, respectively. In the PPK model, AIBW was a statistically significant covariate for MIRV clearance and central volume of distribution, both of which increased with increasing AIBW. However, simulations using the PPK model indicate that with the proposed dose regimen AIBW and total body weight have limited effect on exposure to MIRV). Predicted exposure to DM4 and S-methyl-DM4 increase slightly with increasing AIBW. At steady state, the 6 mg/kg AIBW Q3W dose is predicted to result in 32.5% higher AUC and 38.9% higher C_{max} of S-methyl-DM4 in a patient at the 95th percentile of AIBW and 22.2% lower AUC and 25.3% lower C_{max} in a patient at the 5th percentile of AIBW as compared to the reference patient.

Figure 13: Effect of AIBW on predicted MIRV exposure at steady state (6 mg/kg AIBW Q3W)

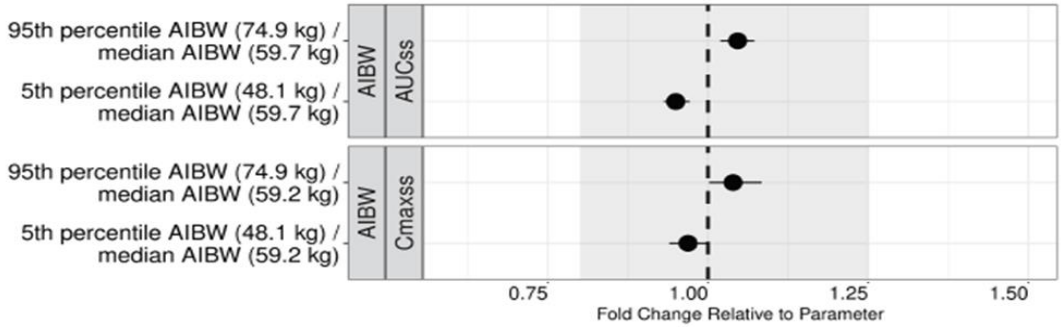


Figure 14: Predicted MIRV AUC and C_{max} at steady state vs. body weight (6 mg/kg AIBW Q3W)

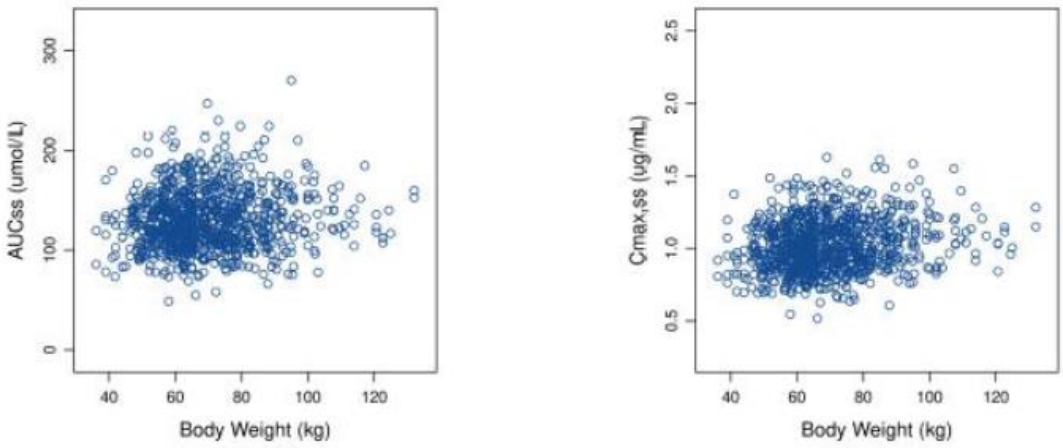
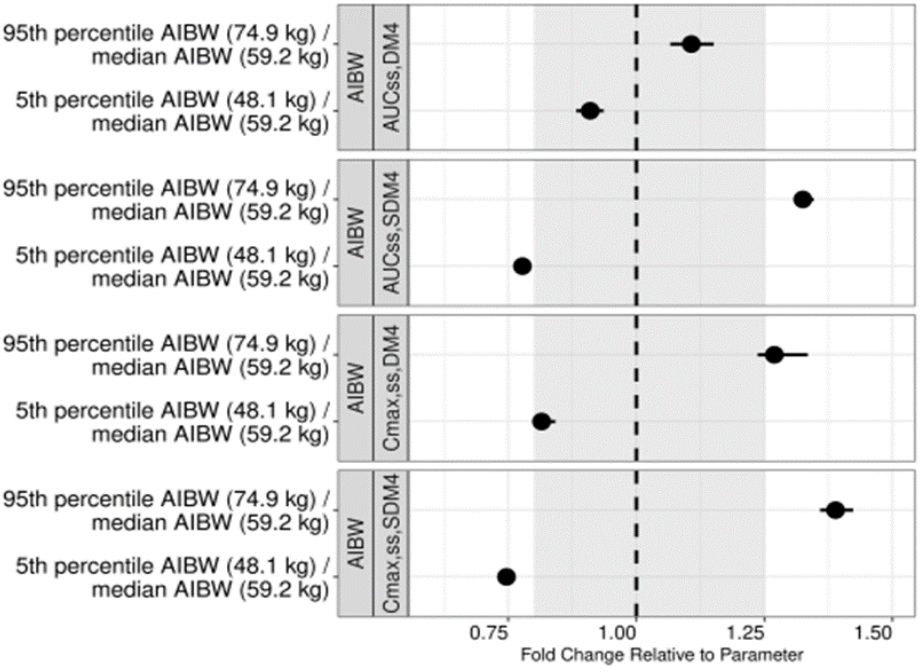


Figure 15: Effect of AIBW on predicted DM4 and S-methyl-DM4 exposure at steady state (6mg/kg AIBW Q3W)



The median (min-max) age at baseline in the dataset was 63 (32-89) years. Breakdown of patients by age group is presented in the below table. Although age was a statistically significant covariate for MIRV central volume of distribution, age had no relevant effect on predicted exposure parameters. Majority of patients (642/758; 84.7%) were White, no differences in predicted drug exposures were observed between race categories.

Table 22: Breakdown of patients by age group in each study

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PK Trials			
Study 0401	37/113	4/113	0/113
Study 0403	78/245	32/245	2/245
Study 0417	39/106	7/106	1/106
Study 0417	229/682	70/682	4/682

Pharmacokinetic interaction studies

In vitro

Results of *in vitro* drug-drug interaction studies are summarized below.

Unconjugated DM4 and S-methyl-DM4 were not direct inhibitors of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4. Unconjugated DM4 was a time-dependent inhibitor (TDI) of CYP3A4 and S-methyl DM4 was a weak TDI of CYP2C8 and CYP2C9. However, relevant inhibition is unlikely at DM4 and S-methyl-DM4 concentrations observed with proposed posology. DM4 and S-methyl-DM4 were not inducers of CYP1A2, CYP2B6, and CYP3A4.

Unconjugated DM4 and S-methyl-DM4 were not inhibitors of P-gp.*In vivo*

Clinical drug-drug interaction studies were not conducted. The applicant evaluated effects of CYP3A4 inhibitors and P-gp inhibitors in PPK analysis.

In the final PPK dataset, there were 19 and 59 patients in the 6 mg/kg AIBW dose group taking mild or moderate CYP3A4 inhibitors listed by the FDA, respectively, at any time during the first 3 cycles of MIRV treatment. In several cases, the inhibitor was taken as single doses (e.g. aprepitant, cimetidine or ranitidine on MIRV dosing days) or for less than 10 days (e.g., ciprofloxacin and fluconazole). In addition, there were 16 patients taking P-gp inhibitors listed by the FDA and 33 patients taking simvastatin, which was considered by the applicant to be a P-gp inhibitor. Only one patient was taking concomitant CYP3A4 inducer.

In covariate analysis, CYP3A4 inhibitors were not found to affect clearance of DM4 and S-methyl-DM4. P-gp inhibitors were not tested as covariate. Visual inspection suggested no major differences in exposure between patients taking CYP3A4 or P-gp inhibitors and those not taking the inhibitors.

Pharmacokinetics using human biomaterials

DM4 and S-methyl-DM4 were metabolized *in vitro* by recombinant human CYP3A4 but not by CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6. Unconjugated DM4 and S-methyl-DM4 were substrates of P-gp.

2.6.2.2. Pharmacodynamics

Mechanism of action

Mirvetuximab soravtansine is an antibody-drug conjugate. The antibody is an engineered IgG1 directed against folate receptor alpha (FRα). The function of the antibody portion is to bind to FRα expressed on the surface of ovarian 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.

Primary and secondary pharmacology

PD endpoints were not evaluated in clinical studies (see section 2.5 Non-clinical aspects).

Exposure-response analyses

To conduct exposure-response (E-R) analyses, individual exposure metrics (C_{max}, C_{trough}, and $AUC_{0\text{-}d21}$ following the first dose) for MIRV, unconjugated DM4, and S-methyl-DM4 were obtained from simulations with the final PPK model. Subjects with no PK observations were excluded from E-R analyses. E-R analyses for efficacy and safety comprised of logistic regression modelling of dichotomous responses and Cox proportional hazards modelling for time to event endpoints.

Stepwise forwards-backwards model selection procedure was conducted, based on Akaike information criterion (AIC). The exposure metric and patient characteristics (at baseline) were both modelled as 'covariates' of the logistic and Cox proportional hazards models and were treated equally in the selection procedure, i.e. if patient characteristics were more predictive of response, the exposure metric that did not improve the model fit could be dropped from that model. This process was conducted for each exposure metric and the model (including exposure metric and/or patient characteristics) with the lowest AIC was chosen as the final model for each endpoint.

The evaluated patient characteristics included age, AIBW, tumour burden (sum of the longest diameters of the target lesions), albumin, soluble folate receptor α (sFR-α) level, tumour FR-α expression category (high, medium, low/very low), baseline ECOG status, lines of prior treatments (1 up to more than 5), exposure to bevacizumab (+/-), and exposure to Poly ADP ribose polymerase inhibitors (PARPi) (+/-).

E-R analyses for efficacy were based on data from the pivotal study IMGN853-0416 (study 0416, aka MIRASOL), in which all patients randomized to MIRV started with the regimen 6 mg/kg AIBW Q3W. The investigated efficacy endpoints were progression free survival (PFS), overall survival (OS), objective response rate (ORR), and duration of response (DOR), each based on the investigator's assessment.

The models based on exposure metric MIRV C_{trough} had the lowest AIC and were selected as the final model for PFS, OS, and ORR. None of the exposure metrics were associated with DOR.

The Kaplan-Meier plot for PFS by MIRV C_{trough} quartile is shown in the figure below. In the full model, PFS increased with increasing MIRV C_{trough} and higher sFR-α, whereas higher tumour burden, higher ECOG score, and prior bevacizumab treatment shortened PFS. In addition, a regional difference, where patients treated in the USA had shorter PFS, was detected.

The Kaplan-Meier plot for OS by MIRV C_{trough} quartile is shown below. In the full model, OS increased with increasing MIRV C_{trough}, higher serum albumin and prior exposure to poly ADP ribose polymerase inhibitors, whereas higher tumour burden, higher ECOG score, and prior bevacizumab treatment shortened PFS.

The regression of ORR against MIRV C_{trough} is shown also below. No additional significant covariates were identified for this efficacy endpoint.

Figure 16: Kaplan-Meier Plot: Progression Free Survival by MIRV C_{trough} Quartile in Study 0416

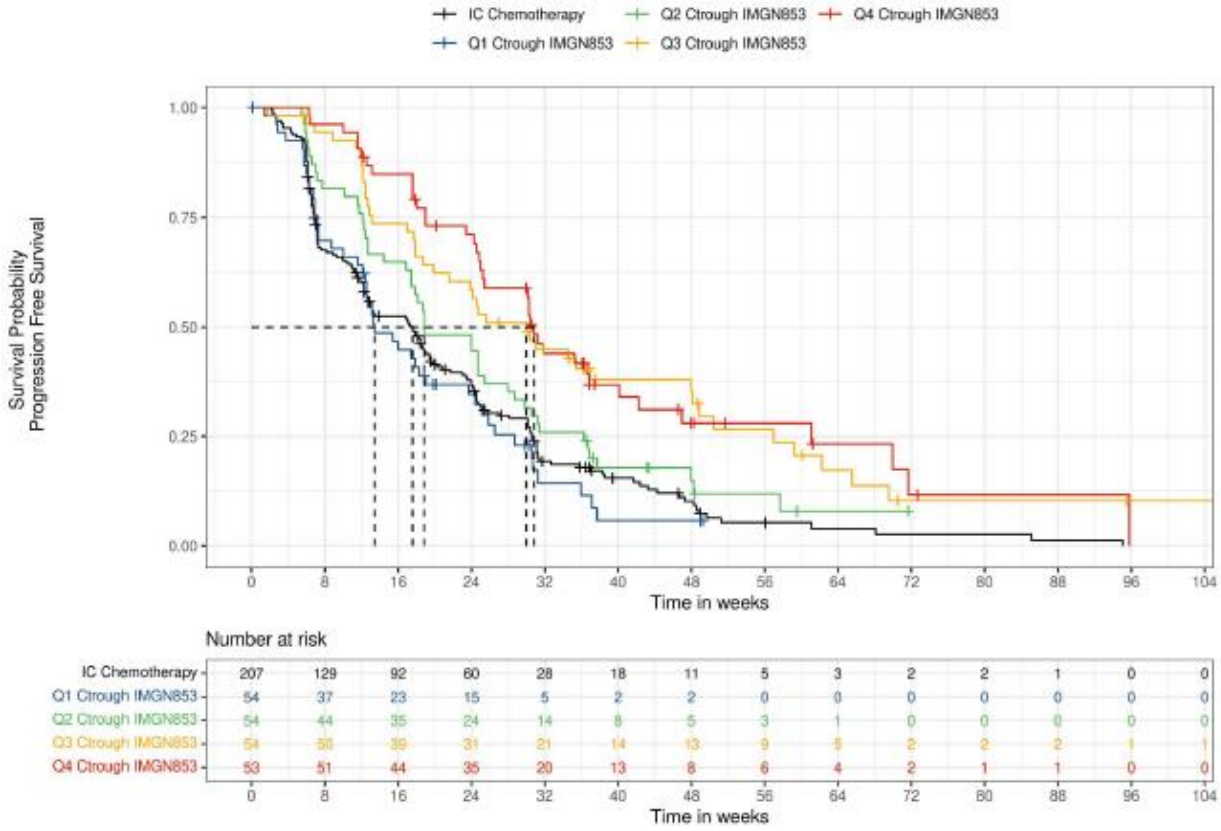


Figure 17: Kaplan-Meier Plot: Overall Survival by MIRV C_{trough} Quartile in Study 0416

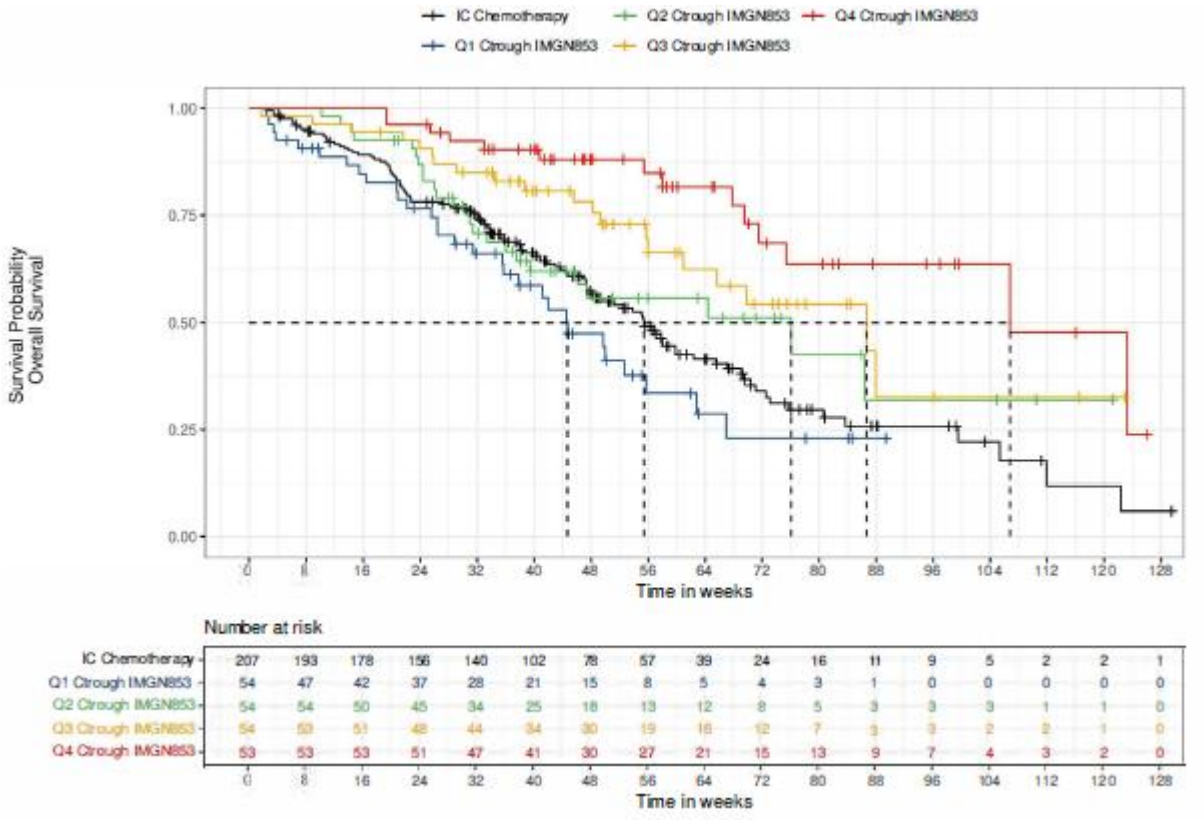
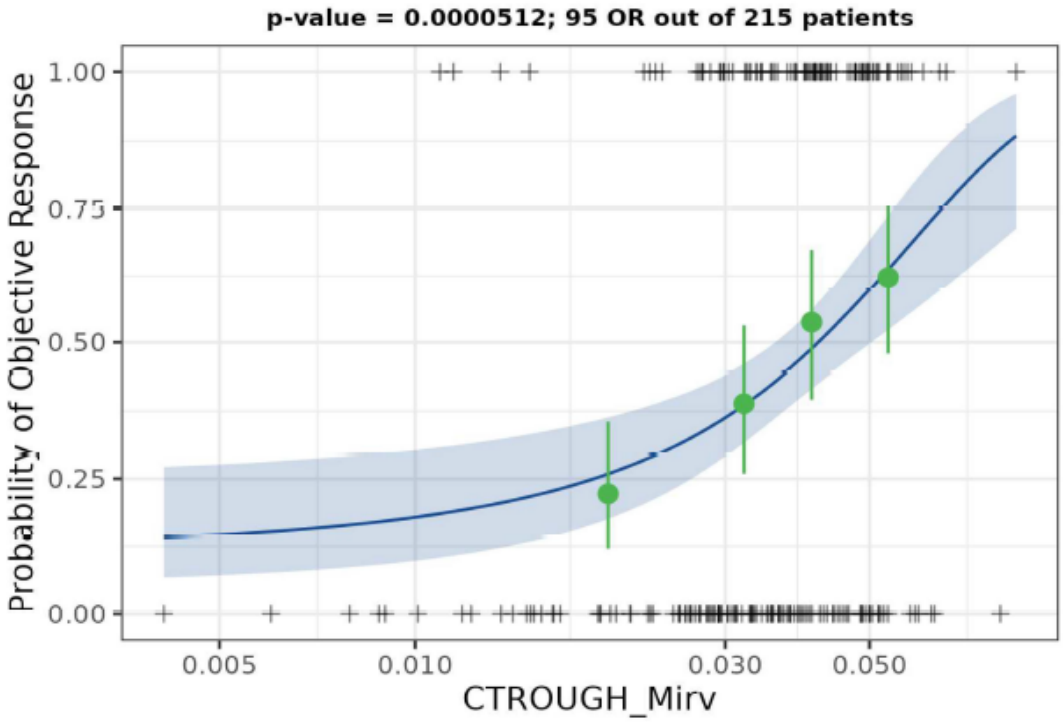


Figure 18: Observed objective response rate in Study 0416 vs. MIRV C_{trough} with model predicted probability overlay.

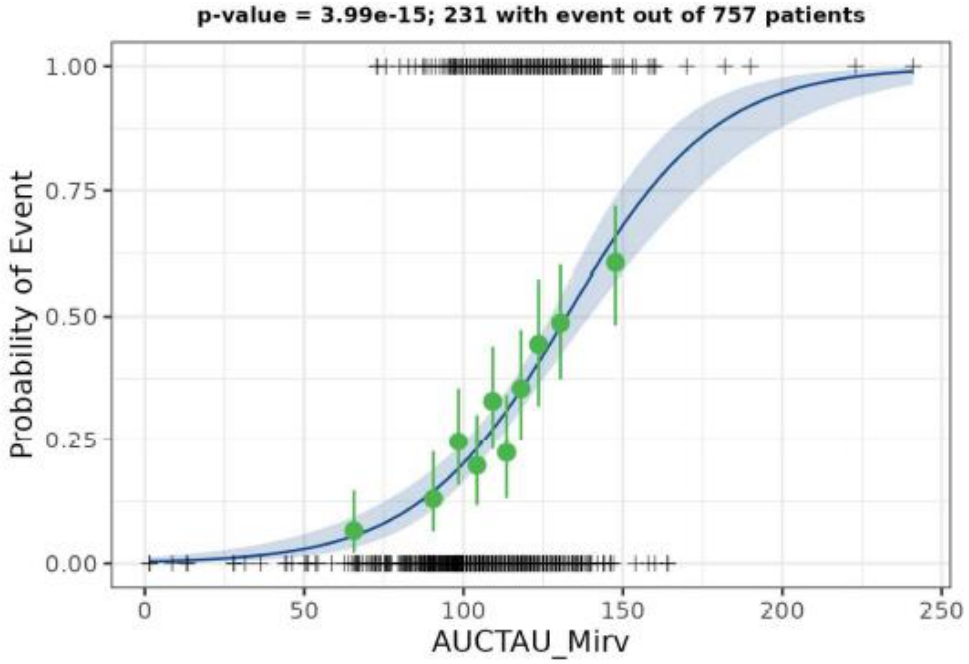


The plot shows the predicted probability (mean + 95% CI) in blue for the variable in the x axis at the median/mode value of any other variables. The green points and range depict the exact binomial estimate of the response for quantiles (4) of the exposure variable. Observed events are indicated by a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

E-R analyses for safety were performed using data pooled from all four clinical studies. The investigated safety endpoints were as follows: 1) Grade ≥2 adverse events (AE) of the ocular system, 2) time to onset of Grade ≥2 ocular AE, 3) Grade ≥2 peripheral neuropathy AE, 4) Grade ≥2 pneumonitis/interstitial lung disease (ILD), 5) any Grade ≥3 treatment emergent adverse event (TEAE), and 6) serious AE (SAE).

A total of 231 of 757 patients reported at least one Grade ≥2 AE of the ocular system. MIRV $AUC_{0\text{-}d21}$, C_{max}, and C_{trough} were the most significant exposure metrics covariates in the logistic regression model; exposure metrics for DM4 and S-methyl-DM4 were less strongly associated with the incidence of Grade ≥2 ocular AE. The model based on MIRV $AUC_{0\text{-}d21}$ had the lowest AIC and was selected as the final model. The regression of Grade ≥2 ocular system AEs against MIRV $AUC_{0\text{-}d21}$ is shown in the figure below. The effects of other statistically significant covariates (sFR-α, tumour burden, AIBW, alanine aminotransferase (ALT), and alkaline phosphatase (ALP)) were minor compared with MIRV $AUC_{0\text{-}d21}$. Similar to the incidence of Grade ≥2 ocular AEs, higher MIRV $AUC_{0\text{-}d21}$ was associated with shorter onset of ocular AEs. No other covariates were found to be significant in this model.

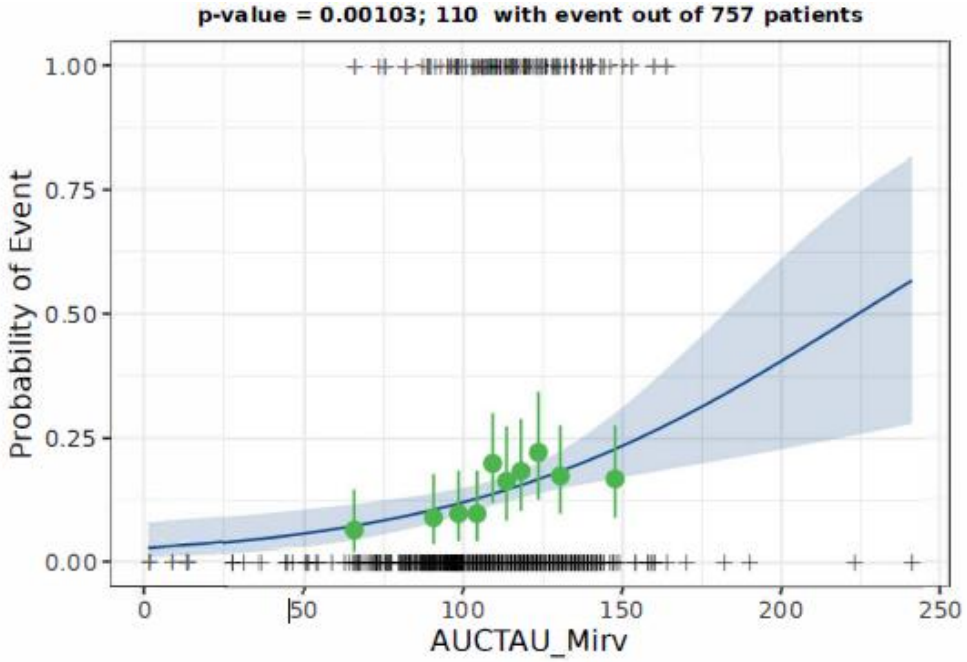
Figure 19: Observed Grade ≥2 ocular system adverse event occurrence vs. MIRV $AUC_{0\text{-}d21}$ with model predicted probability overlay.



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

A total of 110 of 757 patients reported at least one Grade ≥2 peripheral neuropathy AE. The model based on MIRV $AUC_{0\text{-}d21}$ had the lowest AIC and was selected as the final model. The probability of Grade ≥2 peripheral neuropathy AE versus MIRV $AUC_{0\text{-}d21}$ is shown in the figure below. The probability of peripheral neuropathy was also higher in older patients; no additional covariates were identified.

Figure 20: Observed Grade ≥2 peripheral neuropathy occurrence vs. MIRV $AUC_{0\text{-}d21}$ with model predicted probability overlay.



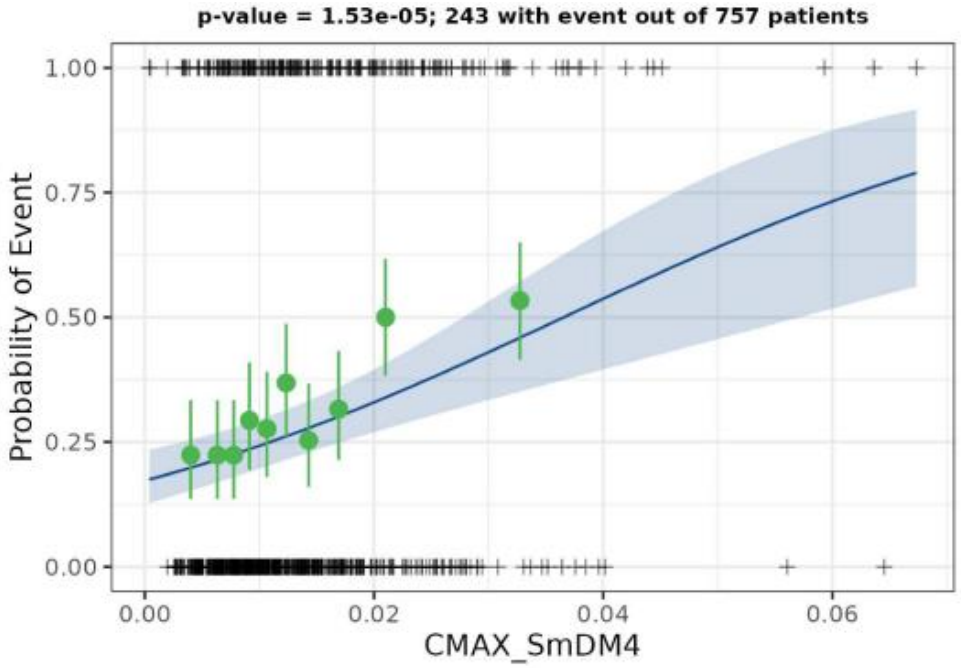
The plot shows the predicted probability (mean + 95% CI) in blue for the variable in the x axis at the median/mode value of any other variables. The green points and range depict the exact binomial estimate of the response for deciles (10) of the exposure variable. Observed events are indicated by a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

A total of 36 of 757 patients reported at least one Grade ≥2 pneumonitis/ILD. No exposure metric or other covariate were found to be associated with incidence of pneumonitis/ILD.

A total of 355 of 757 patients reported at least one Grade ≥3 TEAE. No exposure metric was found to be associated with incidence of Grade ≥3 TEAE. However, lower albumin and higher ECOG score were predictors of Grade ≥3 TEAEs.

A total of 243 of 757 patients reported at least one event of a SAE. Logistic regression analysis indicated that S-methyl-DM4 exposures appeared to be related to incidence of SAEs, with S-methyl-DM4 C_{max} being the best exposure metric. In contrast, MIRV and DM4 exposures were not associated with SAEs. The incidence of SAEs increased with increasing C_{max} of S-methyl-DM4 (see figure below). In addition, the incidence of SAEs increased with decreasing serum albumin, increasing ECOG score, and prior bevacizumab exposure.

Figure 21: Serious adverse events vs. S-methyl-DM4 C_{max} with model predicted probability overlay.



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

Concentration-QTc analysis was conducted using data collected in Dose Escalation and Dose Expansion cohorts in study 0401. A total of 117 patients with evaluable data were used in the concentration-QTc analysis. ECGs were performed in triplicate in Cycles 1 and 3 within one hour prior to the first dose, at the end of MIRV infusion, and 24 ± 2 hours post dose; post dose ECGs were scheduled to coincide with PK sampling. RR and QT intervals were used to obtain corrected QT interval (QTc) by Fridericia's formula and Bazett's formula (QTcF and QTcB, respectively). A linear mixed effects modelling approach was used to quantify the relationship between the observed plasma concentration of MIRV and the change in QTc from baseline (ΔQTc).

The figure below presents the relationship between ΔQTcF vs. MIRV plasma concentrations from paired samples. The table below summarizes the concentration-QTc analysis results and the predicted ΔQTcF at the average C_{max} (146.9 µg/mL). While a significant relationship between MIRV concentration and change in QTcF was observed, the estimated change from baseline at the C_{max} was -0.81 ms for QTcF with the upper bound of the one-sided 95% CI at 1.11 ms. Results for QTcB are not shown for brevity, they were comparable to those for QTcF.

Figure 22: ΔQTcF versus MIRV (IMGN853) concentration

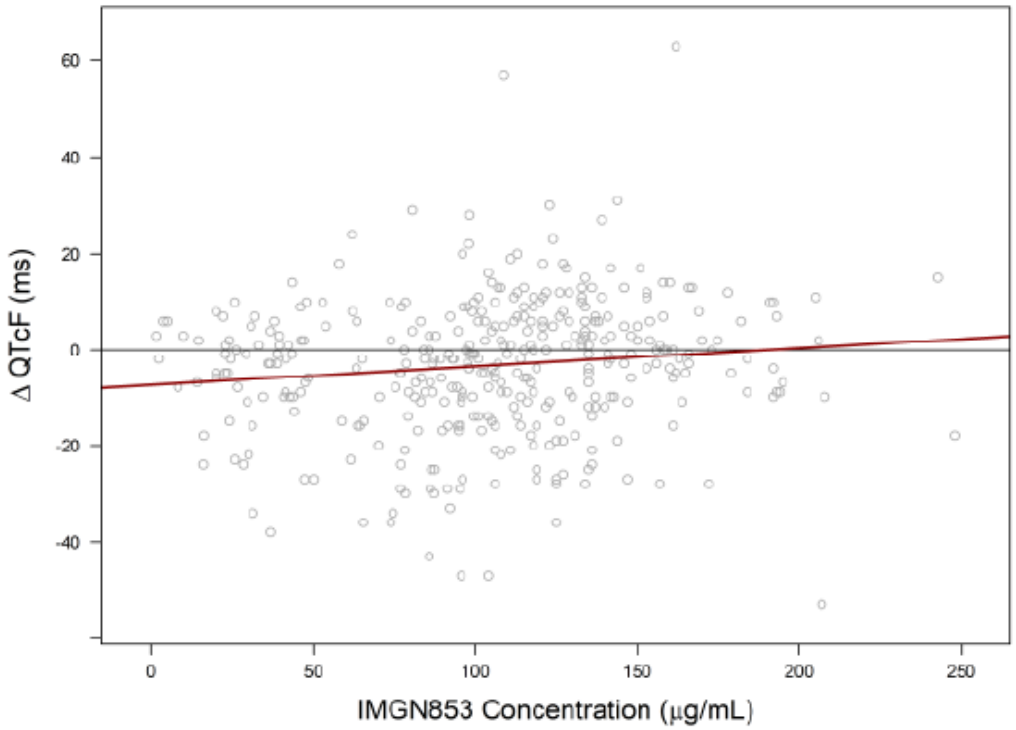


Table 23: ΔQTcF vs. MIRV Concentration: Estimates from Linear Mixed Model

Slope of Plasma Concentration Effect of ΔQTcF	Standard Error of Plasma Concentration Effect on ΔQTcF	p-value Slope of Plasma Concentration Effect on ΔQTcF	Predicted ΔQTcF at Average C_{max} 146.9 µg/mL (ms)	One-sided Upper 95% CI of Predicted ΔQTcF (ms)
0.0572	0.0177	< 0.0001	-0.81	1.11

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

Pharmacokinetics of MIRV, DM4, and S-methyl-DM4 were investigated in patients with cancer, most of whom were women with ovarian cancer. Clinical studies in healthy subjects were not conducted for safety reasons, which is considered acceptable. No dedicated clinical pharmacology studies were conducted which is considered acceptable. Clinical pharmacokinetic (PK) data were collected in four clinical efficacy and safety studies. PK of plasma MIRV, DM4, and S-methyl-DM4 were evaluated using noncompartmental analysis (NCA) in studies 0401 and 0403 and population PK (PPK) analysis; the final PPK dataset included data of all four studies.

Bioanalytical methods were developed for quantitation of the ADC, total antibody, DM4 and its metabolite DM4-Me and soluble folate receptor. In addition, assays were developed for anti-drug antibodies and neutralizing antibodies. All bioanalytical methods were validated according to current guidance. Elahere is administered as an intravenous infusion, hence, bioavailability is 100%. Results of PPK analysis and noncompartmental analyses indicate that MIRV has small volume of distribution, approximately 2.5 to 4 L, suggesting that MIRV is distributed mainly in plasma. *In vitro* human plasma protein binding of DM4 and S-methyl DM4 was >99%.

Mass-balance studies were not conducted in humans, such studies are generally not required for therapeutic proteins. As for the payload component, biliary excretion was the predominant route of elimination following intravenous administration in male Sprague Dawley rats, and in 6 human patients approximately 0.7% of DM4-related material was excreted in urine over 24 hours post-infusion (see section 2.5 Non-clinical aspects for more detailed information). Together these results support the conclusion that renal excretion is a minor elimination pathway of DM4 and its metabolites. Results of *in vitro* studies indicate that DM4 and S-methyl-DM4 are mainly metabolized by CYP3A4, and both are substrates of P-gp.

Dose proportionality was investigated in the dose escalation part of the first-in-human study (study 0401). Exposure to MIRV increased approximately proportionally with dose over the dose range 3.3 to 7 mg/kg total body weight (TBW), which includes the proposed dose 6 mg/kg AIBW. At low doses (0.15 to 0.5 mg/kg TBW), clearance was higher. This was incorporated in the PPK model, which had a Michaelis-Menten elimination in parallel to linear elimination of MIRV. Observed accumulation of MIRV, DM4, and S-methyl-DM4 from Cycle 1 to Cycle 3 was negligible with the dosing regimen 6 mg/kg AIBW Q3W.

Overall incidence of treatment emergent and treatment enhanced anti-drug antibodies (ADA) was modest (<10%). Graphical exploratory analysis indicated no apparent association between ADA status and exposure to MIRV. Because of the low occurrence of ADA, the effect of these antibodies on the PK of MIRV is unknown.

The final PPK model was developed using plasma MIRV, DM4, and S-methyl-DM4 concentration data from all four clinical studies (n=758 patients, 692 (91.3%) of whom were administered 6 mg/kg AIBW Q3W). The model for MIRV was developed first ("ADC model"), subsequently it was expanded to fit a model to the unconjugated DM4 and S-methyl-DM4 concentrations by fixing the MIRV PK parameters to the estimates of the final ADC model. Sequential development of the joint model for the three analytes is acceptable.

The final MIRV (ADC) PPK model was a 2-compartment distribution model with linear and non-linear elimination from the central compartment (V1). The joint model included two compartments (central and target compartment) for DM4 and one (central) compartment for S-methyl-DM4. Formation of unconjugated DM4 was described to happen as 1) deconjugation from the ADC in central compartment, and 2) release from the target compartment. Clearance of DM4 was described to happen by 1) metabolism to S-methyl-DM4 and 2) nonspecific clearance from central compartment. S-methyl-DM4 had one clearance pathway in the model. The following statistically significant covariates were identified (each measured at baseline): AIBW, serum albumin, tumour burden (size) and sFRα level on MIRV CL; AIBW and age on MIRV V1; AIBW and ALT on the formation of S-methyl-DM4 from DM4.

The payload PK model for DM4 and S-methyl-DM4 is structurally unidentifiable, which means that an infinite amount of parameter combinations will be able to characterize the data equally well. The model would not be adequate for supporting claims about the specific PK parameters of DM4 and S-methyl-DM4, and no such claims are presented by the applicant. A pcVPC of DM4 including BLQ observations demonstrated that the model predicted the proportion of BLQ observations adequately. PK in special populations were evaluated using simulations with the PPK model. Exposure to MIRV, DM4, and S-methyl-DM4 was not significantly affected by mild to moderate renal impairment or mild hepatic impairment defined using the NCI-ODWG criteria, no dose adjustment is therefore recommended in these patients. There are insufficient data to evaluate PK and safety in patients with severe renal impairment or end-stage renal disease and the potential need for dose adjustment in these patients cannot be determined. Likewise, there are insufficient data to evaluate PK and safety in patients with moderate to severe hepatic impairment and Elahere should be avoided in these patients. The applicant

plans to conduct a clinical study (IMGN853-0425; Hepatic impairment cohort), a category 3 study in the RMP to evaluate the safety and PK of MIRV, DM4, and S-methyl-DM4 in patients with moderate hepatic impairment (category 3 study in the RMP). Patients up to age 89 years were included in clinical studies. Based on PPK analysis, age (in adults) has negligible effect on exposure to MIRV, DM4, and S-methyl-DM4. No differences in predicted exposure metrics were observed between race/ethnicity categories. AIBW was a statistically significant covariate for parameters MIRV CL and V1 in the PPK model, both of which increased with increasing AIBW. Simulations using the PPK model indicated that with the proposed dose regimen AIBW and actual (total) body weight have limited effect on exposure to MIRV following the proposed posology 6 mg/kg AIBW Q3W. This supports the posology based on AIBW. Simulations suggested that exposure to S-methyl-DM4 increases with increasing AIBW (32.5% higher AUC and 38.9% higher C_{max} of S-methyl-DM4 in a patient at the 95th percentile of AIBW as compared to the reference patient) but observed safety data indicated no need to recommend safety measures based on AIBW or total body weight (see section 2.6.8 Clinical safety).

Baseline albumin, tumour burden (size), and sFRα level were statistically significant covariates on MIRV CL in the PPK model, but they had limited effect on predicted exposure to MIRV with 6 mg/kg AIBW Q3W dosing regimen.

Results of *in vitro* studies using human biomaterials indicate that DM4 and S-methyl-DM4 are not competitive inhibitors of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4. DM4 was a time-dependent inhibitor (TDI) of CYP3A4 and S-methyl DM4 was a weak TDI of CYP2C8 and CYP2C9. However, relevant inhibition is unlikely at DM4 and S-methyl-DM4 concentrations observed with the proposed posology. DM4 and S-methyl-DM4 were not inducers of CYP1A2, CYP2B6, and CYP3A4. DM4 and S-methyl-DM4 are not inhibitors of P-gp and inhibition of other transporter proteins is not expected.

Clinical DDI studies were not conducted which is considered acceptable. Potential effect of strong CYP3A4 inhibitors and inducers on unconjugated DM4 exposure is sufficiently addressed in the product information. The following warning has been included in section 4.5: DM4 is a CYP3A4 substrate. Concomitant use of Elahere with strong CYP3A4 inhibitors may increase unconjugated DM4 exposure (see section 5.2), which may increase the risk of Elahere adverse reactions (see section 4.8). 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 (e.g., phenytoin, rifampicin, carbamazepine) may decrease the exposure of unconjugated DM4.

Whether DM4 and S-methyl-DM4 are substrates of the hepatic uptake transporters OATP1B1 and OATP1B3 *in vitro* and if inhibitors of these transporters might cause clinically relevant drug-drug interactions will be investigated. The applicant will submit the study results once available and update the SmPC as appropriate (sections 4.5 if clinically relevant interactions are expected and 5.2 Transporters systems) **(REC)**

Pharmacodynamics

Mirvetuximab soravtansine is an antibody-drug conjugate. The antibody is an engineered IgG1 directed against folate receptor alpha (FRα). The function of the antibody portion is to bind to FRα expressed on the surface of ovarian 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.

In the exposure-response (E-R) analyses for efficacy and safety, individual exposure parameters following the first dose (C_{max}, C_{trough}, and $AUC_{0\text{-}d21}$ for MIRV, DM4, and S-methyl-DM4) were predicted

using the final PPK model. E-R analyses for efficacy indicated that lower MIRV C_{trough} and $AUC_{0\text{-}d21}$, with some baseline characteristics, were associated with shorter PFS and OS and lower ORR in pivotal study 0416, whereas MIRV C_{max} and DM4 exposure metrics did not show significant association with efficacy endpoints. E-R analyses for safety indicated that higher exposure to MIRV, with some baseline characteristics, was associated with higher probability of Grade ≥2 ocular adverse event (AE) and Grade ≥2 peripheral neuropathy AE as well as the time to the first Grade ≥2 ocular AE; MIRV $AUC_{0\text{-}d21}$ was the best exposure metrics predictor of these safety parameters. In addition, S-methyl-DM4 exposure, especially C_{max}, appeared to be related to incidence of serious AEs (SAEs) whereas MIRV and DM4 exposures were not.

Results of E-R analyses should be interpreted with caution because of the following reasons: A) Only one MIRV dose level (6 mg/kg AIBW Q3W) was used in the pivotal study 0416, and there may be confounding factors that are associated with both increased elimination of MIRV and with lower probability of therapeutic response, B) Predicted exposure metrics following the first 6 mg/kg AIBW dose were used in the analysis. Because a large proportion of patients had dose modification(s) in the studies (infusion interruption or dose reduction/delay/not given), the predicted exposure metrics may not adequately describe patients' exposure to MIRV, DM4, and S-methyl-DM4 during the study. For example, 59.2% of patients in the pivotal study 0416 had dose modification(s), and C) the PPK model for DM4 and S-methyl-DM4 was structurally unidentifiable. Additional E-R analyses with observed DM4 and S-methyl-DM4 exposure parameters were conducted showing overall agreement with those obtained with predicted exposure parameters.

Results of concentration-QTc analysis indicate that the estimated change in QTcF at MIRV C_{max} was -0.81 ms with the upper bound of the one-sided 95% CI at 1.11 ms. Although the CI may be unrealistically narrow because the uncertainty in the intercept parameter was not accounted for, it is agreed that MIRV at the recommended dose has a low likelihood of proarrhythmic effects due to delayed repolarization. The concentration-QTc analyses did not evaluate the potential relationship between concentration of DM4 and S-methyl-DM4 and ΔQTc. This is not pursued for the following reasons: 1) The *in vitro* IC_{50} for the inhibitory effect of both DM4 and S-methyl-DM4 on hERG potassium current was estimated to be greater than 60 μM, markedly higher than their predicted C_{max}, 2) No changes attributed to MIRV in ECG, heart rate, or vital signs were observed in non-clinical studies *in vivo*, and 3) Safety results of the clinical studies do not raise concerns related to cardiac safety of MIRV (see section 2.6.8 Clinical Safety).

The proposed posology 6 mg/kg AIBW Q3W was used for approximately 91% of patients in the dataset, including all patients randomized to MIRV in the pivotal study 0416. Dose finding studies could have been more extensive. Exposure-response analyses cannot determine whether it is the optimal posology, nevertheless the benefit/risk evaluation of the proposed dose regimen can be evaluated based on the observed clinical efficacy and safety data. Results of PK analyses support the proposed AIBW-based posology. Proposed dose modifications are based on observed adverse reactions, which is considered acceptable.

2.6.4. Conclusions on clinical pharmacology

The pharmacokinetics, pharmacodynamic and interaction potential of mirvetuximab soravtansine are considered sufficiently characterised and the relevant information has been included in sections 4.5 and 5.2 of the SmPC.

2.6.5. Clinical efficacy

The development plan includes one pivotal randomised phase 3 study (0416, MIRASOL) and one supportive single arm phase 3 study (0417, SORAYA).. Both studies evaluated MIRV in patients with FRα high, platinum-resistant ovarian cancer. A phase 3 RCT (0403, FORWARD 1) in FRα medium and high, platinum-resistant ovarian cancer and a FIH phase 1 study (0401) provide supportive data.

Table 24: Clinical studies for mirvetuximab soravtansine (MIRV)

Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
IMGN853-0416 (Study 0416, **MIRASOL**)	1st patient enrolled: 03 February 2020 453 patients / 430 patients	Phase 3 Open label 1:1 allocation Chemotherapy by IC	Arm 1: MIRV 6 mg/kg AIBW Q3W IV Arm 2: one of below, determined by investigator prior to randomization, IV: – Pac 80 mg/m² QW within a 4-week cycle – PLD 40 mg/m² Q4W – Topo 4 mg/m² on D 1, 8, and 15 Q4W or 1.25 mg/m² D 1–5 Q3W All until PD, unacceptable toxicity, withdrawal of consent, death, or until the sponsor terminated the study (whichever came 1st)	Inclusion: High-grade serous EOC, primary peritoneal cancer, or fallopian tube cancer Platinum-resistant 1-3 lines prior systemic therapy FRα+ = ⩾ 75% of viable tumor cells with level 2 and/or 3 membrane staining intensity ECOG 0-1 Exclusion: Certain histotypes[a] Primary platinum-refractory[b]
IMGN853-0417 (Study 0417, **SORAYA**)	23 July 2020 106 patients / 110 patients	Phase 3 Single arm	MIRV 6 mg/kg AIBW Q3W IV Until PD, unacceptable toxicity, withdrawal of consent, death, or until the sponsor terminated the study (whichever came 1st)	Inclusion: High-grade serous EOC, primary peritoneal cancer, or fallopian tube cancer Platinum-resistant 1-3 prior systemic lines, including at least 1 containing bevacizumab FRα+ = ⩾ 75% of viable tumor cells with

				level 2 and/or 3 membrane staining intensity ECOG 0-1 Exclusion: Certain histotypes[a] Primary platinum-refractory[b]
IMGN853-0403 (Study 0403, **FORWARD 1**)	02 March 2016 366 patients / 333 patients	Phase 3 Open label 2:1 allocation Chemotherapy by IC	Arm 1: MIRV 6 mg/kg AIBW D1 Q3W IV Arm 2: one of below, determined by investigator prior to randomization, IV: - Pac 80 mg/m² QW within a 4-week cycle - Topo 4 mg/m² on D 1, 8, and 15 Q4W or 1.25 mg/m² D 1–5 Q3W - PLD 40 mg/m² D1 Q4W Until PD, unacceptable toxicity, withdrawal of consent, death, or until the sponsor terminated the study (whichever came 1st)	Inclusion: Advanced EOC, primary peritoneal cancer, fallopian tube cancer Platinum-resistant 1-3 prior systemic lines FRα+ = ⩾ 50% of tumor cells with any FRα membrane staining visible at ⩽ 10X microscope objective ECOG 0-1 Exclusion: Certain histotypes[c] Primary platinum-refractory[d]
IMGN853-0401 (Study **0401**)	28 June 2012 206 patients / 209 patients	FIH Phase 1 dose escalation & dose expansion	Schedule A: MIRV 0.15-7.0 mg/kg (per TBW or AIBW as applicable) Q3W Schedule B: MIRV 1.1-2.5 mg/kg (per AIBW) on D 1, 8, and 15 of each 28-day cycle	Inclusion: Dose escalation[e]: Advanced solid tumor refractory to standard treatment/no standard treatment available/patient refused standard therapy Dose expansion cohort 1: EOC, primary peritoneal cancer, fallopian tube cancer; platinum resistant; max. 5 prior treatment regimens

				cohort 2: advanced or recurrent uterine cancer cohort 3: EOC, primary peritoneal cancer, fallopian tube cancer; progressed following completion of standard therapy, no upper limit for prior therapies cohort 4: NSCLC or bronchoalveolar carcinoma[f] cohort 5: EOC, primary peritoneal cancer, fallopian tube cancer; platinum resistant; at least 3 but no more than 4 prior systemic regimens

AIBW = adjusted ideal body weight, ECOG = Eastern Cooperative Oncology Group Performance Status, EOC = epithelial ovarian cancer, FIH = first in human, FRα = folate receptor alpha, IC = investigator's choice, IV = intravenously, MIRV = mirvetuximab soravtansine, NSCLC = non-small cell lung cancer, pac = paclitaxel, PD = progressive disease, PLD = pegylated liposomal doxorubicin, QW = once weekly, Q3W = every 3 weeks, Q4W = every 4 weeks, TBW = total body weight, topo = topotecan

[a] Endometrioid, clear cell, mucinous, or sarcomatous histology, mixed tumors containing any of these histologies, low-grade or borderline ovarian tumor

[b] Defined as disease that did not respond to (CR or PR) or had progressed within 3 months of the last dose of 1st line platinum-containing chemotherapy

[c] Clear cell, mucinous histology, mixed histology with mucinous component, sarcoma, sarcomatous component, or low-grade ovarian cancer

[d] Progressed during or within 4 weeks of completion of first platinum-based chemotherapy

[e] Enrolment without prior documentation of tumor FRα expression limited to serous or endometrioid epithelial ovarian cancer, primary peritoneal cancer, fallopian tube cancer, endometrial cancer (serous or endometrioid), or NSCLC adenocarcinoma or bronchoalveolar carcinoma. Patients with other tumor types had to have confirmation of ≥ 1% tumor cells with ≥ 1+ FRα positivity by IHC before enrolment

[f] No patients were enrolled in Dose Expansion Cohort 4 because of a company decision to focus on endometrial cancer and EOC for the initial investigation

2.6.5.1. Dose response study

IMGN853-0401 (FIH, study 0401)

Study 0401 was the first-in-human study. MIRV dose was initially escalated as follows: 0.15, 0.5, 1.0, 2.0, 3.3, 5.0, and 7.0 mg/kg total body weight (TBW). At 7 mg/kg TBW, 1 of 5 patients experienced a DLT of Grade 3 punctate keratitis. Accordingly, the dose was reduced to 5.0 mg/kg, which was ultimately received by a total of 11 patients. In this cohort, dose-limiting Grade 3 hypophosphatemia was observed, along with additional ocular AEs during the second dosing cycle. These factors contributed to a further reduction back to 3.3 mg/kg dosing. No further DLTs were observed in this treatment population.

The relationship between ocular TEAEs and pharmacokinetics was explored using preliminary study data. Resulting analyses indicated dose-dependent increases in MIRV C_{max} accompanied with substantial variability between patients, and a positive correlation between MIRV C_{max} and the occurrence of ocular TEAEs.

Dosing by adjusted ideal body weight (AIBW) was implemented via protocol amendment to optimize MIRV exposures while minimizing variability and the potential for ocular TEAEs. Fourteen patients were enrolled and received MIRV at either 5 mg/kg (7 patients) or 6 mg/kg (7 patients) AIBW Q3W. In addition, modified weekly (QW) regimen was implemented via protocol amendment: MIRV was administered on Days 1, 8, and 15 of a 28-days cycle at doses 1.1 (n=5), 1.8 (n=4), 2.0 (n=9), and 2.5 (n=7) mg/kg AIBW.

Evaluation of the TEAEs for these cohorts revealed an increased frequency of ocular TEAE observed between the 5 mg/kg TBW and 7 mg/kg TBW cohorts: Five (45%) of the patients dosed with 5 mg/kg TBW experienced ocular toxicities (vision blurred, vision impairment, and diplopia) and 5 (100%) of the patients in the 7 mg/kg TBW experienced ocular TEAEs (vision blurred, corneal epithelial microcysts, and punctate keratitis). The frequency of TEAEs was lower in the 5 mg/kg and 6 mg/kg AIBW cohorts when compared with the 5 mg/kg and 7 mg/kg TBW cohorts, particularly in the SOCs Gastrointestinal Disorders, Nervous System Disorders, and Eye Disorders.

Following the evaluation of safety and overall response data, IMGN853-0401 study's cohort review committee (CRC) concluded this dose escalation study by identifying 6 mg/kg AIBW Q3W as both the MTD and the RP2D. The CRC also determined that all new patients enrolled in the IMGN853-0401 study (dose expansion cohorts) were to receive mirvetuximab soravtansine at the MTD of 6 mg/kg AIBW once every three weeks. The CRC concluded that the modified weekly regimen did not demonstrate an improvement in the safety profile over the Q3W regimen.

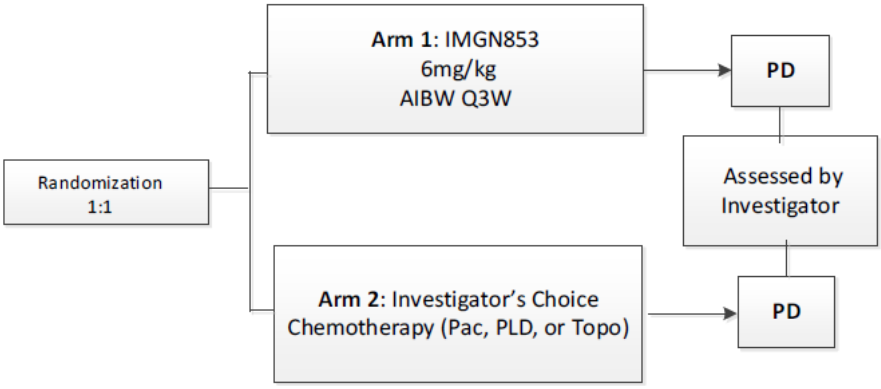
For additional information on study 0401, please also refer to section 2.6.5.6 Supportive studies.

2.6.5.2. Main study

MIRASOL (IMGN853-0416, study 0416)

Title: A Randomized, Open-label, Phase 3 Study of Mirvetuximab Soravtansine vs. Investigator's Choice of Chemotherapy in Platinum-Resistant, Advanced High-Grade Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancers with High Folate Receptor Alpha Expression.

Figure 23: *MIRASOL study schema*



AIBW = adjusted ideal body weight; Pac = paclitaxel; PD = disease progression; PLD = pegylated liposomal doxorubicin; Q3W = every 3 weeks; Q4W = every 4 weeks; Topo= topotecan.

Tumor assessments, including radiological assessments by CT/MRI scans, were performed at screening and subsequently every 6 weeks (± 1 week) from Cycle 1 Day 1 (C1D1) (for all regimens) for the first 36 weeks, and then every 12 weeks (± 3 weeks) until disease progression, death, the initiation of subsequent anticancer therapy, or patient's withdrawal of consent, whichever occurred first.

QoL assessment occurred at the time of tumour assessments approximately every 12 weeks (± 3 weeks) until documentation of PD or the start of new anticancer therapy.

Methods

- **Study Participants**

Key Inclusion Criteria (excerpt)

1. Female patients ≥ 18 years of age

2. Patients must have had a confirmed diagnosis of high-grade serous EOC, primary peritoneal cancer, or fallopian tube cancer

3. Patients must have had platinum-resistant disease

a. Patients who only had 1 line of platinum-based therapy must have received at least 4 cycles of platinum, must have had a response (CR or PR) and then progressed between > 3 months and ≤ 6 months after the date of the last dose of platinum

b. Patients who had received 2 or 3 lines of platinum therapy must have progressed on or within 6 months after the date of the last dose of platinum. Note: Progression was calculated from the date of the last administered dose of platinum therapy to the date of the radiographic imaging showing progression.

4. Patients must have progressed radiographically on or after their most recent line of therapy.

5. Patients must have been willing to provide an archival tumour tissue block or slides, or undergo procedure to obtain a new biopsy using a low risk, medically routine procedure for IHC confirmation of FRα positivity.

6. Patient's tumour must have been positive for FRα expression as defined by the Ventana FOLR1 assay.

7. Patients must have received at least 1 but no more than 3 prior systemic lines of anticancer therapy, and for whom single-agent therapy was appropriate as the next line of treatment:

8. Patient must have had an ECOG PS of 0 or 1.

Companion diagnostic: ≥ 75% of viable tumour cells must have exhibited level 2 and/or 3 membrane staining intensity using the Ventana FOLR1 assay, an IHC assay.

Key Exclusion Criteria (excerpt)

1. Patients with endometrioid, clear cell, mucinous, or sarcomatous histology, mixed tumours containing any of the above histologies, or low-grade or borderline ovarian tumour.

2. Patients with primary platinum-refractory disease, defined as disease that did not respond to (CR or PR) or had progressed within 3 months of the last dose of first-line platinum-containing chemotherapy.

3. Patients with > Grade 1 peripheral neuropathy per CTCAE.

4. Patients with active or chronic corneal disorders, history of corneal transplantation, or active ocular conditions requiring ongoing treatment/monitoring.

5. Patients with serious concurrent illness or clinically relevant active infection.

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

7. Patients with clinically significant cardiac disease.

8. Patients with a history of hemorrhagic or ischemic stroke within 6 months prior to randomization.

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

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

- **Treatments**

Table 25: MIRASOL study drug doses and schedules of administration

Group	Drug	Dose	Dosing Schedule
Arm 1	MIRV	6 mg/kg AIBW IV	Day 1 of a 3-week cycle
Arm 2	Pac	80 mg/m^2 IV	Days 1, 8, 15, and 22 of a 4-week cycle
	PLD	40 mg/m^2 IV	Day 1 of a 4-week cycle
	Topo	4 mg/m^2 IV	Days 1, 8, and 15 of a 4-week cycle
	Topo	1.25 mg/m^2 IV	Days 1 to 5 of a 3-week cycle

Abbreviations: AIBW = adjusted ideal body weight; MIRV = mirvetuximab soravtansine; Pac = paclitaxel; PLD = pegylated liposomal doxorubicin; Topo = topotecan.

Premedication for MIRV:

All patients received 325 to 650 mg of acetaminophen/paracetamol (PO or IV), 10 mg IV dexamethasone, and 25 to 50 mg diphenhydramine (IV or PO) (equivalent drugs of similar drug classes were also acceptable) approximately 30 minutes before each infusion. If individual patients required more intensive treatment to prevent infusion-related reaction (IRRs), investigators may have

modified the regimen accordingly. An antiemetic medication (e.g. 5-HT3 serotonin receptor antagonists such as palonosetron, granisetron, or ondansetron or appropriate alternatives) was recommended before each MIRV dose and may have been used any time at the discretion of the treating physician.

Prophylactic Use of Corticosteroid Eye Drops:

All patients who were randomized to MIRV were required to use corticosteroid eye drops as prescribed by the treating physician unless the risk outweighed the benefit as per the ophthalmologist/physician. All patients were instructed to self-administer 1% prednisolone (Pred Forte or generic equivalent) 6 times daily on Days -1 to 4 and 4 times daily on Days 5 to 8 of each cycle during the study. For individual patients who could not tolerate the preservative contained in 1% prednisolone, other corticosteroid eye drops could be substituted (e.g. difluprednate 0.05%; Durezol) and administered on Days -1 to 8 of each cycle at a frequency prescribed by the ophthalmologist. Given the lack of availability in some regions, if prednisolone eye drops could not be obtained, alternate steroid eye drops were acceptable.

Lubricating Artificial Tears:

All patients who were randomized to MIRV were required to use lubricating artificial tears on a daily basis (as directed by the product label or the treating physician). Preservative-free lubricating drops were recommended.

Duration of treatment:

Patients continued to receive study drug until disease progression, unacceptable toxicity, withdrawal of consent, death, or until the sponsor terminated the study (whichever came first).

Dose reduction and dose modification:

Table 26: Dose reduction schedule used in MIRASOL

	ELAHERE dose levels
Starting dose	6 mg/kg AIBW
First dose reduction	5 mg/kg AIBW
Second dose reduction	4 mg/kg AIBW*

* Permanently discontinue in patients who cannot tolerate 4 mg/kg AIBW.

Table 27: Dose modification for adverse reactions

Adverse reaction	Severity of adverse reaction*	Dosage modification
Keratitis/keratopathy (see sections 4.4 and 4.8)	Nonconfluent superficial keratitis/keratopathy	Monitor
	Confluent superficial keratitis/keratopathy, a cornea epithelial defect, or 3-line or more loss in best corrected visual acuity	Withhold dose until improved or resolved, then maintain at same dose level or consider dose reduction.
	Corneal ulcer or stromal opacity or best corrected distance visual acuity 6/60 or worse	Withhold dose until improved or resolved, then reduce by one dose level.
	Corneal perforation	Permanently discontinue
Pneumonitis (see sections 4.4 and 4.8)	Grade 1	Monitor
	Grade 2	Withhold dose until Grade 1 or less, then maintain at same dose level or consider dose reduction.
	Grade 3 or 4	Permanently discontinue
Peripheral neuropathy (see sections 4.4 and 4.8)	Grade 2	Withhold dose until Grade 1 or less, then reduce by one dose level.
	Grade 3 or 4	Permanently discontinue
Infusion-related reactions/hypersensitivity (see sections 4.4 and 4.8)	Grade 1	Maintain infusion rate
	Grade 2	• Interrupt infusion and administer supportive treatment. • After recovery from symptoms, resume the infusion at 50% of the previous rate, and if no further symptoms appear, increase rate as appropriate until infusion is completed. • Administer additional pre-medication for future cycles.
	Grade 3 or 4	• Immediately stop infusion and administer supportive treatment. • Advise patient to seek emergency treatment and immediately notify their healthcare professional if the infusion-related symptoms recur. • Permanently discontinue
Hematological (see section 4.8)	Grade 3 or 4	Withhold dose until Grade 1 or less, then resume at one lower dose level.
Other adverse reactions (see section 4.8)	Grade 3	Withhold dose until Grade 1 or less, then resume at one lower dose level.
	Grade 4	Permanently discontinue

*: Unless otherwise specified, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.

- **Objectives/endpoints**

Primary :

- The primary objective is to compare PFS of patients randomized to mirvetuximab soravtansine versus Investigator's Choice chemotherapy, as assessed by the investigator using RECIST 1.1 criteria, in patients with high Folate Receptor-α level (≥ 75% of tumour staining at ≥ 2+ intensity). PFS is defined as the time from date of randomization until Investigator-assessed progressive disease (PD) or death, whichever occurs first (PFS_{INV}).

Key secondary:

- To compare ORR of patients randomized to MIRV versus IC Chemo, as assessed by the investigator.
- To compare OS of patients randomized to MIRV versus IC Chemo.
- To compare the primary patient-reported outcome (PRO) using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-OV28 (Abdominal/GI Symptom Scale) assessment from patients randomized to MIRV versus IC Chemo.

Other secondary:

- To compare the safety and tolerability of MIRV vs. IC Chemo.
- To compare the duration of response (DOR) in patients randomized to MIRV versus IC Chemo.
- To compare CA-125 response rate (RR) per Gynecologic Cancer Intergroup (GCIG) CA-125 criteria in patients randomized to MIRV versus IC Chemo.
- To compare the time to progression or death on the next line of treatment (PFS2) in patients randomized to MIRV versus IC Chemo.

Exploratory:

- To assess patient-reported outcomes (PRO) using the EORTC QLQ-C30, EuroQol-5 Dimension 5-level (EQ-5D-5L) and Patient Global Impression of Severity (PGIS) questionnaires
    - This exploratory analysis and subsequent results will be reported in separate documents and has not been included in the CSR.
- To evaluate concentrations of MIRV, total antibody (TAb), DM4 and S-methyl DM4, using sparse sampling.
- To assess the immunogenicity of MIRV via anti-drug antibodies (ADAs).
- To evaluate potential biomarkers in blood and tumor tissue predictive of response to MIRV.

- **Sample size**

The primary endpoint of this study was PFS_{INV}. The study was designed to test the null hypothesis that the survival function for PFS was the same between the MIRV arm and the IC Chemo arm versus the alternative hypothesis that the survival function for PFS was different between the MIRV and IC Chemo groups. The study had 90% power to detect a hazard ratio (HR) of 0.7.

Sample size and power were determined with the following assumptions:

- Median PFS for the IC Chemo arm was 3.5 months.
- Median PFS for the MIRV arm was 5.0 months.
- Overall attrition rate for PFS event was approximately 13% in both groups.
- Median OS for the IC Chemo arm was 12 months.
- Median OS for the MIRV arm was 17.5 months.

- **Randomisation and Blinding (masking)**

Eligible patients were randomly assigned **1:1** to MIRV 6 mg/kg AIBW Q3W (Arm 1) or IC Chemo (Arm 2; Pac, PLD, or Topo).

Patients were **stratified** by:

- Number of prior lines of therapy (1 vs 2 vs 3)
- IC Chemo (Pac vs PLD vs Topo) chosen prior to randomization.

The study was open-label.

- **Statistical methods**

Efficacy endpoints and analyses:

The primary endpoint for study 0416 was PFS_{INV}, estimated using the Kaplan-Meier method, with comparison between treatment groups conducted using Cox proportional hazard regression and log rank test. The study was designed to test the null hypothesis that the survival function for PFS was the same between the MIRV arm and the IC Chemo arm versus the alternative hypothesis that the survival function of PFS was different between MIRV and IC Chemo arms.

Only if the primary endpoint of PFS was statistically significant, a hierarchical testing procedure was used to control the study-wise error rate (SWER) for key secondary endpoints of ORR, OS, and the primary PRO, in that order. There was one interim analysis for OS at the time of the final analysis of PFS. A Lan-DeMets alpha spending function using an O'Brien-Fleming stopping boundary was used to control the overall Type I error at 2-sided alpha level of 0.05. The exact boundary of 0.01313 at the interim OS analysis was determined based on the actual number of death events. Following this hierarchical testing procedure, at the final analysis for PFS, given that the prespecified early stopping boundary at the interim analysis was reached, no additional hypothesis testing on OS was conducted.

Table 28: *PFS definitions in MIRASOL*

Situation	Date of PFS Event or Censoring	Outcome
No baseline tumor assessments or postbaseline radiological assessments, and patient did not die within 105 days of randomization	Date of randomization	Censored
No baseline tumor assessments or postbaseline radiological assessments, and patient died within 105 days of randomization	Date of death	Death
Death	Date of death	Death
Radiological progression	Date of first radiological assessment indicating progression (ie, OR = PD).	Progression
New anticancer therapy prior to PD or death (including palliative radiotherapy during study treatment)	Date of last radiological assessment prior to the start of the new anticancer therapy	Censored
No death or PD	Date of last radiological assessment	Censored
PD or death after missing 2 or more consecutive radiological assessments (PD or death date - last radiological assessment date + 1 $\geq$ 105 days if duration of treatment is less than 36 weeks, otherwise, PD or death date - last radiological assessment date + 1 $\geq$ 231 days)	Date of last adequate radiological assessment showing no PD	Censored

Abbreviations: OR = overall response; PD = disease progression; PFS = progression-free survival.
Note: Includes radiographic progression only; PFS_{INV} is based on the investigator's assessment; PFS_{BICR} is based on BICR assessment.

Population for the primary analysis = ITT population is defined as all patients randomized to the study, regardless of whether or not patients received study treatment (MIRV or IC Chemo). Patients will be analysed based on the randomized treatment.

The Response-Evaluable population is defined as all patients randomized to the study who have received at least 1 dose of MIRV or IC Chemo and have measurable disease at baseline per investigator or BICR.

All randomized patients who received at least 1 dose of MIRV or IC Chemo will be included in the **Safety population.**

Adjustment for multiplicity

For the 3 key secondary endpoints, a hierarchical testing procedure was applied to control the study-wise Type I error only if the null hypothesis for the primary endpoint was rejected at 2-sided α-level of 0.05. The order of the hierarchical testing is as follows:

- ORR_{INV}.
- OS.
- Primary endpoint for quality of life (QoLP): number of patients achieving at least a 15% (or equivalently, 15-point) improvement on the QLQ-OV28 abdominal/gastrointestinal symptom subscale [Items 31-36] at the Week 8/9 assessment.

Interim analyses

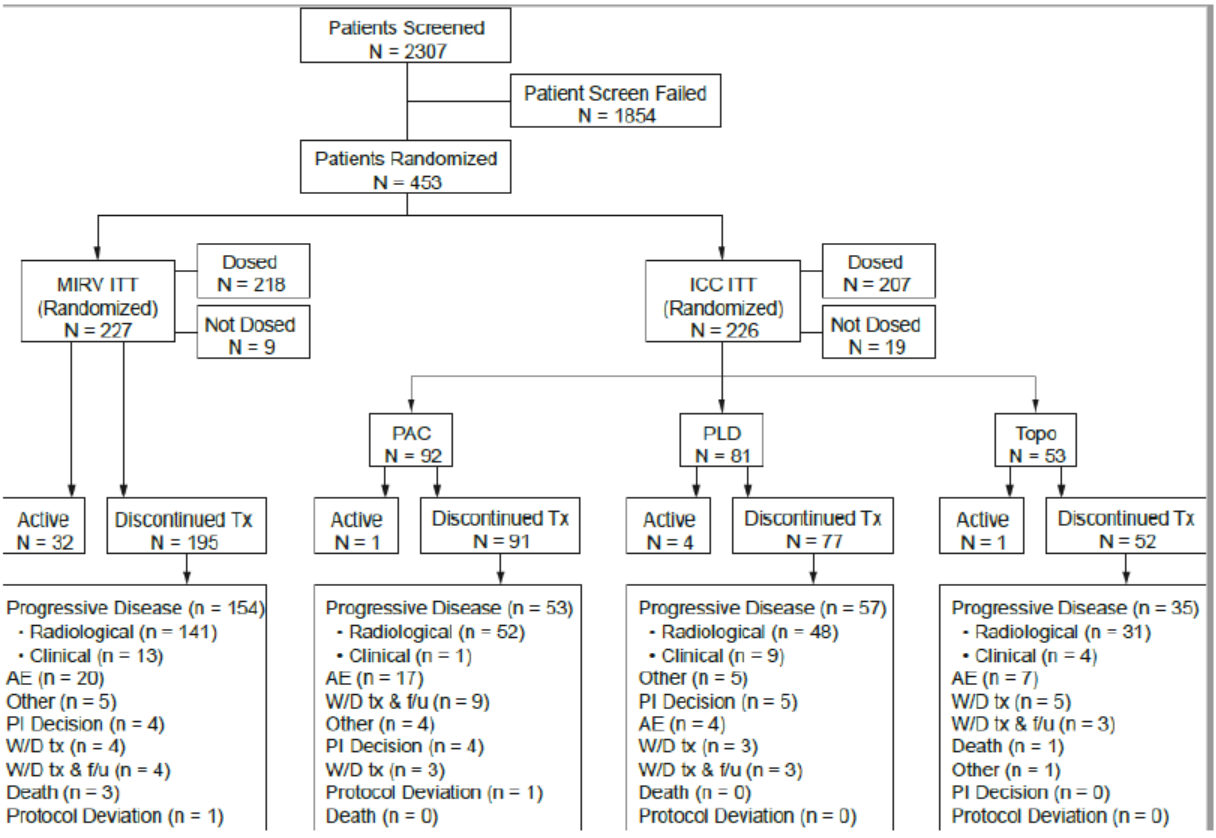
For the **primary endpoint of PFS_{INV}**, the final analysis was conducted when at least 330 events have been observed. An interim futility analysis was designed to be conducted when at least 110 events have been observed. The study would have been terminated for futility at interim analysis if the observed hazard ratio [MIRV to IC chemotherapy] was greater than 1. No alpha spending was planned for this futility analysis. This interim futility analysis (IA1) was conducted with 131 PFS events (data cut 31 January 2022). Independent Data Monitoring Committee (IDMC) reviewed PFS results, confirmed the futility boundary was not hit and recommended the trial to continue without modifications.

For the **key secondary endpoint of OS**, there was one interim analysis for OS at the time of final analysis of PFS at which time approximately 180 (60%) deaths will have been observed. A Lan-DeMets alpha-spending function using an O'Brien-Fleming stopping boundary was used to control overall Type I error for OS at 2-sided alpha level of 0.05. The exact boundary at the interim OS analysis was determined based on the actual number of death events.

Results

- **Participant flow**

Figure 24: Participant flow in MIRASOL



Abbreviations: f/u = follow-up; n = number; tx = treatment; W/D = withdrawal.

Within screen failures (n=1854), the most common reason was FR alpha expression <75% (n=1569, 85%). Of 285 patients with FR alpha expression ≥75%, 170 did not meet other enrolment criteria.

Table 29: Patient disposition in ITT population of MIRASOL

Number of Patients	MIRV (N=227)	IC Chemotherapy			
		Total (N=226)	Pac (N=92)	PLD (N=81)	Topo (N=53)
Randomized (ITT Population) [a]	227 (100)	226 (100)	92 (100)	81 (100)	53 (100)
Randomized but Not Treated	9 (4)	19 (8)	10 (11)	5 (6)	4 (8)
Treated (Safety Population) [b]	218 (96)	207 (92)	82 (89)	76 (94)	49 (92)
Still on Treatment	32 (14)	6 (3)	1 (1)	4 (5)	1 (2)
Discontinued from Treatment	195 (86)	220 (97)	91 (99)	77 (95)	52 (98)
Primary Reason for Treatment Discontinuation					
Adverse Event	20 (9)	28 (12)	17 (18)	4 (5)	7 (13)
Death	3 (1)	1 (< 1)	0	0	1 (2)
PI Discretion	4 (2)	9 (4)	4 (4)	5 (6)	0
Patient Withdrew Consent to Treatment [c]	4 (2)	11 (5)	3 (3)	3 (4)	5 (9)
Patient Withdrew Consent to Treatment and Follow-Up	4 (2)	15 (7)	9 (10)	3 (4)	3 (6)
Progressive Disease	154 (68)	145 (64)	53 (58)	57 (70)	35 (66)
Radiological	141 (62)	131 (58)	52 (57)	48 (59)	31 (58)
Clinical	13 (6)	14 (6)	1 (1)	9 (11)	4 (8)
Protocol Deviation	1 (< 1)	1 (< 1)	1 (1)	0	0
Other	5 (2)	10 (4)	4 (4)	5 (6)	1 (2)
Permanently Discontinued From Study	108 (48)	144 (64)	57 (62)	50 (62)	37 (70)
Primary Reason for Study Discontinuation					
Death	89 (39)	114 (50)	42 (46)	40 (49)	32 (60)
PI Discretion	1 (< 1)	1 (< 1)	1 (1)	0	0
Lost to Follow-up	3 (1)	2 (< 1)	0	2 (2)	0
Withdrew Consent	9 (4)	23 (10)	14 (15)	5 (6)	4 (8)
Other	6 (3)	4 (2)	0	3 (4)	1 (2)

Abbreviations: IC = investigator's choice; ITT = intent-to-treat; MIRV = mirvetuximab soravtansine; Pac = paclitaxel; PI = principal investigator; PLD = pegylated liposomal doxorubicin; TEAE = treatment-emergent adverse event; Topo = topotecan.

[a] The ITT population is defined as all patients randomized to the study, regardless of whether or not patients received study treatment (MIRV or IC Chemo).

[b] The Safety population is defined as all patients in ITT who received at least 1 dose of MIRV or IC Chemotherapy.

[c] Patients who withdrew consent to treatment were continued to be followed.

- **Recruitment**

Planned: approximately 430 patients

Enrolled: 453 patients

1st patient enrolled: 03 February 2020

Date of last patient randomised: 03 August 2022

Date last patient completed: ongoing

Data cut-off for interim futility analysis: 31 January 2022

Data cut-off for primary analysis: 06 March 2023

Date of CSR: 11 September 2023

For PFS_{INV}, the median follow-up is 11.2 months. For OS, the median follow-up time is 13.1 months.

The study had 201 centers globally located in North America, Middle East, Africa, Europe and Asia-Pacific, 136 of which enrolled patients.

Number of patients randomised by countries: Canada 17, USA 126, Belgium 19, Bulgaria 1, Czechia 1, France 75, Germany 2, Italy 45, Netherlands 9, Poland 13, Portugal 3, Russia 14, Serbia 3, Spain 35, UK, 30, Australia 7, China 17, South Korea 26, Taiwan 1, Israel 9.

- **Conduct of the study**

Protocol amendments (only global amendments with excerpts)

Original protocol 10 October 2019

Global amendment #1 09 December 2019

The main elements of the protocol amendment #1 were:

- To ensure patient safety, added MIRV retreatment criterion requiring that any treatment-emergent pneumonitis must have recovered to ⩽ Grade 1 prior to patients receiving any additional doses. Pneumonitis has been observed with MIRV treatment, and this criterion is consistent with other clinical studies with MIRV.
- Added recommendation that patients who have discontinued study drug for reasons other than progressive disease prior to Week 36 (from C1D1) and who have not received another anticancer therapy, be scanned every 6 weeks up to Week 36. This update is consistent with the frequency of disease assessments for all patients on treatment.
- Minor changes made to improve readability and for editorial consistency.

Amendment #1.1. on 06 April 2020 was specific for Belgium, Czech Republic, France, Germany, Italy, Poland, Portugal, Spain, United Kingdom.

Amendment #2 Dated 04 December 2020

Key changes:

- Updates to patient inclusion and exclusion criteria.
- Clarification of pre-screening ICF.
- CT/MRI windows added to allow flexibility around the performance of these scans and for internal

  document consistency.
- Added recommendations for pregnancy testing following the last doses of MIRV and chemotherapy.
- Description of acceptable methods of contraception revised for accuracy and consistency with CTFG Guidelines.
- Details pertaining to FRα evaluation in tumor tissue added.
- Updated description of the end of study and continued access to patients receiving clinical benefit.
- Recording of AEs/SAEs and retention of data updated.

Amendment #2.1 dated 07 June 2021 was China-specific.

Protocol compliance and deviations

Protocol deviations in the study did not impact the safety of the patients, patient rights, or the integrity of the study results.

The Per-Protocol population was defined as all patients randomized to the study who received at least 1 dose of the study drug, excluding patients with critical/major protocol deviations that were deemed to affect primary and/or key secondary objectives. The Per-Protocol population excluded 32 patients, of whom 27 were not dosed and 5 had major eligibility deviations, i.e.:

- Patient 310-002 had FRα <75% and was not dosed
- Patient 013-035 had platinum-sensitive recurrent ovarian cancer
- Patient 492-018 had primary platinum-refractory disease
- Patient 875-001 had endometrioid ovarian tumor (excluded histology)
- Patient 126-001 had primary platinum-refractory disease

- **Baseline data**

Table 30: Demographic and baseline characteristics in MIRASOL – ITT Population

	MIRV (N=227)	IC Chemotherapy				Overall (N=453)
		Total (N=226)	Pac (N=92)	PLD (N=81)	Topo (N=53)	
Age (years)						
n	227	226	92	81	53	453
Mean (SD)	63.3 (9.85)	62.3 (9.30)	62.1 (9.26)	62.6 (9.01)	62.1 (9.95)	62.8 (9.58)
Median	64.0	62.0	62.0	62.0	64.0	63.0
Min, Max	32, 88	29, 87	36, 87	40, 81	29, 83	29, 88
Age Group, n (%)						
18-64	120 (53)	134 (59)	59 (64)	46 (57)	29 (55)	254 (56)
≥ 65	107 (47)	92 (41)	33 (36)	35 (43)	24 (45)	199 (44)
65-74	79 (35)	77 (34)	27 (29)	29 (36)	21 (40)	156 (34)
75-84	27 (12)	14 (6)	5 (5)	6 (7)	3 (6)	41 (9)
≥ 85	1 (< 1)	1 (< 1)	1 (1)	0	0	2 (< 1)
18-69	160 (70)	170 (75)	72 (78)	57 (70)	41 (77)	330 (73)
≥ 70	67 (30)	56 (25)	20 (22)	24 (30)	12 (23)	123 (27)
Female, n (%)	227 (100)	226 (100)	92 (100)	81 (100)	53 (100)	453 (100)
Childbearing Potential	3 (1)	8 (4)	5 (5)	2 (2)	1 (2)	11 (2)
Ethnicity, n (%)						
Hispanic or Latino	12 (5)	15 (7)	6 (7)	5 (6)	4 (8)	27 (6)
Not Hispanic or Latino	177 (78)	163 (72)	64 (70)	60 (74)	39 (74)	340 (75)
Unknown	2 (< 1)	2 (< 1)	2 (2)	0	0	4 (< 1)
Not Reported	35 (15)	45 (20)	19 (21)	16 (20)	10 (19)	80 (18)
Missing	1 (< 1)	1 (< 1)	1 (1)	0	0	2 (< 1)
Race, n (%)						
White	156 (69)	145 (64)	56 (61)	55 (68)	34 (64)	301 (66)
Black or African American	8 (4)	5 (2)	2 (2)	0	3 (6)	13 (3)
Asian	28 (12)	25 (11)	10 (11)	9 (11)	6 (11)	53 (12)
Not Reported	32 (14)	49 (22)	22 (24)	17 (21)	10 (19)	81 (18)
Other	3 (1)	2 (< 1)	2 (2)	0	0	5 (1)
Region, n (%)						
APAC [a]	25 (11)	26 (12)	9 (10)	10 (12)	7 (13)	51 (11)

	MIRV (N=227)	IC Chemotherapy				Overall (N=453)
		Total (N=226)	Pac (N=92)	PLD (N=81)	Topo (N=53)	
Europe [b]	127 (56)	123 (54)	59 (64)	39 (48)	25 (47)	250 (55)
Middle East [c]	1 (< 1)	8 (4)	3 (3)	5 (6)	0	9 (2)
North America [d]	74 (33)	69 (31)	21 (23)	27 (33)	21 (40)	143 (32)
Baseline Weight (kg)						
n	213	198	80	71	47	411
Mean (SD)	68.47 (15.329)	69.24 (15.731)	68.97 (16.471)	70.31 (14.650)	68.11 (16.248)	68.84 (15.510)
Median	65.00	66.60	66.00	68.10	65.30	66.00
Min, Max	39.0, 122.7	39.1, 130.4	40.9, 115.0	50.0, 114.8	39.1, 130.4	39.0, 130.4
Baseline AIBW (kg)						
n	218	–	–	–	–	218
Mean (SD)	59.054 (8.2831)	–	–	–	–	59.054 (8.2831)
Median	58.300	–	–	–	–	58.300
Min, Max	39.10, 84.80	–	–	–	–	39.10, 84.80

Abbreviations: AIBW = adjusted ideal body weight; APAC = Asia Pacific; IC = investigator's choice; MIRV = mirvetuximab soravtansine; Pac = paclitaxel; PLD = pegylated liposomal doxorubicin; SD = standard deviation; Topo = topotecan.

[a] Includes Australia, China, South Korea, and Taiwan.

[b] Includes Belgium, Bulgaria, Czechia, Germany, Spain, France, Great Britain, Italy, Netherlands, Poland, Portugal, Russia, and Serbia.

[c] Includes Israel.

[d] Includes the United States of America and Canada.

Note: Rows with data values of "0" were removed for improved readability.

Table 31: Disease characteristics, prior therapy, and gene mutations in MIRASOL – ITT population

	MIRV (N=227)	IC Chemotherapy				Overall (N=453)
		Total (N=226)	Pac (N=92)	PLD (N=81)	Topo (N=53)	
Primary Diagnosis, n (%)						
Epithelial Ovarian	182 (80)	182 (81)	76 (83)	65 (80)	41 (77)	364 (80)
Fallopian Tube	27 (12)	23 (10)	9 (10)	9 (11)	5 (9)	50 (11)
Primary Peritoneal	16 (7)	20 (9)	7 (8)	6 (7)	7 (13)	36 (8)
Other	2 (< 1) [a]	1 (< 1) [b]	0	1 (1)	0	3 (< 1)
Any *BRCA* Mutations, n (%)						
Positive	29 (13)	36 (16)	16 (17)	14 (17)	6 (11)	65 (14)
BRCA1	24 (11)	29 (13)	14 (15)	10 (12)	5 (9)	53 (12)
BRCA2	9 (4)	7 (3)	2 (2)	4 (5)	1 (2)	16 (4)
Negative/Unknown	198 (87)	190 (84)	76 (83)	67 (83)	47 (89)	388 (86)
Time Since Initial Diagnosis to Randomization Date (months) [c]						
n	208	208	81	78	49	416
Mean (SD)	33.36 (20.130)	34.93 (22.322)	38.14 (20.504)	28.98 (21.653)	39.12 (24.559)	34.15 (21.243)
Median	28.52	29.19	32.49	23.90	33.25	28.83
Min, Max	9.1, 164.2	8.7, 131.4	9.5, 100.7	8.8, 127.7	8.7, 131.4	8.7, 164.2
Number of Prior Lines of Therapy, n (%)						

	MIRV (N=227)	IC Chemotherapy				Overall (N=453)
		Total (N=226)	Pac (N=92)	PLD (N=81)	Topo (N=53)	
1	29 (13)	34 (15)	4 (4)	26 (32)	4 (8)	63 (14)
2	90 (40)	88 (39)	42 (46)	31 (38)	15 (28)	178 (39)
3	108 (48)	104 (46)	46 (50)	24 (30)	34 (64)	212 (47)
Prior Exposure to PARP Inhibitors, n (%)						
Yes	124 (55)	127 (56)	53 (58)	44 (54)	30 (57)	251 (55)
No	97 (43)	94 (42)	36 (39)	35 (43)	23 (43)	191 (42)
Uncertain [d]	6 (3)	5 (2)	3 (3)	2 (2)	0	11 (2)
Prior Exposure to Taxanes, n (%)						
Yes	227 (100)	224 (99)	92 (100)	81 (100)	51 (96)	451 (100)
No	0	2 (< 1)	0	0	2 (4)	2 (< 1)
Prior Exposure to Doxorubicin/PLD, n (%)						
Yes	130 (57)	133 (59)	80 (87)	7 (9)	46 (87)	263 (58)
No	97 (43)	93 (41)	12 (13)	74 (91)	7 (13)	190 (42)
Prior Exposure to Topo, n (%)						
Yes	1 (< 1)	2 (< 1)	1 (1)	1 (1)	0	3 (< 1)
No	226 (100)	224 (99)	91 (99)	80 (99)	53 (100)	450 (99)
Primary Platinum-Free Interval [e], n (%)						
≤ 12 months	146 (64)	142 (63)	52 (57)	57 (70)	33 (62)	288 (64)
> 12 months	80 (35)	84 (37)	40 (43)	24 (30)	20 (38)	164 (36)
Missing	1 (< 1)	0	0	0	0	1 (< 1)
Platinum-Free Interval [f], n (%)						
≤ 3 months	88 (39)	99 (44)	46 (50)	29 (36)	24 (45)	187 (41)
> 3 to ≤ 6 months	138 (61)	124 (55)	45 (49)	52 (64)	27 (51)	262 (58)
> 6 months	1 (< 1)	3 (1)	1 (1)	0	2 (4)	4 (< 1)
ECOG Performance Status, n (%)						
0	130 (57)	120 (53)	50 (54)	48 (59)	22 (42)	250 (55)
1	97 (43)	101 (45)	39 (42)	33 (41)	29 (55)	198 (44)
2	0	3 (1) [g]	2 (2)	0	1 (2)	3 (< 1)
Missing	0	2 (< 1) [h]	1 (1)	0	1 (2)	2 (< 1)
FRα PS2 score (%)						
n	227	226	92	81	53	453
Mean (SD)	85.6 (8.97)	86.2 (8.54)	85.4 (8.62)	86.1 (8.43)	87.7 (8.54)	85.9 (8.75)
Median	85.0	85.0	85.0	85.0	90.0	85.0
Min, Max	70, 100	75, 100	75, 100	75, 100	75, 100	70, 100

Abbreviations: ECOG = Eastern Cooperative Oncology Group; FRα = folate receptor α; min, max = minimum, maximum; MIRV = mirvetuximab soravtansine; Pac = paclitaxel; PLD = pegylated liposomal doxorubicin; PS2 = moderate to strong staining intensity; SD = standard deviation; Topo = topotecan.

[a] Primary diagnoses of 'other' included tubo-ovarian primary (Patient 155-016) and tubo-ovarian (Patient 418-009).

[b] Primary diagnoses of 'other' included tubo-ovarian origin (Patient 278-013).

[c] Time (months) = (randomization date - initial diagnosis date)/30.4375.

[d] For patients who participated in double-blind trials evaluating PARP inhibitor vs placebo and the actual treatment was not known.

[e] Primary platinum-free interval: 3 to ≤ 12 months vs > 12 months, defined as time from last dose of first-line platinum therapy to the date of disease progression and/or relapse following first-line therapy. Two (2) patients were determined to be primary platinum refractory (Patient 126-001: primary platinum-free interval of 1.38 months and Patient 492-018: primary platinum-free interval of 0.59 months).

[f] Time from last dose of latest line platinum therapy to the date of disease progression and/or relapse following that line of therapy.

[g] All patients had ECOG PS of 1 at Screening, which shifted to an ECOG PS of 2 at C1D1 (Pac: Patient 602-007 and Patient 610-023; Topo: Patient 615-003).

[h] The 2 patients with missing ECOG PS were randomized but not dosed; therefore, ECOG PS was not recorded at Screening or EOT (Topo: Patient 019-045; Pac: Patient 420-010)

All (100%) patients in MIRV arm had high-grade serous histology and almost all in ICC arm (225 of 226 patients). In MIRV arm Stage IIIC (47%) and Stage IV (33%) cancer were the most prominent stages at initial diagnosis, as also in ICC arm (Stage IIIC 53% and Stage IV 29%). 138 (61%) of

patients in MIRV arm had received prior bevacizumab and in a similar proportion in ICC arm (143 patients, 63%) .

- **Numbers analysed**

• ITT population: 227 MIRV, 226 IC Chemo

• Safety population: 218 MIRV, 207 IC Chemo

• Per-Protocol population: 217 MIRV, 204 IC Chemo

• CA-125–Evaluable population: 181 MIRV, 155 IC Chemo.

- **Outcomes and estimation**

Primary efficacy endpoint: PFS_{INV}

The last patient was randomised on 03 August 2022, allowing for 216 days prior to the data cut-off which appears sufficient for mature PFS results considering the limited survival times in this indication.

Table 32: Primary efficacy endpoint PFS_{INV} - ITT population in MIRASOL

Measure	MIRV (N=227)	IC Chemo (N=226)
Number of patients with events, n (%)	176 (77.5)	166 (73.5)
Radiological progression	163 (71.8)	150 (66.4)
Death	13 (5.7)	16 (7.1)
Number of patients censored, n (%)	51 (22.5)	60 (26.5)
Estimated PFS time (months)		
Median (95% CI)	5.62 (4.34, 5.95)	3.98 (2.86, 4.47)
25th percentile (95% CI)	2.86 (2.66, 3.02)	1.58 (1.48, 1.64)
75th percentile (95% CI)	8.67 (8.15, 11.24)	7.03 (5.75, 7.52)
Min, Max	0.03+, 24.77+	0.03+, 21.88
Stratified analysis with IRT randomization values		
Cox PH model, Hazard ratio (95% CI)	0.65 (0.521, 0.808)	
Two-sided p-value from Log-rank test	< 0.0001	
Follow-up time (Reverse KM method, months)		
Median (95% CI)	11.20 (9.99, 13.70)	
Estimated probabilities (95% CI) of PFS at:		
3 months	0.70 (0.64, 0.76)	0.55 (0.48, 0.62)
6 months	0.43 (0.36, 0.50)	0.30 (0.24, 0.37)
9 months	0.25 (0.19, 0.31)	0.15 (0.10, 0.22)
12 months	0.17 (0.12, 0.24)	0.05 (0.02, 0.10)
RMST (95% CI) for PFS at:		
3 months	2.70 (2.62, 2.78)	2.41 (2.30, 2.52)
6 months	4.44 (4.20, 4.68)	3.72 (3.44, 4.01)
9 months	5.47 (5.09, 5.85)	4.39 (3.97, 4.80)
12 months	6.13 (5.62, 6.64)	4.72 (4.21, 5.23)
15 months	6.59 (5.96, 7.21)	4.87 (4.30, 5.44)
Supremum Test for Proportional Hazards Assumption	0.0490	

Abbreviations: CI = confidence interval; IC = investigator's choice; IRT = Interactive Response Technology; KM = Kaplan-Meier; MIRV = mirvetuximab soravtansine; PFS = progression-free survival; PH = proportional hazards; RMST = restricted mean survival time.
Note: PFS is defined as the time from the date of first dose of MIRV until the date of progressive disease or death from any cause, whichever occurred first.

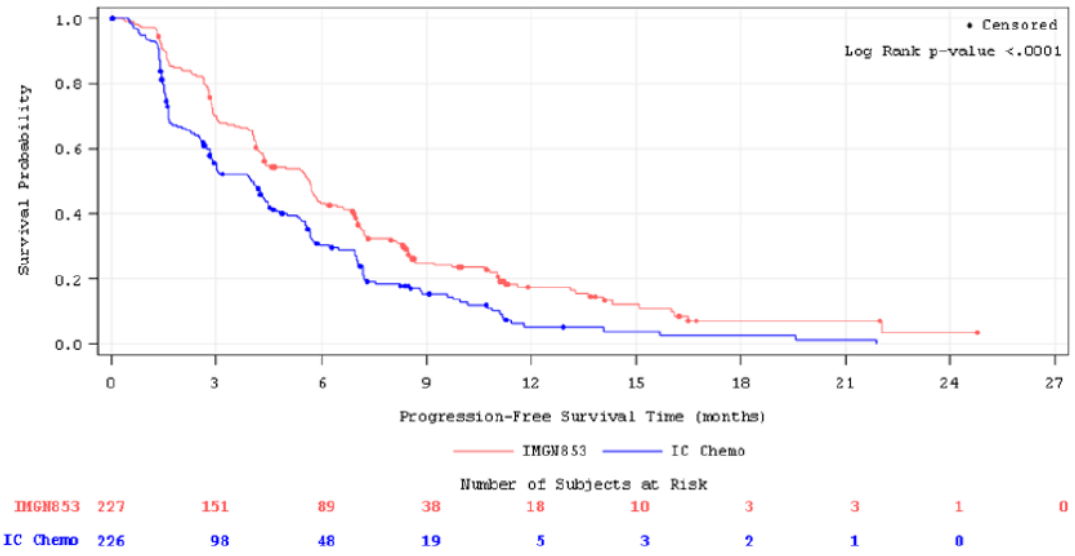
During the evaluation, the amount of follow-up using the reverse KM method were provided, of which the status by week 6 is presented below:

Table 33: Progression free survival by INV by visit and median follow-up time - MIRASOL

Endpoints	Mirvetuximab Soravtansine (N = 227)	IC Chemotherapy (N = 226)
Median Follow-up Time (months)[a] (95% CI)	11.33 (10.71, 16.23)	10.71 (8.38, --)
PFS by Visit		
By Week 6[b], n (%)		
Patients with events, by type	15 (6.6)	25 (11.1)
Radiological progression	12 (5.3)	20 (8.8)
Death	3 (1.3)	5 (2.2)
Patients Censored and still at risk	203 (89.4)	172 (76.1)
Patients censored and no longer at risk, by censoring event	9 (4.0)	29 (12.8)
PD or death after missing >= 2 consecutive radiological assessments	1 (0.4)	2 (0.9)
New anti-cancer therapy prior to PD or death	0	1 (0.4)
No baseline or post-baseline assessment and patient did not die within 105 days of randomization	8 (3.5)	26 (11.5)

[a] Reverse KM method.
[b] Classification will be based on whether PFS event/censored date is during or before the considered week (ie, Week 6, Week 12, Week 18, Week 24) post randomization date.

Figure 25: Kaplan-Meier plot for PFSINV - ITT population in MIRASOL



Abbreviations: IC = investigator's choice; MIRV = mirvetuximab soravtansine (IMGN853); PD = progressive disease; PFS = progression-free survival.
Note: PFS is defined as the time from the date of first dose of MIRV until the date of PD or death from any cause, whichever occurred first.

Key secondary efficacy endpoint: ORR_{INV}

Table 34: Key secondary efficacy endpoint: ORR_{INV} - ITT population of MIRASOL

	Investigator-assessed		BICR-assessed	
	Mirvetuximab Soravtansine (N = 227)	IC Chemotherapy (N = 226)	Mirvetuximab Soravtansine (N = 227)	IC Chemotherapy (N = 226)
Confirmed ORR, n (%)	96 (42.3)	36 (15.9)	82 (36.1)	33 (14.6)
95% CI	(35.8, 49.0)	(11.4, 21.4)	(29.9, 42.7)	(10.3, 19.9)
Confirmed BOR, n (%)				
CR	12 (5.3)	0	16 (7.0)	4 (1.8)
PR	84 (37.0)	36 (15.9)	66 (29.1)	29 (12.8)
SD	86 (37.9)	91 (40.3)	97 (42.7)	107 (47.3)
PD	31 (13.7)	62 (27.4)	32 (14.1)	45 (19.9)
Not evaluable	14 (6.2)	37 (16.4)	16 (7.0)	41 (18.1)
Odds ratio and p-value				
Odds ratio (95% CI)	3.81 (2.440, 5.940)		3.22 (2.043, 5.088)	
p-value	< 0.0001		< 0.0001	

Abbreviations: BICR = blinded independent central review; BOR = best overall response; CI = confidence interval; CR = complete response; IC = investigator's choice; ORR = objective response rate; PD = progressive disease; PR = partial response; SD = stable disease.
Note: ORR is defined as proportion of patients with CR or PR per investigator assessment.

Key secondary efficacy endpoint: OS

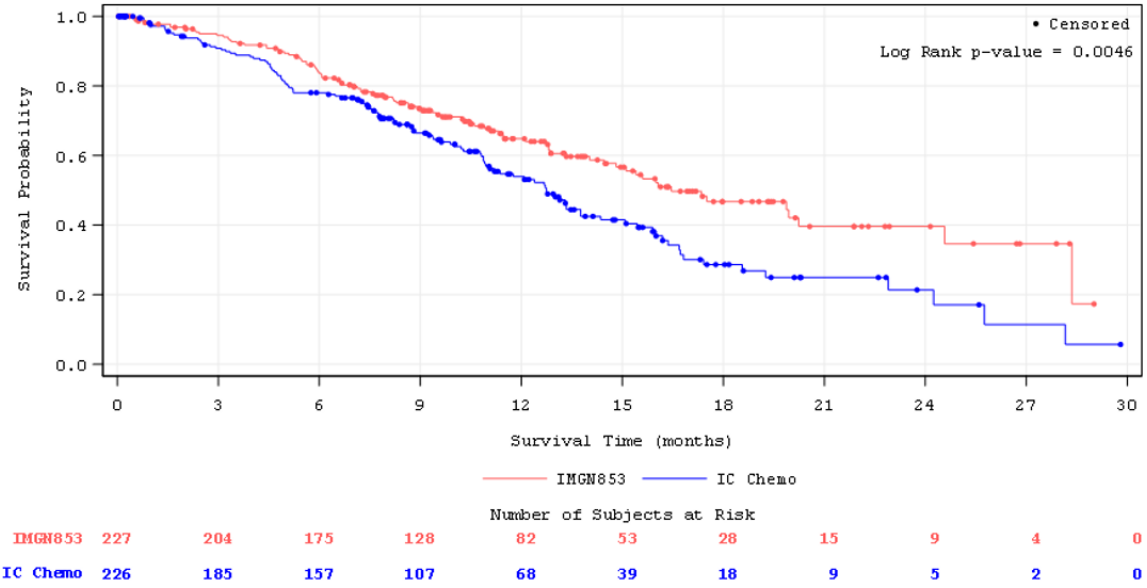
Table 35: Key secondary efficacy endpoint: OS - ITT population in MIRASOL

Number of Patients, n (%)	MIRV (N=227)	IC Chemo (N=226)
Patients with death events, n (%)	90 (39.6)	114 (50.4)
Patients censored, n (%)	137 (60.4)	112 (49.6)
Overall survival time (months)		
Median (95% CI)	16.46 (14.46, 24.57)	12.75 (10.91, 14.36)
25th percentile (95% CI)	8.64 (6.64, 10.61)	7.39 (4.96, 8.28)
75th percentile (95% CI)	28.35 (24.57, ----)	19.25 (16.69, 28.16)

Min, Max	0.03+, 29.01+	0.03+, 29.80+
Stratified analysis with IRT randomization values		
Cox PH model, Hazard ratio (95% CI)	0.67 (0.504, 0.885)	
Two-sided p-value from Log-rank test	0.0046	
Overall survival interim analysis p-value boundary	0.01313	
Follow-up Time (Reverse KM method, months)		
Median (95% CI)	13.11 (12.09, 14.13)	
Estimated probabilities (95% CI) of survival at:		
3 months	0.95 (0.91, 0.97)	0.91 (0.86, 0.94)
6 months	0.84 (0.78, 0.88)	0.78 (0.72, 0.83)
9 months	0.74 (0.67, 0.79)	0.66 (0.59, 0.73)
12 months	0.65 (0.57, 0.71)	0.54 (0.46, 0.61)
15 months	0.57 (0.48, 0.64)	0.42 (0.33, 0.50)
18 months	0.47 (0.37, 0.55)	0.29 (0.20, 0.38)
21 months	0.40 (0.29, 0.50)	0.25 (0.17, 0.34)
RMST (95% CI) for OS at:		
3 months	2.92 (2.87, 2.97)	2.88 (2.82, 2.94)
6 months	5.63 (5.48, 5.78)	5.41 (5.23, 5.60)
9 months	7.98 (7.70, 8.26)	7.61 (7.28, 7.95)
12 months	10.05 (9.62, 10.49)	9.42 (8.92, 9.92)
15 months	11.87 (11.26, 12.48)	10.81 (10.14, 11.47)
18 months	13.40 (12.61, 14.19)	11.84 (11.00, 12.67)
21 months	14.73 (13.74, 15.73)	12.62 (11.61, 13.62)
Supremum Test for Proportional Hazards Assumption	0.4730	

Abbreviations: + = censored; CI = confidence interval; IRT = Interactive Response Technology; KM = Kaplan-Meier; min, max = minimum, maximum; MIRV = mirvetuximab soravtansine; OS = overall survival; PH = proportional hazards; RMST = restricted mean survival time.

Figure 26: Kaplan-Meier plot for OS - ITT population in MIRASOL



Abbreviations: IC Chemo = investigator's choice of chemotherapy; IMGN853 = mirvetuximab soravtansine; ITT = intent-to-treat; OS = overall survival.
Note: OS is defined as the time from the date of first dose until the date of death from any cause.

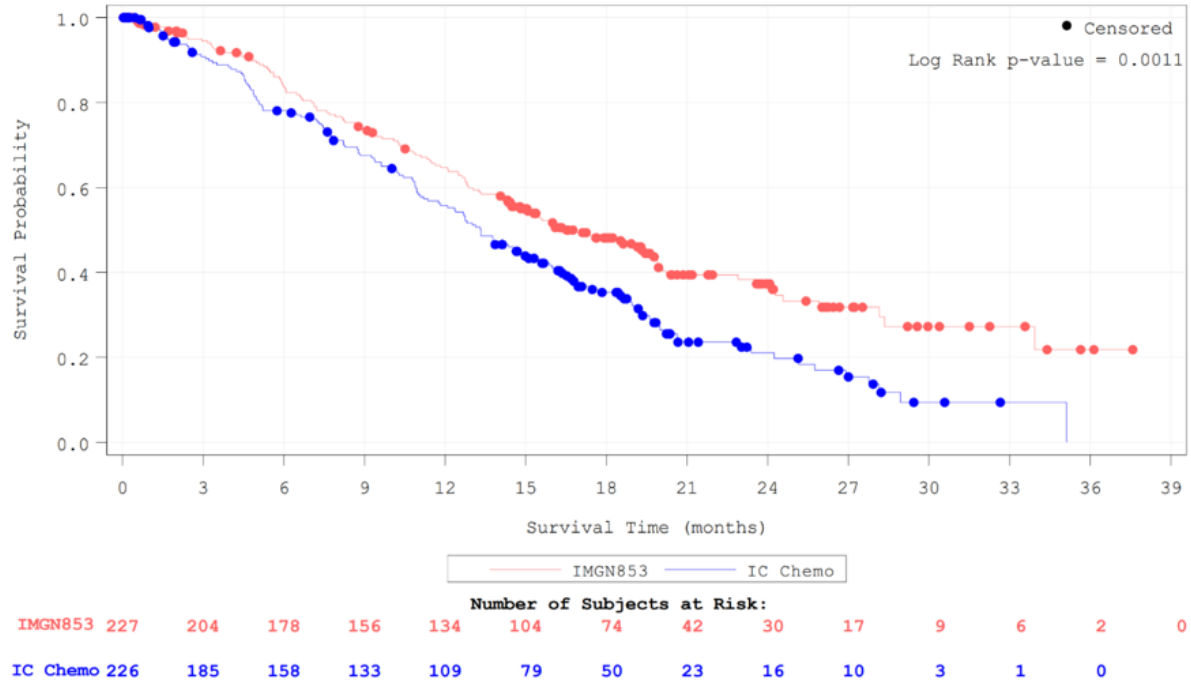
An updated efficacy analysis based on a data cut-off date 27 October 27 2023 was conducted with 61.1% maturity for OS, see below the below table and figure.

Table 36: Overall survival, ITT population, October 27 2023 cut-off

Endpoints	**MIRV (N=227)**	**ICC (N=226)**
Number of Patients with Death Events, n (%)	127 (55.9)	150 (66.4)
Number of patients censored, n (%)	100 (44.1)	76 (33.6)
Database cut	11 (4.8)	0
Estimated overall survival time (months)		
Median (95% CI)	16.46 (14.36, 19.88)	13.34 (11.37, 15.44)
25th Percentile (95% CI)	8.64 (6.70, 10.48)	7.39 (4.96, 8.74)
75th Percentile (95% CI)	33.94 (25.92, ----)	20.63 (19.02, 25.76)
Min, Max	0.03+, 37.59+	0.03+, 35.12
Stratified analysis with IRT randomization values		
Cox PH model, Hazard ratio (95% CI)	0.67 (0.531, 0.857)	
Two-sided P-value from Log-rank test	0.0011	
Follow-up Time (Reverse KM method, months)		
Median (95% CI)	20.44 (19.29, 23.59)	20.24 (18.53, 22.83)

+ indicates censored

Figure 27: Kaplan-Meier curve for overall survival, October 27 2023 cut-off



Key secondary endpoint: PRO EORTC QLQ-OV28 (Abdominal/GI subscale)

For the responder analysis of the QoLP, patients were classified as either improved or unimproved based on change from baseline at Week 8 or 9 on the QLQ-OV28 Abdominal/GI symptom subscale. A 15-point decrease on the symptom subscale was defined as the threshold for improvement (effectively a 16.67-point difference).

This key secondary endpoint was not reached (p = 0.2611). The percentage of patients with a ≥ 15-point decrease on the Abdominal/GI subscale at Week 8/9 was 21% in the MIRV arm vs 15% in the IC chemotherapy arm. This responder analysis included 162 and 150 patients in the mirvetuximab soravtansine and IC chemotherapy arms, respectively.

Selected secondary endpoints

Duration of response by investigator: For patients with a BOR of CR or PR by investigator assessment, median DOR was 6.77 months (95% CI: 5.62, 8.31) in the MIRV arm vs 4.47 months (95% CI, 4.17, 5.82) in the ICC arm (nominal p = 0.0330).

Time to second disease progression: The HR for investigator-assessed PFS2 was 0.63 (nominal p = 0.0001). The median time to PFS2 was 11.04 months (95% CI: 9.36, 12.45) vs 8.05 months (95% CI: 6.74, 9.36) in the MIRV and ICC groups, respectively. Radiological or clinical progression rate was lower in the MIRV arm than in the ICC arm (4.8% vs 7.5%). 21.1% vs 26.1% of patients died, respectively. For PFS2, end of next line treatment was registered in 30.8% in MIRV and 32.7% in ICC.

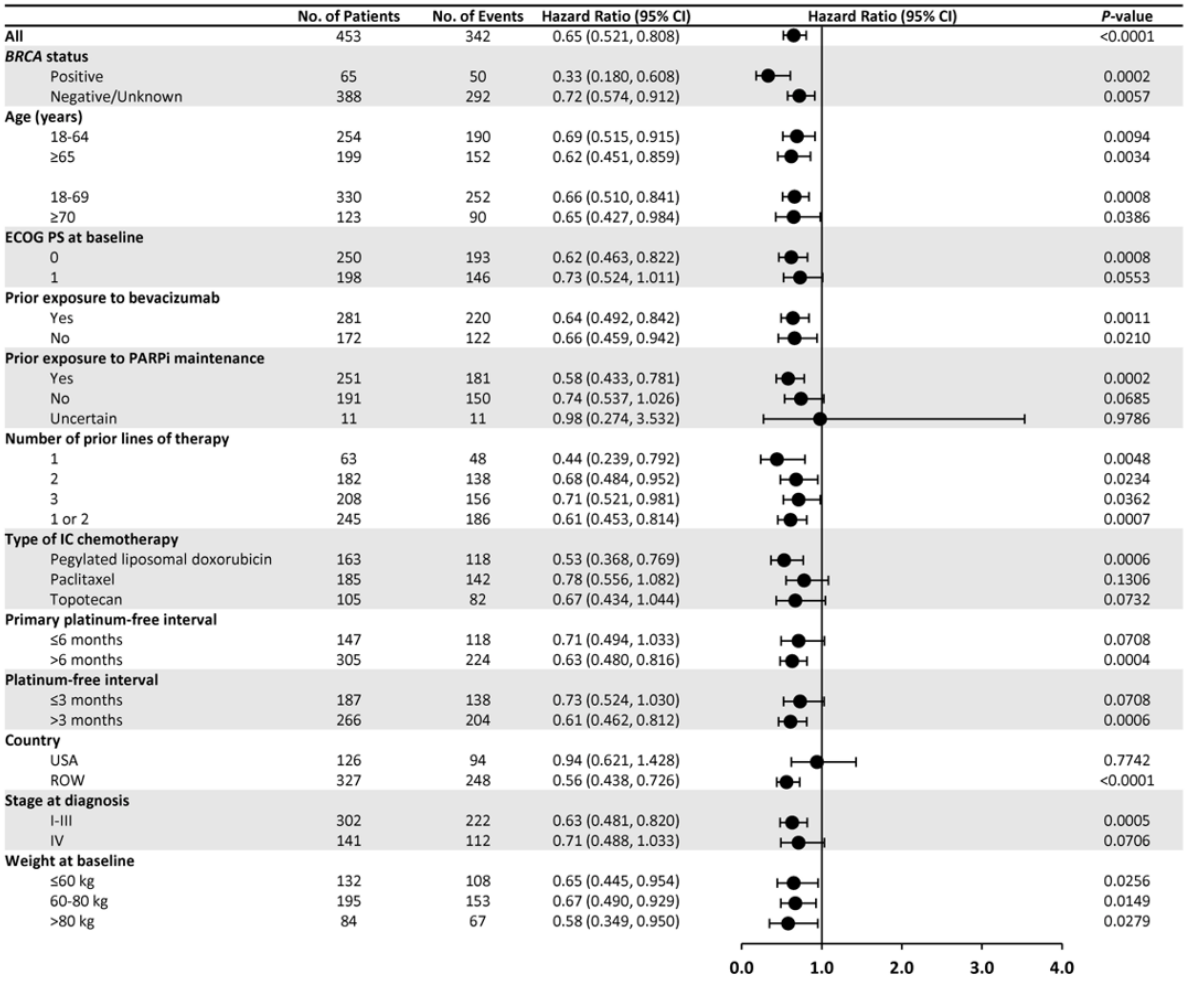
New anticancer therapy: 52.0% (118 patients) and 55.8% (126 patients) treated with MIRV and ICC received new anticancer therapies, respectively. Among patients treated with MIRV, the most common (≥ 10%) new anticancer therapies included taxanes (25.6%), gemcitabine (16.3%), anthracyclines (14.5%), other chemotherapy (14.1%), bevacizumab (12.8%), and platinum compounds (11.0%). Of those treated with ICC, the most common (≥ 10%) new anticancer therapies included gemcitabine (21.2%), taxanes (18.6%), other chemotherapy (16.8%), platinum compounds (11.9%), and bevacizumab (11.1%).

- **Ancillary analyses**

PFS_{BICR} was evaluated as **a sensitivity analysis**. Among patients randomized to MIRV, 64.3% had events of radiological progression or death with a median PFS_{BICR} of 5.91 months (95% CI: 4.93, 6.97 months). A total of 54.4% of patients randomized to IC Chemo had events of radiological progression or death with a median PFS_{BICR} of 4.34 months (95% CI: 3.52, 4.99 months). Analysis of PFS_{BICR} yielded an HR of 0.72 (95% CI: 0.558, 0.920).

Subgroup analysis for primary endpoint: PFS by investigator assessment

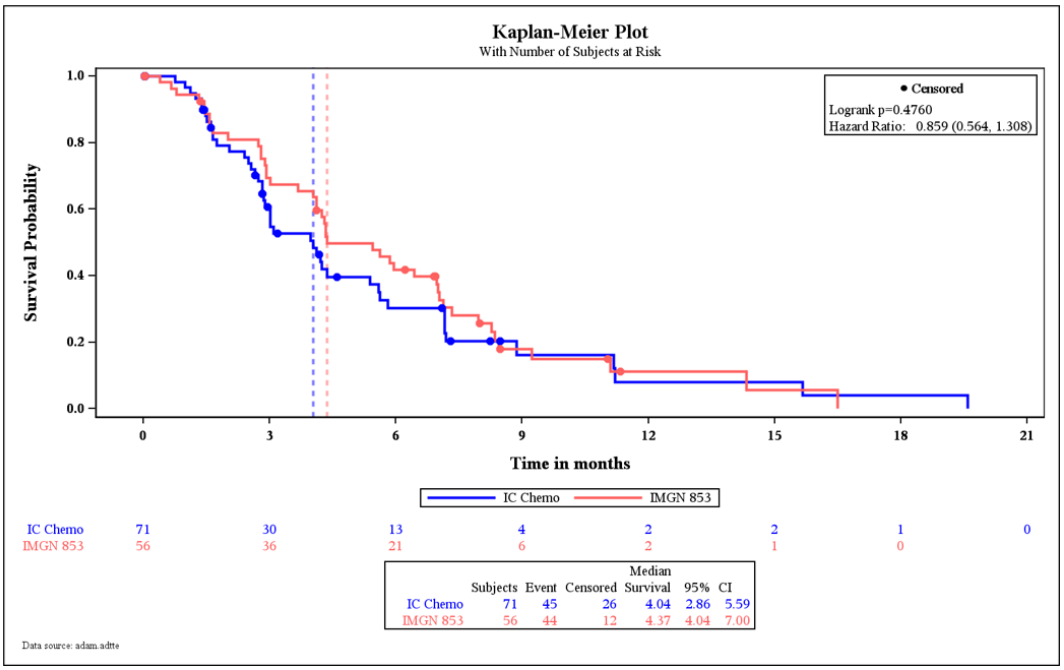
Figure 28: Forest Plot for PFS subgroup analysis per investigator – ITT population in MIRASOL



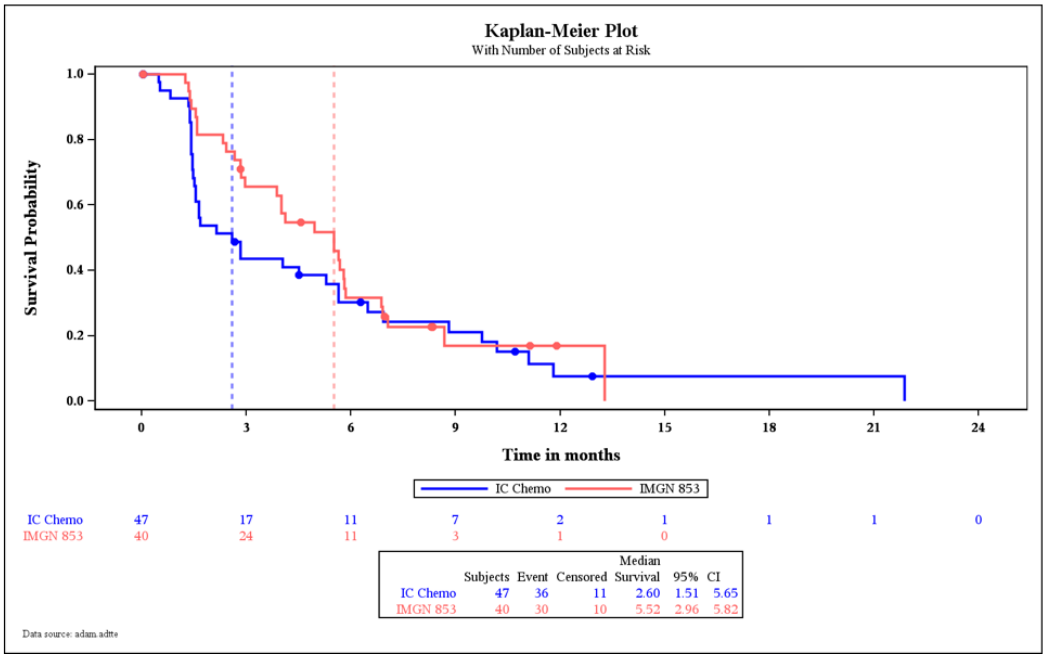
Abbreviations: *BRCA* = breast cancer susceptibility gene; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; IC chemo = investigator's choice of chemotherapy; PARPi = poly adenosine diphosphate-ribose polymerase inhibitor; PS = performance status; ROW = rest of world.

Figure 29: Kaplan Meier Plot - Progression Free Survival Per Investigator by FRα - ITT Population (MIRV and ICC) (March 06 2023 data cut-off)

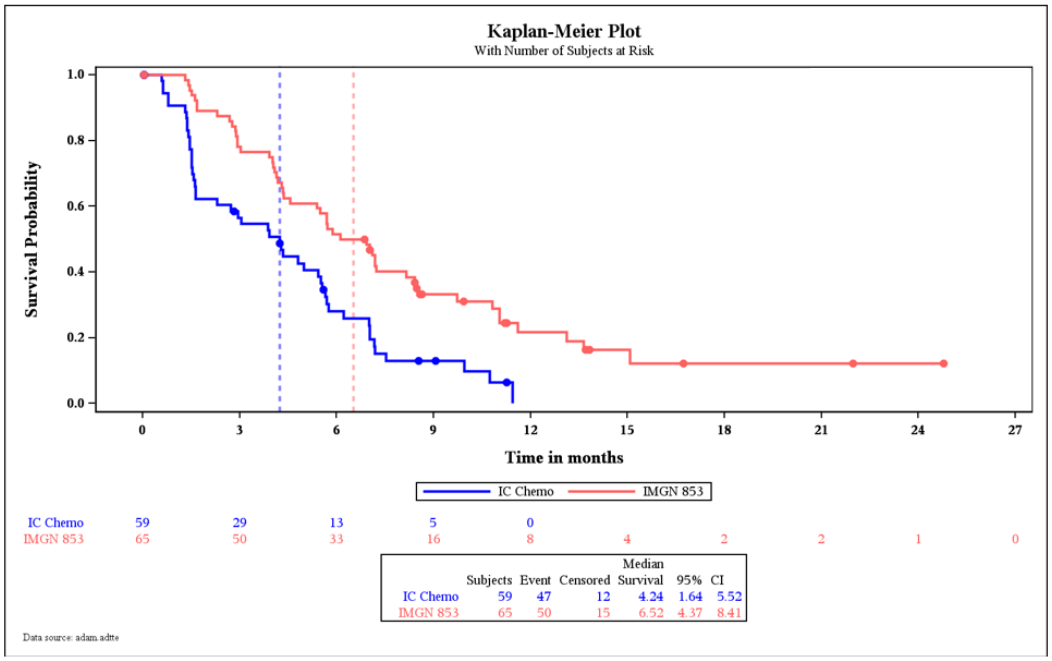
FR alpha >75% - 85%



FR alpha >85% - <95%



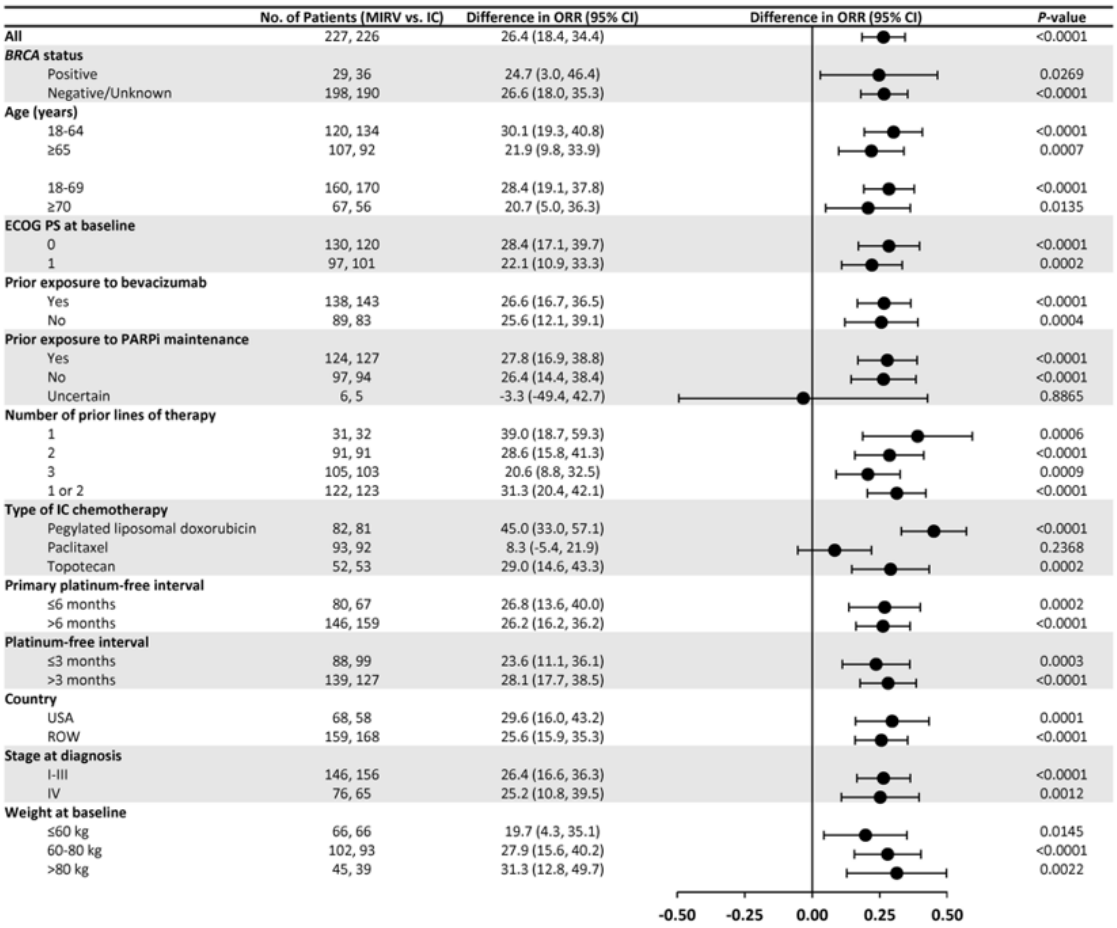
FR alpha ≥95%



The category FR alpha exactly 75% likely contains patients with all levels of FR alpha expression ≥75%. Due to the complexity of the scoring process and the CDx being validated more for binary assessment (scoring algorithm is positive or negative for FOLR1 status ≥75%), patients with FR alpha exactly 75% were not included.

Subgroup analysis for key secondary endpoint: ORR by investigator assessment

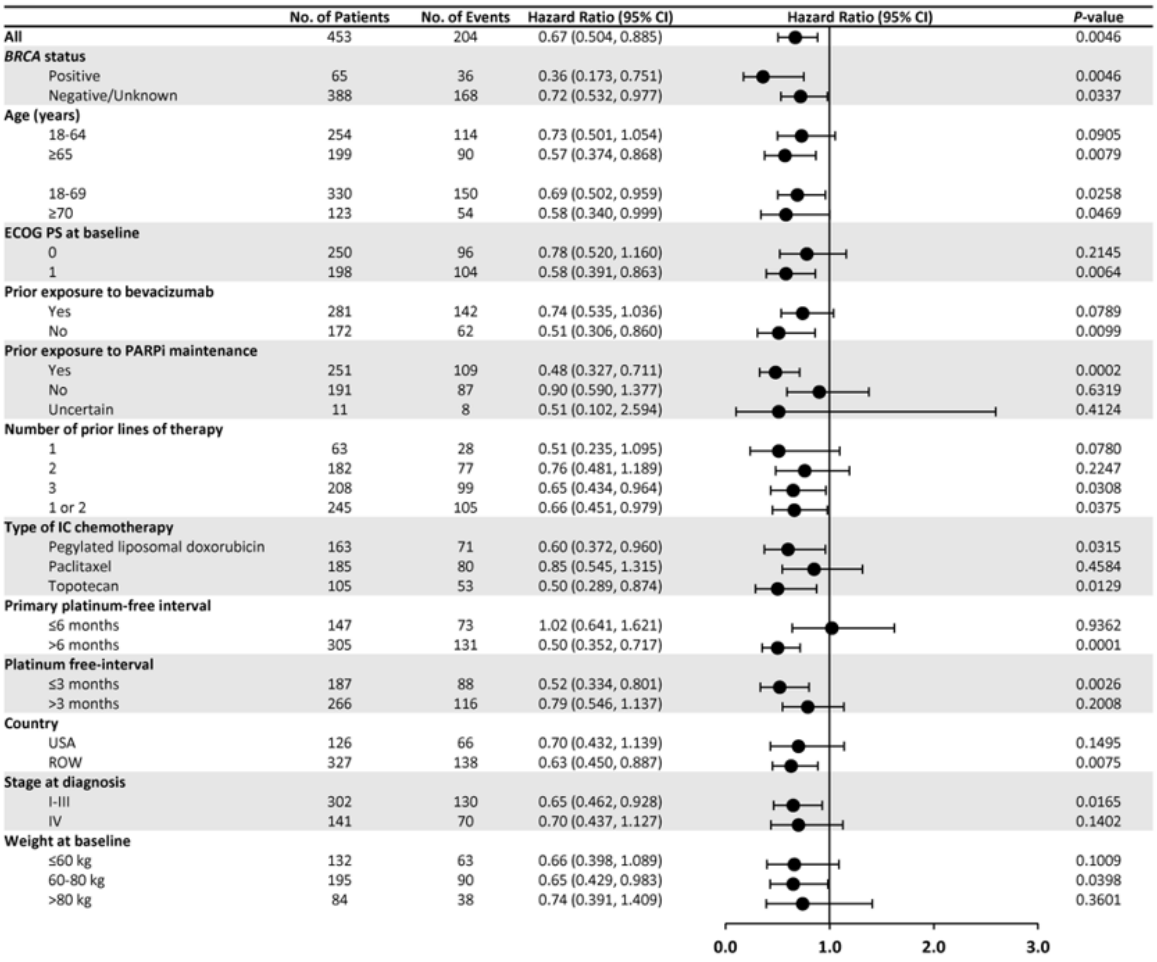
Figure 30: Forest Plot for ORR_{INV} subgroup analysis - ITT population in MIRASOL



Abbreviations: *BRCA* = breast cancer susceptibility gene; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; IC chemo = investigator's choice of chemotherapy; PARPi = poly adenosine diphosphate-ribose polymerase inhibitor; PS = performance status; ROW = rest of world.

Subgroup analysis for key secondary endpoint: OS

Table 37: Forest Plot for OS subgroup analysis - ITT population MIRASOL



Abbreviations: *BRCA* = breast cancer susceptibility gene; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; IC chemo = investigator's choice of chemotherapy; PARPi = poly adenosine diphosphate-ribose polymerase inhibitor; PS = performance status; ROW = rest of world.

- **Summary of main efficacy results**

The following table summarises the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 38: Summary of efficacy for trial IMGN853 -0416 (MIRASOL)

Title: MIRASOL: A Randomized, Open-label, Phase 3 Study of Mirvetuximab Soravtansine vs. Investigator's Choice of Chemotherapy in Platinum-Resistant Advanced High-Grade Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancers with High Folate Receptor-Alpha Expression	
Study identifier	IMGN853 -0416 EudraCT 2019-003509-80

Design	Study 0416 (MIRASOL) is a randomized, Phase 3 trial in platinum-resistant ovarian cancer (PROC) patients with high folate receptor alpha (FRα) expression as determined by the Ventana FOLR1 (FOLR-2.1) CDx assay. The study was a global, open-label, multi-center trial designed to evaluate the efficacy and safety of mirvetuximab soravtansine vs investigator's choice (IC) chemotherapy in patients who received 1 to 3 prior systemic anticancer therapies. Patients with primary platinum-refractory disease were excluded. Eligible patients were randomized 1:1 to the following treatment arms: • Arm 1: mirvetuximab soravtansine 6 mg/kg adjusted ideal body weight (AIBW) intravenously (IV) every 3 weeks (Q3W) (N = 227) • Arm 2: IC single-agent chemotherapy (N = 226) – Paclitaxel 80 mg/m^2 IV every week (QW) (n = 92) – Pegylated liposomal doxorubicin (PLD) 40 mg/m^2 IV every 4 weeks (Q4W) (n = 81) – Topotecan 4 mg/m^2 IV on Days 1, 8, and 15 within 4-week cycles; 1.25 mg/m^2 on Day 1 to Day 5 within 3-week cycles (n = 53) Stratification factors were number of prior lines of therapy (1 vs 2 vs 3) and intended IC chemotherapy (i.e. paclitaxel, PLD, or topotecan). Study drugs were administered until PD, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first.		
	Duration of main phase:		First patient enrolled (C1D1): 03 February 2020 Last patient completed: Ongoing Data cut-off: 06 March 2023
Hypothesis	Superiority		
Treatment groups	Mirvetuximab soravtansine (MIRV)		Mirvetuximab soravtansine 6 mg/kg AIBW IV Q3W (N = 227)
	IC single-agent chemotherapy (IC)		IC single-agent chemotherapy (N = 226) – Paclitaxel 80 mg/m^2 IV QW (n = 92) – PLD 40 mg/m^2 IV Q4W (n = 81) – Topotecan 4 mg/m^2 IV on Days 1, 8, and 15 within 4-week cycles; 1.25 mg/m^2 on Day 1 to Day 5 within 3-week cycles (n = 53)
Endpoints and definitions	Primary endpoint	Progression-free survival (PFS)	PFS, defined as the time from randomization until investigator-assessed progressive disease (PD) or death, whichever occurred first
	Key secondary endpoint Key secondary endpoint	Objective response rate / overall response rate (ORR)	ORR, which includes best overall response (BOR) of complete response (CR) or partial response (PR) as assessed by the investigator
		Overall survival (OS)	OS, defined as the time from date of randomization until the date of death
		Primary patient-reported outcome (PRO)	PRO assessment (QoLP), defined as the number of patients with an improvement $\geqslant$ 15 points at Week 8/9 on the Abdominal/Gastrointestinal (GI) subscale of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Ovarian Cancer Module (EORTC QLQ-OV28)
	Additional secondary endpoint	Duration of response (DOR)	DOR, defined as the time from initial response until investigator-assessed PD or death for all patients who achieve a confirmed objective response (CR or PR)

		Progression-free survival on the next line of treatment (PFS2)	PFS2, defined as the time from date of randomization until second disease progression or death, whichever occurs first
		PFS and ORR by blinded independent central review (BICR) (sensitivity analyses)	
Database lock	06 March 2023		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	**PFS by investigator assessment (primary endpoint)** Intent-to-Treat (ITT) population (all patients randomized to the study, regardless of whether or not patients received study treatment) Time from randomization until investigator-assessed PD or death, whichever occurred first		
Descriptive statistics and estimate variability	Treatment group	MIRV	IC
	Number of subjects	227	226
	PFS (median months)	5.62	3.98
	95% CI	4.34, 5.95	2.86, 4.47
Effect estimate per comparison	PFS	Comparison groups	MIRV vs IC
		Hazard ratio (95% CI)	0.65 (0.521, 0.808)
		P-value	< 0.0001
Analysis population and time point description	**ORR by investigator assessment (key secondary endpoint)** ITT population As assessed during the study		
Descriptive statistics and estimate variability	Treatment group	MIRV	IC
	Number of subjects	227	226
	ORR (n (%))	96 (42.3)	36 (15.9)
	95% CI	35.8, 49.0	11.4, 21.4
	CR (n (%))	12 (5.3)	0
	PR	84 (37.0)	36 (15.9)

	(n (%))		
	SD (n (%))	86 (37.9)	91 (40.3)
	PD (n (%))	31 (13.7)	62 (27.4)
	Not evaluable (n (%))	14 (6.2)	37 (16.4)
Effect estimate per comparison	ORR	Comparison groups	MIRV vs IC
		Odds ratio (95% CI)	3.81 (2.440, 5.940)
		P-value	< 0.0001
Analysis population and time point description	**OS (key secondary endpoint)** ITT population Time from date of randomization until the date of death		
Descriptive statistics and estimate variability	Treatment group	MIRV	IC
	Number of subjects	227	226
	Patients with death events (n (%))	90 (39.6)	114 (50.4)
	Patients censored, n (%)	137 (60.4)	112 (49.6)
	OS (median months)	16.46	12.75
	95% CI	14.46, 24.57	10.91, 14.36
Effect estimate per comparison	OS	Comparison groups	MIRV vs IC
		Hazard ratio (95% CI)	0.67 (0.504, 0.885)
		P-value	0.0046
Analysis population and time point description	**PRO assessment (key secondary endpoint)** Patients who had PRO assessments at baseline and week8/9, and patients PD or death prior to week8/9		
Descriptive statistics and estimate variability	Treatment group	MIRV	IC
	Number of subjects	162	150
	Change from baseline: 15-point (effective16.67) reduction in QLQ-OV28 Abdominal subscale. MIRV vs ICC	Baseline: 25.13	Baseline: 28.02
	Improved, n (%)	34 (21.0)	23 (15.3)
Effect estimate per comparison		p-value	0.2611
Analysis population and time point description	**DOR (additional secondary endpoint)** Patients with confirmed CR or PR		

	Time from initial response until investigator-assessed PD or death for all patients who achieve a confirmed objective response (CR or PR)		
Descriptive statistics and estimate variability	Treatment group	MIRV	IC
	Number of subjects	96	36
	DOR (median months)	6.77	4.47
	95% CI	5.62, 8.31	4.17, 5.82
Effect estimate per comparison	DOR	Comparison groups	MIRV vs IC
		P-value (nominal)	0.0330
Analysis population and time point description	**PFS2 (additional secondary endpoint)** ITT population Time from date of randomization until second disease progression or death, whichever occurs first		
Descriptive statistics and estimate variability	Treatment group	MIRV	IC
	Number of subjects	227	226
	PFS2 (median months)	11.04	8.05
	95% CI	9.36, 12.45	6.74, 9.36
Effect estimate per comparison	PFS2	Comparison groups	MIRV vs IC
		Hazard ratio	0.63
		P-value (nominal)	0.0001
Analysis population and time point description	**PFS by BICR (additional secondary endpoint, sensitivity analysis)** ITT population Time from randomization until BICR-assessed PD or death, whichever occurred first		
Descriptive statistics and estimate variability	Treatment group	MIRV	IC
	Number of subjects	227	226
	PFS (median months)	5.91	4.34
	95% CI	4.93, 6.97	3.52, 4.99
Effect estimate per comparison	PFS	Comparison groups	MIRV vs IC
		Hazard ratio (95% CI)	0.72 (0.558, 0.920)
		P-value	0.0082
Analysis population and time point description	**ORR by BICR (additional secondary endpoint, sensitivity analysis)** ITT population As assessed during the study		
	Treatment group	MIRV	IC

Descriptive statistics and estimate variability	Number of subjects	227	226
	ORR (n (%))	82 (36.1)	33 (14.6)
	95% CI	29.9, 42.7	10.3, 19.9
	CR (n (%))	16 (7.0)	4 (1.8)
	PR (n (%))	66 (29.1)	29 (12.8)
	SD (n (%))	97 (42.7)	107 (47.3)
	PD (n (%))	32 (14.1)	45 (19.9)
	Not evaluable (n (%))	16 (7.0)	41 (18.1)
Effect estimate per comparison	ORR	Comparison groups	MIRV vs IC
		Odds ratio (95% CI)	3.22 (2.043, 5.088)
		P-value	< 0.0001

2.6.5.3. Clinical studies in special populations

Table 39: Number of Patients by Age Groups in Controlled and Non-Controlled Trials

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials	153	59	3
Non Controlled trials	76	11	1

Controlled Trials = Study 0416 and Study 0403; Non-Controlled Trials = Study 0417 and Study 0401 (Patients with EOC and treated with 6 mg/kg AIBW).

Table 40: Clinical Studies in Special Populations

	Controlled Trials (Study 0416)	**Non-controlled trials (Study 0417)**
Renal impairment* patients (Subjects number /total number)	8/218	4/106
Hepatic impairment** patients (Subjects number /total number)	32/218	18/106
Paediatric patients <18 years (Subjects number /total number)	0/218	0/106

* Renal impairment is defined as having CKD Stage 3b, 4, or 5 (KDIGO definition).
** Hepatic impairment is defined as NCI-ODWG Criteria mild, moderate, or severe.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

ImmunoGen entered into an agreement with Ventana Medical Systems, Inc. (Ventana) to develop a fully automated and standardized IHC CDx assay to aid in identifying patients with FRα (FOLR1)-positive advanced ovarian cancer, including primary peritoneal cancer and primary fallopian tube cancer, who are eligible for treatment with MIRV.

During the preclinical development and early stages of the MIRV Phase 1 study 0401, the commercially available Leica FRα IHC assay (clone NCL-L-FRalpha BN3.2), a fit-for-purpose assay appropriate to support the early-stage development, was used. At the end of the escalation stage of the Phase 1 study 0401, ImmunoGen migrated all FRα IHC testing to the newly developed assay known as the Ventana robust prototype assay (RPA; The Ventana RPA Assay). This assay used an ImmunoGen antibody, FOLR-2.1-clone 353.2.1. The Ventana RPA Assay was used to prospectively select patients for enrolment into the expansion cohorts of study 0401. Additionally, this assay was used to retrospectively assess FRα expression for those patients who had been enrolled in the escalation stage of study 0401 by the Leica assay.

Prior to the start of the Phase 3 study 0403 (FORWARD 1), Ventana refined the RPA to ensure commercial readiness, resulting in the final assay format, which is the VENTANA FOLR1 (FOLR1-2.1) CDx Assay (Ventana FOLR1 Assay). This same assay format and staining protocol were used for the prospective enrolment of all subsequent studies (0403 FORWARD 1, 0417 SORAYA, and 0416 MIRASOL).

Although the same assay was used for slide staining, 2 different scoring methods were used by pathologists to determine FRα expression. 10X method was used in study 0403 and PS2+ in studies 0401, 0417, and 0416. The Ventana FOLR1 Assay (including the PS2+ scoring method and threshold) used for patient enrolment was locked under design control prior to its use in studies 0417 and 0416.

Table 41: FRα IHC Assay Formats and Conditions

Assay	IHC Platform	Detection	Ab Concentration	Ab Incubation Time	Diluent	Antigen Retrieval
Ventana RPA Assay	BenchMark XT	OptiView	3 µg/ml	16 min	Tris-based with Azide	32 min CC1 (pH 8 EDTA)
Ventana FOLR1 Assay (both CDx and RxDx labelled versions)	BenchMark ULTRA	OptiView	5.6 µg/ml	32 min	Tris-HCl based with ProClin	64 min CC1 (pH 8 EDTA)

Abbreviations: Ab = antibody; EDTA = ethylenediaminetetraacetic acid; FOLR1/FRα = folate receptor alpha; HCl = immunohistochemistry; RPA = robust prototype assay.

FRα IHC Assay Description

VENTANA FOLR1 (FOLR1-2.1) RxDx Assay is a qualitative IHC assay using mouse monoclonal anti-FOLR1, clone FOLR1-2.1 that is intended for use in the assessment of folate receptor alpha (FOLR1) protein in formalin-fixed, paraffin-embedded (FFPE) epithelial ovarian, fallopian tube, or primary peritoneal cancer tissue specimens by light microscopy. This assay is for use with OptiView DAB IHC Detection Kit for staining on a BenchMark ULTRA instrument.

This assay is indicated as an aid in identifying patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer who may be eligible for treatment with MIRV. Test results of the VENTANA

FOLR1 (FOLR1-2.1) RxDx Assay should be interpreted by a qualified pathologist in conjunction with histological examination, relevant clinical information, and proper controls. This product is intended for IVD use.

Epithelial ovarian cancer (EOC) tissues stained with the Ventana FOLR1 Assay are scored for viable tumour cell percentage, which is defined as the proportion of viable tumour cells exhibiting moderate (level 2) or strong (level 3+) membrane staining out of the total number of viable tumour cells.

Assay Performance Testing and Validation

The Ventana FOLR1 Assay analytical performance validation has consisted of the key studies listed below to ensure the analytical performance of the assay using multiple, unique cases of indication tissue and system level control tissue. These studies have been conducted in accordance with FDA-published guidance documents: Guidance for Submission of Immunohistochemistry Applications to the FDA - Final Guidance for Industry (1998) and Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product – Draft Guidance (2016).

- Immunoreactivity of FOLR1 Assay in Normal and Neoplastic Tissues
- Intermediate Precision (Interlot and Interinstrument) for FOLR1 Assay Staining in Epithelial Ovarian Cancer at a 75% Tumour Cell Staining Cut-off for the PS2+ Scoring Algorithm
  - Interantibody lot
  - Interdetection kit lot
  - Interinstrument
  - Nonspecific staining
  - Morphology
- Reader Precision

FOLR1 status was determined using IHC in FFPE tissues obtained from patient samples. The IHC staining for FOLR1 was performed in the Pharma Services CAP/CLIA Laboratory using commercial Ventana's FOLR1 assay developed with ImmunoGen's anti-FOLR1 (353.2.1) mouse monoclonal primary antibody. Hematoxylin and eosin (H&E) stains (Ventana's BenchMark® XT staining platform) were performed to assess tissue quality and presence of tumor and were evaluated by the reviewing pathologist. Ki67 antibody was used as a system control and mouse IgG was used as negative reagent control for FOLR1. Anti-Ki67 staining on tonsil specimens was used to verify system performance for each run (system control).

Table 42: Antibodies used in the ICH assay

Antibody Target	Vendor	Catalog No.	Species	Clonalities	Clone No.	Lot(s)
Anti-FOLR1 (Protocol 268)	ImmunoGen	N/A	Mouse	Monoclonal	353.2.1	E002317-34-001
Mouse IgG (Protocol 668)	VMSI	760-2014	Mouse	Monoclonal	MOPC21	C00277, D02936, E08495, F07105
Anti-Ki67 (Protocol 998)	VMSI	790-4286	Rabbit	Monoclonal	30-9	D05827, D08440, D09097, E01291, E02055, E06573, E07806, E10075, F01139, F05615, F07111

Table 43: Materials used as staining controls.

Control	Used in Assay	Vendor	Catalog/Part No.
CONFIRM anti-Ki67 (System Control)	Ki67 (998)	VMSI	790-4286
Negative Control Monoclonal	FOLR1 (Neg) (668)	VMSI	760-2014

Collection methods for the specimens were controlled by the local sites and managed by Immunogen. However, a Laboratory Manual was provided to the sites delineating recommendations for optimal detection of antigens in tissues.

Ki-67 (30-9), FOLR1 positive, and FOLR1 negative runs were detected using the OptiViewTM detection kit (VMSI, Catalog No. 760-700). Enzymatic detection of the FOLR1 antibody was accomplished with a secondary goat anti-mouse and anti-rabbit IgG conjugated to hydroquinone (HQ), followed by an anti-HQ conjugated with HRP. A tyramide-based amplification strategy was used to increase the sensitivity of detection. Chromogen was deposited by a reaction with hydrogen peroxide in the presence of DAB and copper sulfate. During scoring, the pathologists were blinded to specimen details, including treatment conditions and patient outcomes. A second pathologist reviewed the generated scores in 10% randomly selected cases according to the Pathology Quality Control Review WI1707-005. The second pathologist confirmed and agreed with the scores from the initial read in all reviewed cases.

Slide Interpretation and Scoring Methodology

Two different pathologist scoring methodologies have been used to determine FRα expression during the clinical development of MIRV. The scoring methodology was initially PS2+ in early development and then changed to 10X for the Phase 3 study 0403 (FORWARD 1). However, all subsequent studies, including 0417 (SORAYA) and 0416 (MIRASOL), utilized the PS2+ methodology.

PS2+ Methodology

The PS2+ methodology uses an intensity-based scoring algorithm where the reading pathologist uses multiple microscope objectives to evaluate the tumour sample and makes a determination of the percentage of tumour cells with FRα membrane staining at each level of staining intensity (level 0, 1, 2, and 3). Subsequently, a PS2+ score for each sample is determined by adding the percentage of cells staining at level 2 (moderate) and level 3 (strong) staining intensity. Patient samples are classified as follows based on the PS2+ score: ≥25% to 49% (low expression), ≥50% to 74% (medium expression), and ≥75% (high expression).

This scoring method requires the pathologist to distinguish the contribution of cells based on staining intensity: level 2 and 3 staining vs level 0 and 1 staining. This methodology was applied during the early phase of clinical development (e.g. study 0401) as it provided detail on both the intensity and heterogeneity of FRα expression within tumour samples.

10X Methodology

For study 0403, based on limited comparative data, Ventana proposed to switch from PS2+ to the 10X method. This methodology used a magnification-based assessment of any staining observed at 10X rather than a PS2+ methodology, which also required assessment of staining intensity level at multiple magnifications. With the 10X scoring method, the pathologist assessed the percentage of viable tumour cells with any membrane FRα staining visible using a 10X microscope objective. This approach was based on the hypothesis that membranous FRα expression visible by 10X magnification would be equivalent to the level 2+ and 3+ intensity staining. This method was expected to reduce the time required for the pathology review. Medium FRα expression was defined as ≥50% to 74% of tumour cells with any membrane staining visible at 10X magnification. High FRα expression was defined as ≥75% tumour cells with any membrane staining at 10X magnification.

Table 44: FRα IHC Assay and Scoring Method Used in Clinical Studies

Study	Ventana Assay Used	Scoring Method	Protocol-Defined FRα Inclusion Requirement
Study 0401 (EOC expansion)	Ventana RPA Assay	PS2+	≥25% PS2+
Study 0403	Ventana FOLR1 Assay	10X	≥50% (medium) and ≥75% (high) per 10X
Study 0417	Ventana FOLR1 Assay	PS2+	≥75% PS2+
Study 0416	Ventana FOLR1 Assay	PS2+	≥75% PS2+

Abbreviations: EOC = epithelial ovarian cancer; FOLR1/FRα = folate receptor alpha; IHC = immunohistochemistry; RPA = robust prototype assay.

Rationale for the Selection of the PS2+ Method for Studies 0417 and 0416 and Future Studies and for Commercial Use

The efficacy observed in study 0403 was less than anticipated based on study 0401, and a review of all changes made between the 2 phases of development was undertaken. The review included the change in the scoring method from PS2+ in study 0401 to 10X in study 0403. An exploratory analysis utilizing the PS2+ scoring method was conducted on the study 0403 data, and the outcomes suggested that the 10X scoring method for the Ventana FOLR1 Assay misclassified the FRα expression level of some patients. Patients classified as FRα high by the PS2+ scoring method had a stronger treatment effect from mirvetuximab soravtansine, including ORR, PFS and OS, compared with chemotherapy controls.

The rationale for the use of the PS2+ scoring method is also supported by histopathology data demonstrating that FRα expression within a given ovarian cancer can vary across the specimen with areas of level 3, 2, 1, and 0 intensity staining. By removing the assessment of intensity staining, the 10X scoring method may have inadvertently resulted in the inclusion of level 1 intensity with level 2, resulting in the classification of samples as having higher FRα expression than appropriate. Thus, a more detailed analysis of the entire specimen using multiple microscope objectives is believed to be a more reliable method for assessing patient eligibility through explicit differentiation of level 1 vs level 2 intensity staining using the PS2+ scoring method. These data supported the decision to select patients in studies 0417 and 0416, future studies, and commercial use using the PS2+ scoring method.

Positivity Threshold Rationale for Single-Agent Mirvetuximab Soravtansine

The threshold for FRα positivity has evolved with the accumulation of clinical data. In study 0401, patients enrolled in the EOC expansion cohorts were required to have ≥25% tumour cells FRα positive by the PS2+ scoring method. Data from this early study indicated that the strongest signals of mirvetuximab soravtansine activity were associated with higher FRα expression.

The Phase 3 study 0403 used a minimum threshold of ≥50% of tumour cells as determined by the 10X scoring method for study eligibility.

Analysis of study 0403 per the original statistical analysis plan (10X scoring method) as well as the exploratory PS2+ analysis, supported the decision to raise the threshold for FRα positivity to ≥75% (high expression) by the PS2+ method for future studies of MIRV. Studies 0417 and 0416 used a positivity threshold of ≥75% by the PS2+ method.

In the IMGN-0401 (FIH) study, FOLR1 levels were assayed in all 749 patients by IHC at Ventana's CAP/CLIA lab using Ventana's FOLR1 assay developed with the ImmunoGen's mouse monoclonal anti-human FOLR1 antibody (clone 353.2.1/ FOLR1 2.1). FOLR1 expression was quantified by board

certified pathologist using an H score scoring algorithm (1* % cells with 1+ staining; +2* % cells with 2+ staining; +3* % cells with 3+ staining). 710 (95%) of the FOLR1 results were evaluable for tumour cell membrane and cytoplasm staining. Membrane and cytoplasmic staining were scored separately, and only membrane staining was used to determine the FOLR1. 666 of the cases were submitted for prospective testing for trial enrolment and 83 cases were submitted for retrospective analysis of FOLR1 after enrolment. Cases were excluded from examination for several reasons, including insufficient tumour content, insufficient viable tumour cells, and loss of tissue from the slide. Of the 636 prospectively tested and reported specimens that were evaluable for tumour cell membrane staining, approximately 18% of the cases were devoid of FOLR1 expression (H score = 0). In the 82% of cases demonstrating FOLR1 expression a wide distribution of H scores from 1 to 300 was observed. Of the 74 retrospective cases evaluable for tumour cell membrane staining, approximately 22% of the cases were devoid of FOLR1 expression (H score = 0). In the 78% of cases demonstrating FOLR1 positivity a wide distribution of H scores from 1 to 280 was observed.

According to IMH28-026 (Exploratory biomarker studies in FIH 0401 study), for the concordance of expression in archival and pre-dose biopsy samples, 27 patients met enrolment criteria of ≥25% of tumour cells with ≥2+ staining intensity, based on FRα expression of their archival tissue samples. Six patients (22%) did not have pre-dose biopsies evaluable for FRα IHC due to insufficient tumour cells present. Of the 21 evaluable pre-dose samples, 15 met the eligibility criteria, resulting in 71% concordance with archival tumour. The remaining 6 were scored as very low/negative (i.e., <25% with ≥2+ staining).

Further according to Exploratory biomarker studies in FIH 0401 study, biopsies were taken at Cycle 2 Day 8 in order to evaluate any changes in FRα receptor expression while patients were undergoing MIRV therapy. Seventeen matched pre- and post-treatment biopsy pairs were available for analysis. In the majority of the cases, FRα expression remained stable following two doses of MIRV, although reductions in post-treatment levels were seen in some patients (primarily low expressors).

The **cut-offs** for negative (<25%), low (25%-49%), medium (50%-74%), and high (≥75%) have been originally set by the applicant in the FIH (0401) trial. FOLR1 expression was initially quantified by board certified pathologist using an H score scoring algorithm. For the purposes of data analysis H-Score readouts were replaced during the FIH study by a scoring system that only included the high intensity 2+ and 3+ FOLR1 membrane staining.

The central efficacy parameter in the FIH trial is ORR. ORR was 24% in low, 27% in medium, and 29% in high FOLR1 expressors, but the actual patient numbers are low and the differences small. In addition to FOLR1 expression the efficacy of MIRV in PROC correlated to the number of prior treatment lines: with 1-3 prior lines and low expression ORR was 33%, while 47% with medium and high expression. Some responses were also seen in low expressors. The reasons for this are unclear. Theoretically other factors associated to responses could be e.g., clonal heterogeneity within the patient's tumour burden and errors in scoring. With >3 prior lines for PROC, ORR was 11% for low expression and 10% for medium and high. Thus, with heavy prior treatment even the medium and high expressors have a low ORR, possibly related to e.g. resistance mechanisms. The 47% ORR in PROC with 1-3 prior lines in medium and high expressors in the FIH trial was considered by the applicant to compare favourably to literature data for chemotherapies used in PROC.

The FIH study results were used to plan the **phase 3 FORWARD 1** (0403) study. It enrolled PROC patients with FR alpha expression of ≥50% of tumour cells with any FR alpha membrane staining visible at ≤ 10X microscope objective. In the ITT population there was no difference in PFS_{BICR} (HR 0.981 (95% CI: 0.734, 1.310). For the FR alpha high population (≥ 75%), the results demonstrated a numerical benefit of MIRV (HR 0.693 (95% CI: 0.480, 1.00). Subgroup analyses in the FR alpha medium (50-74%) population show a PFS_{BICR} 2.9 months with MIRV and 5.6 months with ICC.

ORR_{BICR} does not differ in FR alpha high and FR alpha medium (24% and 20%, respectively), nor in ITT population (ORR 22%). An exploratory post hoc analysis using the PS2+ method for rescoring showed that 114 patients would have been scored as FR alpha <50% and would not have been enrolled. With PS2+ rescoring the population with FR alpha ≥75% had a median PFS_{BICR} of 5.6 months with MIRV vs 3.2 months with ICC, HR 0.549.

For **SORAYA** (study 0417), the PS2+ scoring method and a higher bar (≥75%) were adopted for enrolment. In this single arm study an ORR_{INV} of 32.4% was reported.

Also in **MIRASOL** (study 0416), the PS2+ scoring and the bar of at least 75% were used. The study reached the primary endpoint of PFS_{INV} (HR 0.65. 95% (CI: 0.521, 0.808)). Also the difference in OS was statistically significant. However, the study suffers from difference in proportion of early drop out and open label bias. Despite central assessment 25% of patients were charted to have FR alpha expression exactly as 75%. This is likely due to the fact. that the pathologists were not obliged to provide data beyond binary assessment, and thus the results in this category cannot be reliably assessed. For PFS_{INV} with a 06 March 2023 cut-off, the HR ranges from 0.47 (FR alpha ≥95%) to 0.86 (FR alpha >75%, ≤85%). However, in the FR alpha >75%, ≤85% category the time difference in mPFS is only 0.33 months. For OS, HR was 0.4 for patients with FR alpha ≥95%, while there is no effect in FR alpha >85%, <95% (HR 1.02). The updates with the 27 October 2023 cut-off provided overall similar results. Overall, some predictive nature of FR alpha level on efficacy can be concluded from the provided results, which is plausible. It is important to note that no sign of detrimental effect is observed in any of the provided analyses, although the benefit if MIRV appears minimal as compared to ICC with FR alpha expression below 85%.

Central assessment: In the FIH and FORWARD studies the FR alpha expression was evaluated at a central lab. For SORAYA the FR alpha evaluated was conducted at 2 HistoGeneX (now named CellCarta) central laboratories. For MIRASOL, the evaluation of FR alpha was also made at the central laboratories.

In the FIH CSR, the applicant referred to scientific literature concerning FOLR1 expression. E.g. cited reports include data, that recurrent tumours retain the expression comparably by serial biopsy sampling. Exploratory analyses in the FIH trial included an analysis for soluble FOLR1 biomarker. ORR_{INV} demonstrated a trend for FOLR1 level quartiles corresponding to response (<Q1 ORR INV 16%, Q1-Q2 27%, ≥Q2 to <Q3 32%, ≥Q3 43%).

Overall the dossier does not provide a comprehensive view of the types of samples used for enrolment in the central clinical studies (whether the samples were from initial diagnosis, from the 1st relapse, or after multiple lines of therapy).

In conclusion, the FORWARD 1 trial failed to reach its primary endpoint in the ITT population (≥50%) and in the FR alpha high (≥75%) population with any FR alpha membrane staining visible at ≤ 10X microscope objective. MIRASOL met its primary endpoint when enrolling with the cutoff ≥75% and PS2+ scoring.

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Table 45: Efficacy analyses performed

Efficacy Analysis Description	Study	Number of Patients per Study (n)	Total Patients per Group (n)	Analysis Endpoints
All patients randomized to mirvetuximab soravtansine in Study 0416	0416	227	227	PFS, ORR, DOR, and OS for all analyses
All patients who received prior bevacizumab, including all patients in Study 0417 and those randomized to mirvetuximab soravtansine in Study 0416	0417	106	106 + 138 (Pooled)	
	0416	138		
All bevacizumab-naïve patients randomized to mirvetuximab soravtansine in Study 0416	0416	89	89	

Abbreviations: DOR = duration of response; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

Table 46: *Kaplan-Meier PFS (ITT population)*

Assessment	Efficacy Analysis Populations		
	Study 0416 (n = 227)	Prior Bevacizumab: Study 0416 and Study 0417 (n = 244)	Bevacizumab-naïve: Study 0416 (n = 89)
	INV	INV	INV
Events, n (%)	176 (77.5)	206 (84.4)	65 (73.0)
Kaplan-Meier PFS estimates (months)			
Median (95% CI)	5.62 (4.34, 5.95)	4.34 (4.04, 5.32)	7.03 (5.59, 8.41)

Abbreviations: INV = investigator-assessed; ITT = intent-to-treat; PFS = progression-free survival.

Table 47: ORR by INV assessment (ITT population)

	Efficacy Analysis Populations		
	Study 0416 (n = 227)	Prior Bevacizumab: Study 0416 and Study 0417 (n = 244)	Bevacizumab-naïve: Study 0416 (n = 89)
ORR, n (%) [a]	96 (42.3)	89 (36.5)	41 (46.1)
95% CI [b]	(36, 49)	(30, 43)	(35, 57)

Abbreviations: CR = complete response; ITT = intent-to-treat; ORR = objective response rate; PR = partial response.

[a] ORR is defined as the proportion of patients with a best overall response of CR or PR.

[b] The 95% CI for ORR is estimated using the Clopper-Pearson method.

Table 48: ***OS (ITT population)***

Assessment	Efficacy Analysis Populations		
	Study 0416 (n = 227)	Prior Bevacizumab: Study 0416 and Study 0417 (n = 244)	Bevacizumab-naïve: Study 0416 (n = 89)
Deaths, n (%)	90 (40)	129 (53)	23 (26)
Kaplan-Meier estimates for OS (months)			
Median (95% CI)	16.46 (14.46, 24.57)	14.98 (12.12, 17.51)	20.24 (14.82, NE)

Abbreviations: NE = not evaluable; OS = overall survival.

2.6.5.6. Supportive studies

SORAYA (IMGN853-0417, study 0417)

Title: A Phase 3, Single Arm Study of Mirvetuximab Soravtansine in Advanced High-Grade Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancers with High Folate Receptor-Alpha Expression

Methods

All enrolled patients received MIRV 6 mg/kg AIBW IV Q3W until PD, unacceptable toxicity, withdrawal of consent, death, or until the sponsor terminated the study, whichever occurred first.

Tumor assessments, as radiologic tumour evaluation by CT or MRI of chest, abdomen, and pelvis was performed within 28 days before first dose of study drug and every 6 weeks (± 1 week) from C1D1 for the first 36 weeks on study and every 12 weeks (± 3 weeks) thereafter. Patients who discontinued study drug for reasons other than PD continued with tumour assessments until documentation of PD or the start of a new anticancer therapy, whichever came first.

- **Study Participants**

Key Inclusion Criteria (excerpt)

- Female patients ≥ 18 years of age.
- Patients must have had a confirmed diagnosis of high-grade serous epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer.
- Patients must have had platinum-resistant disease:
    - Patients who only had 1 line of platinum-based therapy must have received at least 4 cycles of platinum, must have had a response (complete response [CR] or partial response [PR]), and then progressed between > 3 months and ≤ 6 months after the date of the last dose of platinum.
    - Patients who had received 2 or 3 lines of platinum therapy must have progressed on or within 6 months after the date of the last dose of platinum.
    - Note: Progression was calculated from the date of the last administered dose of platinum therapy to the date of the radiographic imaging showing progression.

- Patient's tumor must have been positive for FRα expression as defined by the Ventana FOLR1 Assay.
- Patients must have received at least 1 but no more than 3 prior systemic lines of anticancer therapy, including at least 1 line of therapy containing bevacizumab, and for whom single-agent therapy was appropriate as the next line of treatment:

Companion diagnostic: ⩾ 75% of viable tumour cells must have exhibited level 2 and/or 3 membrane staining intensity using the Ventana FOLR1 assay, an IHC assay.

Key Exclusion Criteria (excerpt)

- Patients with endometrioid, clear cell, mucinous, or sarcomatous histology, mixed tumours containing any of the above histologies, or low-grade/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 had progressed within 3 months of the last dose of first-line platinum-containing chemotherapy.

- **Treatments:** all patients received single-agent MIRV at 6 mg/kg AIBW IV administered Q3W.

Premedication, **prophylactic use of corticosteroid eye drops**, and **lubricating artificial tears**: identical to MIRASOL.

Dose reduction schedule and dose modifications for MIRV-related AEs: identical to MIRASOL.

- **Objectives/Endpoints**

Primary:

- ORR, which includes best response of CR or PR, as assessed by the Investigator.

Key Secondary Objective

- Duration of response (DOR), defined as the time from initial Investigator-assessed response (CR or PR) until progressive disease (PD) as assessed by the Investigator.

Additional Secondary Objectives were

- TEAEs and laboratory test results, physical examination or vital signs
- CA-125 response by GCIG criteria
- PFS, defined as the time from first dose of MIRV until investigator-assessed radiological PD or death, whichever occurred first, and
- OS, defined as the time from first dose of mirvetuximab soravtansine until death.

Exploratory Objectives included e.g., intact ADC, total Ab, DM4, and S-methyl DM4 concentration data, seroconversion of ADA to MIRV and soluble FRα levels and their association to safety and efficacy.

- **Sample size**

Approximately 110 patients were to be enrolled so that a total of 105 patients were efficacy evaluable. A sample size of 105 efficacy evaluable patients achieves 90% power to detect a difference in ORR of 12% (24% vs 12%) using a 1-sided binomial test. The target significance level (1-sided α level) was 0.025. The actual significance level achieved by this test was 0.0242. These results assumed that the ORR is 12% under the null hypothesis and 24% under the alternative hypothesis.

- **Randomization** and **blinding** were not applicable in this single-arm, open-label study.
- **Statistical methods**

The **Screened** population included all patients entered into the clinical database who had signed an informed consent.

The **Efficacy Evaluable** population was defined as all patients in the Safety population who had measurable disease at Baseline.

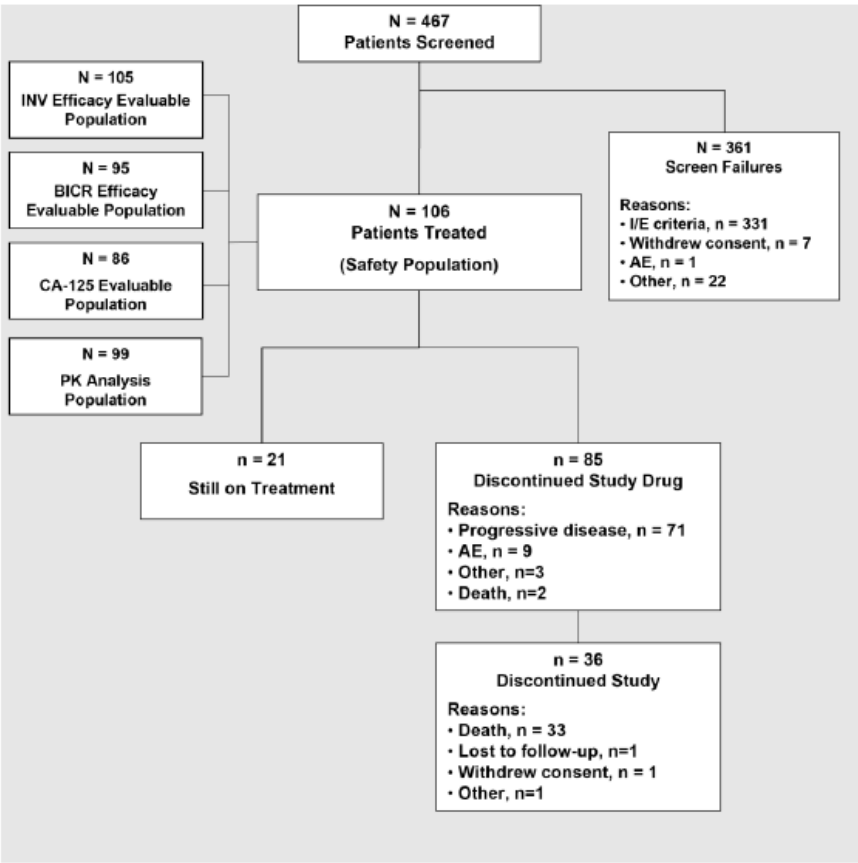
- Efficacy Evaluable population for efficacy measurements based on INV assessment (ORR, DOR, PFS_{INV}): all patients in the Safety population who had measurable disease at Baseline by INV.
- Efficacy Evaluable population for efficacy measurements based on BICR assessment (ORR, DOR, PFS_{BICR}): all patients in the Safety population who had measurable disease at Baseline by BICR.

All patients who received at least 1 dose of MIRV were included in the **Safety population**. Other populations were **CA-125–Evaluable population** and **Pharmacokinetic Analysis Population**.

Results

Participant flow

Figure 31: *Participant flow in SORAYA*



Abbreviations: AE = adverse event; BICR = blinded independent central review; CA-125 = cancer antigen 125; I/E = inclusion/exclusion; INV = investigator; PK = pharmacokinetic(s); RECIST = Response Evaluation Criteria in Solid Tumors; ULN = upper limit of normal.
Note: The Safety population is defined as patients who received at least 1 dose of mirvetuximab soravtansine.
Note: The INV Efficacy Evaluable population is defined as all patients in the Safety population who had measurable disease at baseline by investigator assessment per RECIST 1.1.
Note: The BICR Efficacy Evaluable population is defined as all patients in the Safety population who had measurable disease at baseline by BICR per RECIST 1.1.
Note: The CA-125-Evaluable population is defined as all patients in the Safety population whose pretreatment sample was ≥ 2.0 times the ULN, within 2 weeks prior to first dose of mirvetuximab soravtansine, and who had at least 1 postbaseline CA-125 evaluation.
Note: The PK Analysis population is defined as all patients who had at least 1 non-missing PK concentration data point.

The most common reason for screen failure was FRα negativity by the Ventana FOLR1 Assay (70%).

Table 49: Patient disposition in SORAYA

	All Patients (N = 106) n (%)
Patients treated (Safety Population)	106 (100)
INV Efficacy Evaluable Population	105 (99)
BICR Efficacy Evaluable Population	95 (90)
Patients still on study drug	21 (20)
Primary reason for study drug discontinuation	85 (80)
Adverse event	9 (8)
Death	2 (2)
PI discretion	0 (0)
Patient withdrew consent to treatment	0 (0)
Patient withdrew consent to treatment and follow-up	0 (0)
Progressive disease	71 (67)
Radiographic	62 (58)
Clinical	9 (8)
Protocol deviation	0 (0)
Study terminated by sponsor	0 (0)
Other[a]	3 (3)
Entered response follow-up	20 (19)
Entered survival follow-up	57 (54)
Primary reason for study discontinuation	36 (34)
Death	33 (31)
PI discretion	0 (0)
Lost to follow-up	1 (1)
Withdrew consent	1 (1)
Study terminated by sponsor	0 (0)
Other[b]	1 (1)

Abbreviations: BICR = blinded independent central review; INV = investigator; PI = principal investigator.

[a] The primary reason for discontinuation of mirvetuximab soravtansine in these 3 patients was clinical deterioration/disease worsening.

[b] The primary reason for study discontinuation was that the patient failed to attend a scheduled visit and decided to withdraw from the study.

Recruitment

Planned: approximately 110 patients

Enrolled: 106 patients

1st patient enrolled: 23 July 2020

Date of last patient enrolled: not provided

Date last patient completed: ongoing

No interim analysis

Data cut-off for primary analysis: 16 November 2021

Date of CSR: 04 March 2022

This study was conducted at 72 global sites, of which 39 sites enrolled patients (North America [13 sites (United States)], Europe [25 sites: Belgium-3, Germany-2, Ireland-5, Israel-2, Italy-4, Spain-9], and Asia Pacific [1 site (Australia)]).

Conduct of the study

Original protocol: 23 October 2019 (no patients were enrolled under the original protocol)

Protocol amendments (only global amendments with excerpts)

Amendment 1 :18 December 2019 had the following main elements:

- Increase in the total number of enrolled/evaluable patients.
- Added an exploratory objective to evaluate tumour-based biomarkers predictive of response to MIRV.
- Added recommendation that patients who have discontinued study drug for reasons other than PD prior to Week 36 (from C1D1), and who have not received another anticancer therapy, be scanned every 6 weeks up to Week 36.
- Revised the definition of efficacy evaluable population.

Amendment 2: 28 August 20 had the following main elements:

- Updates to patient inclusion and exclusion criteria
- Clarification of pre-screening ICF
- Mirvetuximab soravtansine discontinuation criteria further defined
- CYP3A4/MRD1 interaction language updated
- Radiographical imaging assessment timing and details updated
- Recording of AEs/SAEs and retention of data updated.

Protocol compliance and deviations: 4 patients had major deviations related to protocol eligibility criteria:

- Patient 028-102 did not have measurable disease at Baseline as assessed by INV and was excluded from the primary efficacy analysis.
- Patient 825-102 had a platinum-free interval of 18.07 months.
- Patient 504-117 had received 4 lines of prior systemic therapy.
- Patient 502-103 had PD documented 2 months and 26 days after the last dose of 1st line platinum containing chemotherapy (i.e. patient was primary platinum-refractory).

Baseline data

Table 50: Demographic and baseline characteristics in SORAYA – safety population

	All Patients (N = 106)
Age (years)	
n	106
Mean (SD)	62 (10)
Median (min, max)	62 (35, 85)
Age Group, n (%)	
18-64	59 (56)
≥ 65	47 (44)

Table 51: Disease Characteristics, Prior Therapy, and Gene Mutations – Safety Population in SORAYA

	All Patients (N = 106)
Primary diagnosis, n (%)	
Epithelial ovarian	85 (80)
Primary peritoneal	12 (11)
Fallopian tube	8 (8)
Other[a]	1 (1)
Histology, n (%)	
High grade serous	106 (100)
Time since initial diagnosis (months)[b]	
n	92
Mean (SD)	32.3 (15.8)
Median (min, max)	31.3 (9.1, 93.8)
Stage at initial diagnosis, n (%)	
Stage I/II	2 (2)
Stage IIIA	6 (6)
Stage IIIB	5 (5)
Stage IIIC	52 (49)
Stage IV	40 (38)
Missing	1 (1)

	All Patients (N = 106)
Histologic grade, n (%)	
Well differentiated	3 (3)
Moderately differentiated	3 (3)
Poorly differentiated	49 (46)
Undifferentiated	0
Unknown	51 (48)
Prior radiotherapy, n (%)	7 (7)
Prior cancer-related surgery, n (%)	99 (93)
Prior systemic therapy, n (%)	
1	10 (9)
2	41 (39)
3	54 (51)
> 3	1 (1)[c]
Prior exposure to PARP inhibitors, n (%)	
Yes	51 (48)
No	51 (48)
Uncertain[d]	4 (4)
Prior exposure to doxorubicin, n (%)	75 (71)
Prior exposure to topotecan, n (%)	0
Prior exposure to taxanes, n (%)	103 (97)
Prior exposure to bevacizumab, n (%)	106 (100)
Primary platinum-free interval, n (%)[e]	
≤ 12 months	64 (60)
> 12 months	42 (40)
Platinum-free interval, n (%)[f]	
0-3 months	39 (37)
> 3-6 months	64 (60)
> 6 months[g]	3 (3)

	All Patients (N = 106)
Any BRCA mutations, n (%)	
Yes	21 (20)
BRCA1	15 (14)
BRCA2	6 (6)
No/Unknown	85 (80)
ECOG Performance Status, n (%)	
0	60 (57)
1	46 (43)

Abbreviations: min, max = minimum, maximum; SD = standard deviation.

[a] One patient (Patient 301-104) with primary diagnosis categorized as "other" had histopathology consistent with the inclusion/exclusion criteria (intraepithelial tubo-ovarian carcinoma) (Listing 16.2.4.4).

[b] Time since initial diagnosis is defined as the time from initial diagnosis to the date of the first treatment.

[c] Patient 504-117 received 4 lines of prior systemic therapy. This was documented as a protocol deviation. Please refer to the protocol deviation listing (Listing 16.2.2.2) for additional details.

[d] Uncertain: Patients who reported receiving a PARP inhibitor or placebo in a clinical trial.

[e] Time from last dose of the first-line platinum therapy to the date of radiographic disease progression and/or relapse following the first-line therapy.

[f] Time from last dose of the latest line platinum therapy to the date of radiographic disease progression and/or relapse following that line of therapy.

[g] Three patients had platinum-free intervals > 6 months: Two patients (Patient 003-108 and Patient 504-119) had a platinum-free interval of 6.01 months; 1 patient (Patient 825-102) had a platinum-free interval of 18.07 months. Please refer to the protocol deviation listing (Listing 16.2.2.2) for additional details about this patient.

Outcomes and estimation

Primary endpoint: ORR by INV

Table 52: Confirmed Objective Response Rate by Investigator – INV Efficacy Evaluable Population in SORAYA

	INV Efficacy Evaluable Population (N = 105)
Confirmed ORR, n (%)[a]	34 (32.4)
95% CI[b]	(23.6, 42.2)
Confirmed BOR, n (%)	
CR	5 (4.8)
PR	29 (27.6)
SD	48 (45.7)
PD	20 (19.0)
Not evaluable	3 (2.9)

Abbreviations: BOR = best overall response; CI = confidence interval; CR = complete response; INV = investigator; ORR = objective response rate; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

[a] ORR is defined as the proportion of patients with a confirmed CR or PR in the INV Efficacy Evaluable population.

[b] 95% exact confidence interval is estimated by Clopper-Pearson method. Clopper-Pearson exact CI.

Note: The denominator for the percentages is the number of patients in the INV Efficacy Evaluable population.

Note: Patients without at least 1 postbaseline RECIST assessment were treated as not evaluable.

Key secondary endpoint: DOR by INV

Table 53: Duration of Response Using RECIST by Investigator – INV Efficacy Evaluable Population with Confirmed Complete or Partial Response in SORAYA

Measure	All Responders (N = 34)
DOR events, n (%)	
Radiological progression	18 (52.9)
Death without documented progression	0
Censored, n (%)	
New anticancer therapy prior to progression or death	1 (2.9)
No death or progression	15 (44.1)
Progression or death after missing 2 or more consecutive radiological assessments	0
Kaplan-Meier estimates for DOR (months)	
Median (95% CI)	5.9 (5.6, 7.7)
1st quartile (95% CI)	4.2 (2.8, 5.7)
3rd quartile (95% CI)	7.7 (6.9, NR)
Range	1.4+, 9.8

Abbreviations: + = censored; CI = confidence interval; CR = complete response; DOR = duration of response; INV = investigator; NR = not reached; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors.
Note: DOR is defined as the time from the date of first response (CR or PR) to the date of PD or death from any cause, whichever occurred first.

CA-125 response: Of the 106 patients, 86 (81%) had a pretreatment sample that was ≥2 times the ULN within 2 weeks prior to the 1st dose of MIRV and had ≥ 1 postbaseline CA-125 evaluation. The GCIG CA-125 response rate was 46.5%.

PFS and OS: The median PFS in the INV Efficacy Evaluable population was 4.3 months (95% CI: 3.7 to 5.1 months). With a median follow-up of 8.5 months, 31% of patients had died, and median OS was not reached.

ORR by BICR and DOR by BICR (sensitivity analyses): The ORR_{BICR} was based on 95 efficacy evaluable population. The confirmed ORR_{BICR} was 31.6% (30 patients) (95% CI: 22.4% to 41.9%). 5 patients had a confirmed response of CR and 25 patients of PR. Among the 30 patients in the BICR Efficacy Evaluable population with a confirmed CR or PR, the median DOR per RECIST was 11.7 months (95% CI: 5.0 months, not reached).

Based on updated information with data as of 29 April 2022, median DOR_{INV} was 6.9 months (95% CI 5.6, 9.7) and by BICR not reached. Radiological progression was recorded for 70.6% by INV and 31% by BICR.

Ancillary analyses

Table 54: ORR by INV – subgroup analysis in SORAYA

Clinical Parameter Subgroup	N	ORR, n (%)	95% CI
INV Efficacy Evaluable Population	105	34 (32.4)	23.6, 42.2
Number of prior lines of therapy[a]			
1 or 2	51	18 (35.3)	22.4, 49.9
3	53	16 (30.2)	18.3, 44.3
Prior exposure to PARPi[b]			
Yes	50	19 (38.0)	24.7, 52.8
No	51	14 (27.5)	15.9, 41.7

Abbreviations: CI = confidence interval; CR = complete response; INV = investigator; N = total number of patients; n = number of patients with an objective response; ORR = objective response rate; PARPi = PARP inhibitor; PR = partial response.

[a] One patient with 4 prior lines of therapy is not included in the categories shown in this table. This patient did not have an objective response as assessed by the investigator.

[b] Four patients with uncertain exposure (reporting receiving a PARP inhibitor or placebo in a clinical trial) are not included in the categories shown in this table. One of these patients had an objective response as assessed by the investigator.

Note: ORR is defined as the proportion of patients with a confirmed CR or PR in the INV Efficacy Evaluable population.

Note: 95% exact CI is estimated by Clopper-Pearson method. Clopper-Pearson exact CI.

Table 55: DOR by INV – subgroup analysis in SORAYA

Clinical Parameter Subgroup	N	Events (%)	Median (95% CI) (months)
INV Efficacy Evaluable Population	34	18 (52.9)	5.9 (5.6, 7.7)
Number of prior lines of therapy			
1 or 2	18	8 (44.4)	5.9 (4.2, NR)
3	16	10 (62.5)	7.0 (3.5, NR)
Prior exposure to PARPi[a]			
Yes	19	11 (57.9)	5.7 (3.5, NR)
No	14	7 (50.0)	5.9 (2.8, NR)

Abbreviations: BICR = blinded independent central review; CI = confidence interval; CR = complete response; DOR = duration of response; INV = investigator; N = total number of patients with an objective response; NR = not reached; PARPi = PARP inhibitor; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors.

[a] One patient with uncertain exposure (reporting receiving a PARP inhibitor or placebo in a clinical trial) who had a confirmed response by investigator assessment is not included in the categories shown in this table.

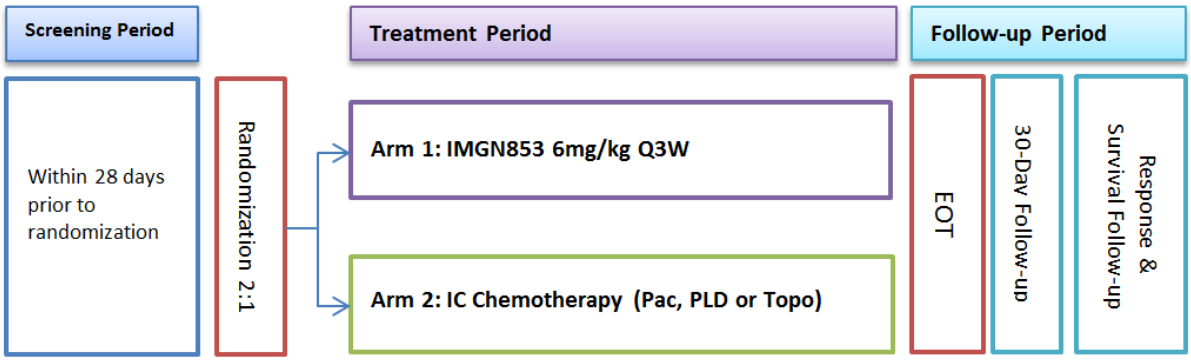
Note: DOR is defined as the time from the date of first response (CR or PR) to the date of PD or death from any cause, whichever occurred first.

FORWARD 1 (IMGN853-0403, study 0403)

Study 0403 was a global Phase 3, randomized, open-label, multi-center study designed to evaluate the efficacy and safety of MIRV 6 mg/kg AIBW IV Q3W compared to ICC (paclitaxel, PLD, or topotecan) in patients with FRα-positive PROC who had received 1 to 3 prior systemic anticancer therapies.

Initially this was a 2-stage, Phase 2 study to select the dosing schedule for MIRV (Stage 1) and to compare the efficacy of MIRV with ICC (Stage 2) in patients with advanced PROC. Following an IDMC review, amendm. 5 closed enrollment to Stage 1, and the dosing schedule for MIRV was selected (6 mg/kg AIBW Q3W) on the basis of IMGN853-0401 safety data and the design was changed from Phase 2 to a Phase 3 study.

Figure 32: *Study design of phase 3 in FORWARD*



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

Methods

- **Study population:**

Key inclusion criteria (excerpt):

- Patients must have had platinum-resistant, pathologically documented, definitively diagnosed advanced EOC, primary peritoneal cancer, or fallopian tube cancer.
    - Platinum-resistant ovarian cancer defined as progression within 6 months from completion of a minimum of 4 cycles of platinum-containing therapy.
- Patients must have received at least 1 but no more than 3 prior systemic lines of anti-cancer therapy.
- Patients must have had confirmation of FRα positivity by Ventana IHC test in archival or fresh biopsy tumour sample.
    - Minimum FRα expression level allowed was ≥ 50% of tumour cells with any FRα membrane staining visible at ≤ 10X microscope objective.
    - Patients with FR alpha expression on ≥ 50% to < 75% of tumour cells with any FRα membrane staining visible were considered to have a 'medium' level of FRα expression and those with FRα expression on ≥ 75% of tumour cells with any FRα membrane staining visible a 'high' level of FRα expression.

Key exclusion criteria (excerpt):

- Patients with clear cell, mucinous histology, mixed histology with mucinous component, sarcoma, sarcomatous component, or low-grade ovarian cancer
- Patients with primary platinum-refractory disease.

During the **Phase 3** portion of the study, patients were **randomized** 2:1 into 2 groups:

• Arm 1: MIRV 6 mg/kg AIBW Q3W

• Arm 2: ICC (weekly paclitaxel Q4W, or pegylated liposomal doxorubicin Q4W, or topotecan on Days 1, 8, and 15 every 4 weeks or for 5 consecutive days Q3W).

Randomization was **stratified** by number of prior lines of therapy (1 or 2 versus 3), FR alpha levels (high or medium expression), and ICC (paclitaxel, pegylated liposomal doxorubicin, or topotecan).

Open-label study

- **Objectives/endpoints:**

The **primary objective/endpoint** was BICR-assessed PFS in:

- All patients randomized to the study (ITT population)
- Patients with high FR alpha expression

PFS was defined as the time from randomization to the first documentation of PD or death due to any cause. Scan intervals were fixed at every 6 weeks for the first 36 weeks and then every 12 weeks thereafter.

Key secondary objectives/endpoints:

- ORR (BICR-assessed with investigator-assessed ORR as a sensitivity analysis)
- OS: the time from date of randomization until the date of death
- Primary PRO: QLQ-OV28 questionnaire.

Other secondary objectives/endpoints included e.g. safety and tolerability, DOR_{BICR} (DOR_{INV} as sensitivity analysis), CA-125 response, $PFSI_{NV}$, PK, ADAs, and PROs.

Sample size determination:

The study was designed to test the null hypothesis that the survival function for PFS was the same between the MIRV arm and the ICC arm versus the alternative hypothesis that the survival function for PFS was different between the MIRV and ICC arms. The Hochberg procedure was used to control the study-wise type I error.

Approximately 333 patients were to be randomized 2:1 (222 MIRV arm to 111 IC arm). The final analysis was to be conducted when at least 236 PFS events were observed. The study had 91% power to detect a HR of 0.583 in the FRα-high expression subgroup and 96% power in all randomized patients at a study-wise alpha level of 5%; the study had a 39% probability of stopping for futility at the interim analysis under the null hypothesis. Sample size and power were determined with the following assumptions:

• Median PFS for the IC arm is 3.5 months.

- Median PFS for the MIRV arm is 6 months.
- Exponential distribution for both event and censoring processes.
- Ratio of FRα high to FRα medium is 2:1.
- Annual censoring rate is 20% in both arms.

Amendments: The original protocol was approved on 18 August 2015, and the conduct of the study was modified by 8 global and 2 regional amendments to the original protocol.

Results**Patient disposition**

Table 56: Patient disposition – ITT population in FORWARD 1

Parameter	MIRV (N=248)	IC Chemotherapy			
		Total (N=118)	PAC (N=37)	PLD (N=54)	TOPO (N=27)
Randomized (ITT Population)	248	118	37	54	27
Treated (Safety Population)	243 (98)	109 (92)	33 (89)	50 (93)	26 (96)
Patients Still on Active Treatment	27 (11)	2 (2)	1 (3)	1 (2)	0
Primary Reason for Study Treatment Discontinuation	216 (87)	107 (91)	32 (86)	49 (91)	26 (96)
Adverse Event	15 (6)	10 (8)	5 (14)	3 (6)	2 (7)
Death	6 (2)	3 (3)	1 (3)	1 (2)	1 (4)
PI Discretion	0	7 (6)	1 (3)	6 (11)	0
Patient Withdrew Consent to Treatment	4 (2)	3 (3)	1 (3)	1 (2)	1 (4)
Patient Withdrew Consent to Treatment and Follow-up	6 (2)	1 (1)	0	1 (2)	0
Progressive Disease	185 (75)	83 (70)	24 (65)	37 (69)	22 (81)
Radiographic	165 (67)	68 (58)	21 (57)	31 (57)	16 (59)
Clinical	20 (8)	15 (13)	3 (8)	6 (11)	6 (22)
Patients Entered Post-Treatment Follow-up	192 (77)	93 (79)	30 (81)	39 (72)	24 (89)
Patients Entered Survival Follow-up	146 (59)	61 (52)	17 (46)	26 (48)	18 (67)
Patients Discontinued from Study	119 (48)	63 (53)	17 (46)	27 (50)	19 (70)
Primary Reason for Study Discontinuation					
Death	96 (39)	50 (42)	13 (35)	19 (35)	18 (67)
PI Discretion	1 (<1)	0	0	0	0
Lost to Follow-up	2 (1)	0	0	0	0
Withdrew Consent	16 (6)	9 (8)	2 (5)	6 (11)	1 (4)
Other	4 (2)	4 (3)	2 (5)	2 (4)	0

Abbreviations: IC = investigator's choice; MIRV = mirvetuximab soravtansine; PAC = paclitaxel; PI = Principal Investigator; PLD = pegylated liposomal doxorubicin; TOPO = topotecan.

Note: 1 patient randomized to paclitaxel received topotecan so the safety population in subsequent tables shows the actual treated number in the IC Chemotherapy group.

Baseline data

Table 57: Demographic and baseline characteristics – ITT population in FORWARD 1

Parameter	MIRV (N=248)	IC Chemotherapy			
		Total (N=118)	PAC (N=37)	PLD (N=54)	TOPO (N=27)
Age (years)					
N	248	118	37	54	27
Mean (SD)	62.7 (10.29)	62.9 (10.51)	60.7 (11.89)	63.4 (10.63)	65.0 (7.71)
Median	64.0	64.0	60.0	63.0	67.0
Min, Max	34, 89	31, 86	38, 86	31, 84	49, 78
Age Group, n (%)					
18-64	133 (54)	61 (52)	20 (54)	30 (56)	11 (41)
≥ 65	115 (46)	57 (48)	17 (46)	24 (44)	16 (59)
Sex, n (%)					
Female	248 (100)	118 (100)	37 (100)	54 (100)	27 (100)
Of Childbearing Potential	0	0	0	0	0
Ethnicity, n (%)					
Hispanic or Latino[a]	12 (5)	9 (8)	2 (5)	5 (9)	2 (7)
Not Hispanic or Latino	225 (91)	102 (86)	34 (92)	44 (81)	24 (89)
Not Reported	11 (4)	7 (6)	1 (3)	5 (9)	1 (4)
Race, n (%)					
White	225 (91)	105 (89)	36 (97)	45 (83)	24 (89)
Black or African American	7 (3)	3 (3)	1 (3)	1 (2)	1 (4)
Asian	6 (2)	2 (2)	0	2 (4)	0
American Indian or Alaskan Native	0	1 (1)	0	0	1 (4)
Other	2 (1)	2 (2)	0	2 (4)	0
Not Reported	8 (3)	5 (4)	0	4 (7)	1 (4)
Height (cm)					
n	243	109	33	50	26
Mean (SD)	161.02 (6.567)	161.35 (6.215)	161.23 (4.841)	162.01 (6.925)	160.21 (6.372)
Median	161.00	162.00	162.00	163.00	159.90

Parameter	MIRV (N=248)	IC Chemotherapy			
		Total (N=118)	PAC (N=37)	PLD (N=54)	TOPO (N=27)
Min, Max	145.0, 180.3	144.8, 181.0	150.0, 172.0	145.0, 181.0	144.8, 170.2
Baseline Weight (kg)					
n	243	109	33	50	26
Mean (SD)	70.15 (16.045)	71.46 (17.630)	70.07 (16.831)	71.38 (18.013)	73.38 (18.377)
Median	67.00	69.00	66.00	68.85	71.40
Min, Max	36.1, 126.1	43.0, 135.7	47.0, 135.7	43.0, 124.8	48.0, 117.7

Abbreviations: IC = investigator's choice; Max = maximum; Min = minimum; MIRV = mirvetuximab soravtansine; PAC = paclitaxel; PLD = pegylated liposomal doxorubicin; TOPO = topotecan.

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

Note: Baseline adjusted ideal body weight for the MIRV group and baseline body surface area for the IC Chemotherapy group is summarized in the source table.

Table 58: Disease characteristics and prior therapy – ITT and FR alpha high populations in FORWARD 1

Parameter	All Patients		FRα-High	
	MIRV (N=248)	IC Chemotherapy (N=118)	MIRV (N=147)	IC Chemotherapy (N=71)
Primary Diagnosis, n (%)				
Epithelial Ovarian	206 (83)	105 (89)	122 (83)	65 (92)
Fallopian Tube	14 (6)	5 (4)	10 (7)	1 (1)
Primary Peritoneal	27 (11)	8 (7)	14 (10)	5 (7)
Other[a]	1 (<1)	0	1 (1)	0
Histology, n (%)				
High Grade Serous	245 (99)	114 (97)	147 (100)	69 (97)
Endometrioid	0	1 (1)	0	0
Serous Adenocarcinoma	2 (1)	3 (3)	0	2 (3)
Mixed	1 (<1)	0	0	0
Stage at Initial Diagnosis, n (%)				
Missing	6 (2)	0	2 (1)	0
Stage IC	5 (2)	2 (2)	1 (1)	1 (1)
Stage II (A/B/C)	7 (3)	3 (3)	3 (2)	2 (3)
Stage III A/B	31 (13)	12 (10)	22 (15)	6 (8)
Stage IIIC	128 (52)	67 (57)	76 (52)	42 (59)
Stage IV	71 (29)	34 (29)	43 (29)	20 (28)
Extent of Disease (for the selected sites below only), n (%)				
Liver	79 (32)	51 (43)	47 (32)	31 (44)
CNS/Brain	0	0	0	0
Bone	6 (2)	4 (3)	4 (3)	1 (1)

Parameter	All Patients		FRα-High	
	MIRV (N=248)	IC Chemotherapy (N=118)	MIRV (N=147)	IC Chemotherapy (N=71)
Prior Anti-cancer Therapies, n (%)				
Paclitaxel	238 (96)	113 (96)	140 (95)	68 (96)
Bevacizumab	121 (49)	55 (47)	72 (49)	31 (44)
Doxorubicin	114 (46)	52 (44)	62 (42)	30 (42)
PARP Inhibitors[b]	44 (18)	19 (16)	30 (20)	11 (15)
Topotecan	1 (<1)	0	1 (1)	0
Platinum-Free Interval[c], n (%)				
0-3 months	97 (39)	45 (38)	62 (42)	28 (39)
3-6 months	141 (57)	68 (58)	78 (53)	40 (56)
≥ 6 months[d]	10 (4)	5 (4)	7 (5)	3 (4)
Any *BRCA* Mutation, n (%)				
BRCA1	17 (7)	5 (4)	11 (7)	5 (7)
BRCA2	6 (2)	3 (3)	5 (3)	1 (1)
ECOG performance status, n (%)				
0	141 (57)	60 (51)	88 (60)	36 (51)
1	106 (43)	57 (48)	58 (39)	34 (48)
Time since Initial Diagnosis[e] (months)				
Median	24.8	30.6	24.0	28.3
Min, Max	6.9, 128.1	7.2, 119.3	7.4, 128.1	7.2, 119.3

Abbreviations: CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; IC Chemotherapy = investigator's choice of select chemotherapies (paclitaxel, pegylated liposomal doxorubicin, or topotecan); Max = maximum; Min = minimum; MIRV = mirvetuximab soravtansine; PARP = poly (ADP-ribose) polymerase; PLD = pegylated liposomal doxorubicin.

[a] Includes 1 patient with a diagnosis of 'Other; tubal/ovarian'.

[b] Includes ~6% of patients on both treatment arms with an unknown prior exposure to a PARPi based on participation in a previous blinded investigational study.

[c] Time from last dose of prior platinum therapy to date of progressive disease or relapse.

[d] Patients in this category represent protocol deviations.

[e] Time since initial diagnosis is defined as the time from initial diagnosis to the date of randomization.

Summary of primary PFS per BICR endpoint:

The log-rank p-value (stratified by factors used for randomization) for PFS_{BIRC} was 0.897 in the ITT population and 0.049 in the FRα-high population. Because the larger of the 2 p-values (0.897) is > 0.05, Hochberg procedure required that the smaller of the 2 p-values (0.049) must be ≤ 0.025 to meet statistical significance. Thus, the primary endpoint of PFS_{BIRC} did not meet statistical significance in ITT population nor in FRα-high expression subgroup.

• The median PFS_{BIRC} in the ITT population in patients in MIRV arm was 4.1 months (95% CI 3.75, 4.53) vs 4.4 months (95% CI 2.83, 5.59) in ICC (p 0.897; HR 0.981).

• The median PFS_{BIRC} in the FRα-high population in patients in MIRV arm was 4.8 months (95% CI: 4.11, 5.68) vs 3.3 months (95% CI: 1.97, 5.59) in ICC (p 0.049; HR 0.693).

Key secondary endpoint: ORR by BIRC and by investigator

Table 59: Key secondary endpoint: ORR by BIRC and by investigator - FORWARD 1

Endpoints	ITT Population		FRα-High Population	
	Mirvetuximab Soravtansine (N = 248)	IC Chemotherapy (N = 118)	Mirvetuximab Soravtansine (N = 147)	IC Chemotherapy (N = 71)
ORR (BICR-assessed), n (%) [95% CI]	55 (**22**) [17.2, 27.9]	14 (**12**) [6.6, 19.1]	35 (**24**) [17.2, 31.5]	7 (**10**) [4.1, 19.3]
CR	11 (4)	4 (3)	8 (5)	1 (1)
PR	44 (18)	10 (8)	27 (18)	6 (8)
p-value (2-sided, stratified CMH)[a]	0.015		0.014	
ORR (investigator-assessed), n (%) [95% CI]	71 (29) [23.1, 34.7]	19 (16) [10.0, 24.0]	43 (29) [22.0, 37.3]	9 (13) [6.0, 22.7]
CR	7 (3)	2 (2)	6 (4)	0
PR	64 (26)	17 (14)	37 (25)	9 (13)
p-value (2-sided, stratified CMH)[a]	0.008		0.007	

Abbreviations: BICR = blinded independent central review; CMH = Cochran-Mantel-Haenszel; CR = complete response; FRα = folate receptor alpha; IC = investigator's choice (of select chemotherapies, ie, paclitaxel, PLD, or topotecan); ITT = intent-to-treat; ORR = objective response rate; PLD = pegylated liposomal doxorubicin; PR = partial response.

[a] The CMH tests for differences between treatment groups were stratified by factors used for randomization.

Key secondary endpoint: OS

ITT population: 96 of 248 patients (39%) in MIRV arm died, while 50 of 118 patients (42%) in ICC arm died. In MIRV arm the median OS was 16.4 months (95% CI: 12.81, -) vs 14.0 months (95% CI: 11.01, -) (p 0.248; HR 0.815) in ICC arm.

FR alpha high population: 50 of 147 patients (34%) with FRα-high expression in MIRV arm died, while 33 of 71 patients (46%) in ICC arm died. In MIRV arm, the median OS was not reached (95% CI: 12.58, not estimable) vs 11.8 months (95% CI: 9.20, not estimable) (p 0.033; HR 0.618) in ICC arm.

With clinical cut-off date 18 March 2020, in the ITT population 152 of 248 patients (61%) in MIRV arm died, while 75 of 118 patients (64%) in ICC arm died. In MIRV arm, the median OS was 15.57 months (95% CI: 12.85, 18.04) vs 13.93 months (95% CI: 11.40, 18.50) (p 0.276; HR 0.855) in ICC. For the FR alpha high population, 82 of 147 patients (56%) in MIRV arm died, while 45 of 71 patients (63%) in

ICC arm died. In patients with FRα-high expression in MIRV arm, the median OS was 17.31 months (95% CI: 12.81, 20.50) vs 12.02 months (95% CI: 9.20, 18.07) (p 0.063; HR 0.706) in ICC.

Key secondary endpoint: EORTC QLQ-OV28

The proportion of subjects who improved by ≥15 points on the Abdominal/GI scale at Week 8/9 was higher in MIRV arm compared to ICC arm (31.7% vs 14.0%, p 0.0162). A similar difference was observed in the FRα-high population (27.3% vs 13.3%), but it did not reach statistical significance (27.3% vs 13.3%; p 0.1426).

Subgroup analyses are not shown.

FIH (IMGN853-0401, study 0401)

A Phase 1, **First-In-Human** Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of IMGN853 in Adults with Ovarian Cancer and Other FOLR1-Positive Solid Tumours.

Study was designed to establish MTD and RP2D of MIRV when given IV as a single agent in adult patients with FRα-positive solid tumours who had relapsed or were refractory to standard therapies. FRα positivity for EOC expansion cohorts was defined as ≥ 25% cells stained at 2+ intensity by a Ventana FOLR1 assay.

The study consisted of 2 stages: dose escalation and dose expansion. For results of dose escalation phase see also Chapter Clinical efficacy, Dose-response studies.

The dose-escalation phase evaluated 2 regimens (Schedule A [Q3W] and Schedule B [QW]) as well as dosing using TBW and AIBW. Based upon the totality of the safety, pharmacokinetic, and antitumor activity data, 6 mg/kg AIBW IV Q3W was declared the MTD/RP2D for the expansion cohorts.

Four expansion cohorts were enrolled and treated at the 6 mg/kg AIBW IV Q3W dose, with 3 of these cohorts enrolling patients with advanced EOC.

Radiologic evaluations were performed within 28 days before the first dose, then at 6-week intervals from the date of the first dose until the 28-day follow-up visit.

Preliminary antitumor activity was evaluated by the investigator using RECIST v1.1. The endpoints included ORR (confirmed objective response [CR or PR]), DOR and PFS.

Population: 206 patients with FRα-positive tumours, including 113 patients with EOC in the expansion cohorts. Of the 113 patients with EOC, 101 patients had epithelial ovarian cancer, 8 fallopian tube cancer, and 4 primary peritoneal cancer. The majority (85%) had platinum-resistant disease. 50% of patients had received 1 to 3 prior therapies while 50% had received ≥ 4 prior therapies. The majority in the EOC expansion cohort had received prior bevacizumab (68%). Evaluation of FRα expression by PS2+ scoring showed, that 20% of patients with EOC had low expression (25% - 49% of tumour cells), 26% had medium expression (50% - 74%), and 54% had high expression (75% - 100%).

Of the 113 patients with EOC, 27 patients had PROC with high FRα expression and had received 1-3 prior lines. In this FRα-high subgroup, the median age was 65 years (range 46-81 years), and the predominant race was White (82%). The majority had epithelial ovarian cancer (85%) and histology was predominantly serous (78%). Prior bevacizumab had been administered in 52% of the patients in the FRα-high subgroup.

Efficacy results:

Table 60: Summary of Efficacy in Patients With Epithelial Ovarian Cancer and the Subgroup of Patients With FRα-High PROC (Study 0401)

Endpoints	Patients With EOC in Expansion Cohorts (n = 113)	FRα-High Subgroup [a] (n = 27)
ORR (investigator-assessed), n (%) [95% CI]	34 (30) [21.8, 39.4]	12 (44) [25.5, 64.7]
CR (objective response), [b] n (%)	5 (4)	2 (7)
PR (objective response), [b] n (%)	29 (26)	10 (37)
Duration of response [c] (months), median (95% CI)	4.4 (4.1, 7.8)	7.8 (4.1, 13.8)
Number of events	26	8
PFS (months), median (95% CI)	4.3 (3.9, 5.4)	6.7 (3.9, 9.0)
Number of events	89	21

Abbreviations: AIBW = adjusted ideal body weight; BOR = best overall response; CR = complete response; EOC = epithelia ovarian cancer; FRα = folate receptor alpha; ORR = objective response rate; PFS = progression-free survival; PR = partial response; PROC = platinum-resistant ovarian cancer (includes epithelial ovarian, fallopian tube, and primary peritoneal cancers).

[a] The subgroup of patients with high FRα expression PROC (≥ 75% of tumor cells by PS2+ scoring method) had received 1 to 3 lines of prior therapy and received the 6 mg/kg AIBW dose of mirvetuximab soravtansine in the expansion phase.

[b] Objective response was defined as investigator assessment, with CR/PR confirmed by a follow-up scan at least 4 weeks later.

[c] Duration of response is summarized for patients who achieved a BOR of CR or PR only.

Table 61: Summary of Anti-tumor Activity in Patients with Platinum-Resistant EOC by Prior Lines of Therapy and FOLR1 Expression Level (Response Evaluable Population)

	1-3 Prior Lines of Therapy (n=48)	>3 Prior Lines of Therapy (n=48)	FOLR1 Expression Low (n=21)	FOLR1 Expression Medium (n=26)	FOLR1 Expression High (n=49)	FOLR1 Expression Medium +High (n=75)
PFS Number of Events	40	37	20	22	35	57
PFS Median (months) (95% CI)	5.7 (4.2, 6.8)	3.4 (2.6, 4.3)	3.9 (2.7, 6.8)	4.1 (2.6, 4.9)	5.4 (3.9, 6.7)	4.4 (3.9, 5.6)
ORR[a, b] [n (%)]	21 (44)	5 (10)	5 (24)	7 (27)	14 (29)	21 (28)
95% CI	(29.5, 58.8)	(3.5, 22.7)	(8.2, 47.2)	(11.6, 47.8)	(16.6, 43.3)	(18.2, 39.6)
Objective Response CR [n (%)]	2 (4)	1 (2)	0	0	3 (6)	3 (4)
Objective Response PR [n (%)]	19 (40)	4 (8)	5 (24)	7 (27)	11 (22)	18 (24)
Objective Response SD [n (%)]	20 (42)	33 (69)	14 (67)	13 (50)	26 (53)	39 (52)
Objective Response PD [n (%)]	6 (13)	6 (13)	1 (5)	4 (15)	7 (14)	11 (15)
Objective Response IND [n (%)]	1 (2)	4 (8)	1 (5)	2 (8)	2 (4)	4 (5)
DOR Number of Events	17	5	5	7	10	17
DOR Median (weeks) (95% CI)	20.1 (18.0, 37.3)	16.1 (10.9, 36.4)	20.1 (15.1, 37.3)	17.7 (12.6, 19.1)	34.0 (18.0, 44.1)	19.3 (17.7, 34.0)

CR = complete response; IND = indeterminate; PD = progressive disease; PR = partial response; SD = stable disease

[a] Objective Response is defined as investigator assessment, confirmed by a follow-up scan at least 4 weeks later for CR/PR.

[b] ORR=CR+PR/total.

Note: DOR is summarized for patients who achieved a best overall response of CR or PR only.

Table 62: Summary of Anti-Tumor Activity in Patients with Platinum-Resistant EOC 1-3 or >3 Prior Lines of Therapy, Each by FOLR1 Expression Level (Response Evaluable Population)

	1-3 Prior Lines of Therapy FOLR1 Expression Low (n=12)	1-3 Prior Lines of Therapy FOLR1 Expression Medium + High (n=36)	>3 Prior Lines of Therapy FOLR1 Expression Low (n=9)	>3 Prior Lines of Therapy FOLR1 Expression Medium + High (n=39)
PFS Number of Events	12	28	8	29
PFS Median(months) (95% CI)	5.3 (2.7, 8.7)	6.7 (4.1, 8.3)	2.8 (1.2, 3.9)	3.9 (2.6, 4.9)
ORR [n (%)]	4 (33)	17 (47)	1 (11)	4 (10)
ORR 95% CI	(9.9, 65.1)	(30.4, 64.5)	(0.3, 48.2)	(2.9, 24.2)
Objective Response CR [n (%)]	0	2 (6)	0	1 (3)
Objective Response PR [n (%)]	4 (33)	15 (42)	1 (11)	3 (8)
Objective Response SD [n (%)]	8 (67)	12 (33)	6 (67)	27 (69)
Objective Response PD [n (%)]	0	6 (17)	1 (11)	5 (13)
Objective Response IND [n (%)]	0	1 (3)	1 (11)	3 (8)
DOR Number of Events	4	13	1	4
DOR Median (weeks) (95% CI)	19.6 (15.1, 37.3)	25.1 (18.0, 42.0)	36.4 (-, -)	14.6 (10.9, 19.3)

[a] Objective Response is defined as investigator assessment, confirmed by a follow-up scan at least 4 weeks later for CR/PR.
[b] ORR=CR+PR/total.
Note: DOR is summarized for patients who achieved a best overall response of CR or PR only.

2.6.6. Discussion on clinical efficacy

Dose finding and dose recommendation Study FORWARD 1 (IMGN853-0403)

Dosing based on TBW was initially used in study 0401 (FIH), but dose-limiting toxicities were observed, together with notable between-subject variability in exposure to MIRV. Subsequently, dosing by AIBW was implemented based on analysis of preliminary data and found to be better tolerated. Thus, 6 mg/kg AIBW Q3W was determined as the MTD and the RP2D and was used in subsequent studies, including the pivotal study MIRASOL.

PK modelling and simulations using data from the 4 clinical studies support the conclusion, that between-subject variability in exposure to MIRV is lower using a dose based on AIBW compared with dose based on TBW or a flat dose. Therefore, posology based on AIBW is endorsed. There is more uncertainty regarding the dosing frequency. A modified QW regimen was tested in study 0401, but it was concluded that it did not demonstrate an improvement in the safety profile over the Q3W regimen. However, this conclusion was based on a low number of patients and may have been premature. Use in patients with moderate hepatic impairment has been included as missing information in the RMP and

the MAH will conduct a clinical study to address this safety concern. Study IMGN853-0425 (hepatic impairment cohort) is a category 3 PASS whereas the other cohort of Study IMGN853-0425 (randomized phase 2 cohort) aims to characterize the safety of an alternative dosing schedule (4 mg/kg AIBW at Days 1 and 15 of a 28-day cycle) and the 6 mg/kg AIBW Q3W dosing schedule. The applicant has agreed to provide results of the randomized phase 2 cohort when available and to amend the posology if warranted (**REC)**.

The applicant conducted exposure-response (E-R) analyses to justify the proposed posology, but their results are inconclusive because only 1 dose regimen (6 mg/kg AIBW Q3W) was evaluated in subsequent studies and dose modifications were common in the studies and not accounted for in the E-R analyses.

Nevertheless, the B/R assessment of the proposed posology can be done because it was used in the pivotal study.

The pivotal study supporting this application is the MIRASOL study (IMGN853-0416).

Design and conduct of clinical studies

MIRASOL is a global phase 3 RCT against an active comparator with 1:1 allocation. its design and size are considered adequate and the open label setting unavoidable. Declaring investigator's choice of chemotherapy prior randomization is considered appropriate. The trial did not allow cross-over, which aids the assessment of OS. The doses and regimens for ICC were adequately justified and the stratification factors (number of prior lines and type of ICC) considered appropriate.

The choices of ICC (paclitaxel, pegylated liposomal doxorubicin, or topotecan) were nearly concordant with current European guidelines by ESMO. ESMO also recommends bevacizumab with chemotherapy to patients without contraindications and without prior exposure. For enrolment the patients had to be considered as 'for whom single-agent therapy was appropriate as the next line of treatment'. While 38% of patients had no prior bevacizumab, they were treated with MIRV or ICC monotherapy. Having 3 chemotherapy choices reflects the fact that there is no universally established single option for PROC. Overall the choices in the comparator arm are considered acceptable and were endorsed in the scientific advice (EMEA/H/SA/3384/1/2016/PA/III).

Patients had to have a confirmed diagnosis of high grade serous epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer and have a platinum resistant disease. This was defined as PD between > 3 months and ≤ 6 months after the date of the last platinum dose, if only 1 line of prior therapy or within 6 months after the date of the last platinum dose, if 2 or 3 prior lines of platinum. Primary platinum refractory patients were excluded. This was justified by the very poor prognosis in this setting, selecting thus patients with a better prognosis. Patients were required to have an ECOG 0-1. However, in PROC with patients who have received up to 3 prior treatment lines, it is expected that a non-negligible part would be of ECOG 2. According to Roncolato et al (Oncologist 2017), 13% of the patients with PROC were of ECOG ≥2. Thus, these inclusion criteria raise the issue of representativeness of the population. No clear signals for reduced efficacy were noted in efficacy analyses in a subgroup of patients of ≥65 years. However, it is uncertain whether this age bar correctly captures future frail patients, elderly and/or those with worse performance score.

High FRα expression was defined as ≥75% of viable tumour cells with a level 2 and/or 3 membrane staining intensity by the Ventana FOLR1 assay. The evaluation of FRα expression was conducted at 3 central laboratories. The wording of the indication states "patients with folate receptor-alpha (FRα) positive" and the detailed definition for FR alpha positive is provided in section 4.2 of the SmPC.

Allowing 1-3 prior lines for advanced EOC adds heterogeneity in the patient population. However, development of platinum resistance varies between patients and allowing 1-3 prior lines is clinically beneficial for the patients. This also allows conclusions to be made for a broader patient population. Contrary to many oncologic indications reflecting the requirements of named prior therapies mandated in the protocols, MIRASOL did not specify other than platinum resistance and 1-3 prior lines but excluded patients treated with >3 prior lines. The unmet medical need in heavily pretreated patients is acknowledged. The limited indication for patients with 1-3 prior lines was justified based on extremely scarce data in patients with platinum resistant disease, ≥4 prior lines and FR alpha ≥75%.

The treatment was to be continued until disease progression, unacceptable toxicity, withdrawal of consent, death, or until the sponsor terminated the study. The proposed dosage of MIRV by AIBW is unusual and the total dose must be calculated with a formula described in section 4.2 of the SmPC. This could potentially be a source of miscalculation, leading to an incorrect administered dose. To reduce such risks an example of a patient's calculation was included in section 4.2 of the SmPC .

Two global amendments were made which do not threaten the integrity of the study results. In amendment #2 enrolment criteria regarding platinum resistance and primary platinum resistant disease were clarified. No relevant concerns can be raised regarding patients enrolled before and after amendment #2. Furthermore, no clear signs of a chronological bias can be noted with the midpoint analyses. OS would have been the preferred primary endpoint and was recommended during scientific advice (EMEA/H/SA/3384/1/FU/1/2019/PA/II). However, PFS_{INV} as primary endpoint is considered acceptable, as OS was included as key secondary endpoint. PFS was defined as the time from date of randomization until investigator-assessed progressive disease or death, whichever occurs first. Investigator assessment in an open label study can be subject to bias, hampering the interpretation of the primary endpoint. Thus, $PFS_{BICR,}$ used for a sensitivity analysis, would have been preferred. On the other hand, in some instances disease evaluation by the investigator could be more accurate in patients with PROC (e.g. considering disseminated peritoneal spread, ascites, and symptoms). The clinical relevance of ORR as a key secondary endpoint is limited and also subject to bias due to open label design. Albeit PRO measurements can provide important results for QoL, their relevance is reduced by the open label setting.

The sample size was based on an estimated 1.5-month difference between arms. This is a very small absolute difference and needs to be supported by the totality of evidence including OS and safety.

A request for routine GCP inspection was adopted by the CHMP for clinical study IMGN 853-0416 (MIRASOL). At the inspection of the sponsor site (Waltham, USA), there were 11 major and 10 minor findings. At the inspection of Severance Hospital, Seoul, Republic of Korea, there were 4 major and 9 minor findings. At the inspection of Fondazione Policlinico Universitario, Rome, Italy, there were 2 major and 5 minor findings. Based on the inspections and the findings observed, the inspection report concluded, that despite the non-compliances detected, the trial has overall been conducted by the two investigational sites and the sponsor in sufficient compliance with GCP and internationally accepted ethical standards. The findings observed during the three inspections are unlikely to constitute a critical risk for patient safety or data quality.

The data is considered to be acceptable for the evaluation and assessment of the Elahere marketing authorisation application.

Efficacy data and additional analyses

- Pivotal study: MIRASOL (IMGN853-0416)

Protocol deviations were frequent (79% in MIRV, 77% in ICC) and major deviations more frequent in the MIRV arm (58% vs. 48%). IP dosing/dispensing errors and premedication errors were more frequent in the MIRV arm (21% vs. 8% and 18% vs. <1%, respectively). In major protocol deviations `lab or assessment not done' concerned 36% in the MIRV arm vs. 28% in the ICC arm. The most common category in them was missing ocular symptom assessment/ophthalmic examination. Considering that the ocular toxicity is well characterised, low grade and reversible in general, this issue was not pursued further. Also ICF deviations were more frequent in the MIRV than in the ICC arm (11% vs. 5%).

Of the 453 patients, 227 were randomised to MIRV and 226 to ICC (of which 92 were treated with paclitaxel, 81 with PLD, and 53 with topotecan). Most patients (66%) were White and 55% were from Europe, while 32% were from North America and 11% from APAC. Median age was 63 (min. 29, max. 88) years and ovarian cancer dominated (80%), followed by fallopian tube cancer (11%) and primary peritoneal cancer (8%). Overall, demographic and baseline characteristics were balanced between treatment groups. 14% had a BRCA1/2 mutation, which is lower than current literature indicates. The true proportions of patients with BRCA1/2 mutations and HRD are not known, as these were not systematically tested and negative BRCA status was not disentangled from unknown BRCA status.

The median time from initial diagnosis to randomisation was 28.82 months. Primary platinum free interval and platinum free interval from last line of platinum were similar in all treatment groups. 14% had been treated with 1 line of therapy, 39% with 2 and 47% with 3. There were no patients with ≥4 prior treatment lines. Distribution of prior lines was similar between the MIRV and the ICC arms. Practically all had prior taxane exposure, as platinum-taxane is a typical (neo)adjuvant therapy. Rechallenge with paclitaxel in relapsed disease follows current guidelines. 58% had prior exposure to doxorubicin/PLD, while 99% had no prior exposure to topotecan. More than half (55%) had prior exposure to PARPi as well as to bevacizumab (62%). Details on disease burden and the presence of visceral metastases were not provided. Overall, the population is relevant for B/R assessment in Europe.

The main reason for discontinuation in all treatment groups was progressive disease. At data cut-off for primary analysis on 06 March 2023, 14% of patients in the MIRV arm and 3% of patients in the ICC arm were still on treatment. 48% of patients in the MIRV arm and 64% of patients in the ICC arm had permanently discontinued from the study.

Between the MIRV and the ICC arms, there is an uneven distribution of patients, who did not receive treatment (19 in the ICC compared to 9 in the MIRV arm) or who withdrew (17 in the ICC and 8 in the MIRV arm). This is related to the open label setting, in which patients randomised to ICC leave the trial more readily than patients in the experimental arm. Partly these patients have been impacted by investigator decisions, searching further options for patients randomised to ICC. Thus, informative censoring impacts the analysis of all time-to-event endpoints. However, the patient characteristics of the early drop-outs e.g. their prognosis, number of prior treatments, and ECOG are not known. Hence, if these patients were among the ones with expected poor outcomes, the magnitude of benefit in PFS may be underestimated, and if these patients were among the ones with expected good outcomes, the magnitude of benefit in PFS may be overestimated, or the impact on the efficacy results may be negligible.

To address these concerns, several additional analyses were conducted. This was to address the uneven withdrawal and not receiving the intended treatment, for reasons of censoring, duration of follow-up, and for updated PFS data. For PFS, the number of patients with events is higher in the MIRV

arm despite the primary analysis showing a benefit for MIRV. The proportions of patients censored for new anticancer therapy before PD/death or without baseline or post-baseline assessment are higher in the ICC arm. In conclusion, the additional data and analyses provided during the evaluation show that the study has suffered from open label bias and hence the study integrity has been compromised in a way that cannot be retrospectively corrected and the impact is difficult to accurately quantify.

Most prominently the open-label bias can be demonstrated looking at the number of early drop-outs in the comparator arm (13% by week 6) and the low concordance between the INV and BICR results. Also the lack of benefit in the US patients is noteworthy considering that the open-label bias appears to not be equally distributed by country and region. Furthermore, the absolute difference in efficacy between the arms is small and, hence, some of the sensitivity analyses provide a result which would not be clinically meaningful. Importantly, the provided additional analyses or any other data does not appear to suggest that there may be a detriment in PFS or OS. It is also important to note that the active arm was a substitution therapy compared to single agent chemotherapy. Therefore a smaller treatment effect may be considered clinically relevant than for an add-on treatment. Hence, though the magnitude of the treatment effect cannot be accurately estimated based on data collected in MIRASOL and results are clearly impacted by open-label bias, in the absence of any sign of worse efficacy than in the comparator arm, the B/R profile can be considered positive.

The study met its **primary endpoint PFS_{INV}** (HR 0.65, p<0.0001), but the time gain is only 1.6 months (5.62 (95% CI 4.34, 5.95) months with MIRV versus 3.98 (95% CI 2.86, 4.47) months with ICC). The data is considered mature as 75% of the patients have had a PFS event. Albeit the PFS benefit is limited, efficacy based on the totality of evidence is clinically relevant. The Kaplan-Meier curves for PFS show an early separation of the curves.

The results from PFS_{BICR} sensitivity analysis are relevant. Median PFS by BICR was 5.91 (4.93, 6.97) months and 4.34 (3.52, 4.99) months in MIRV and ICC arm, respectively (HR 0.72), illustrating a similar but shorter increase in PFS.

There are more PFS events in the MIRV arm (77.5% and 64.3% by INV and BICR, respectively) than in the ICC arm (73.5% and 54.4% by INV and BICR, respectively), assumingly due to the high drop-out rate. The PFS definition of the protocol follows FDA censoring rules. In the provided tables for censoring reasons (PP population, as tables for ITT were not found), there were notably more patients censored due to "new therapy prior to PD or death" in the ICC arm than in the MIRV arm. Thus, a PFS analysis in ITT population by INV and BICR with censoring rules according to the EMA guidelines was evaluated. These results do not change the overall interpretation of the study results. Overall, there is poor concordance between INV and BICR results (PFS by INV and BICR with 61.2% of agreement in the MIRV arm and 53.76% of agreement in ICC arm). The cause appears to be differences in the actual assessment between INV and BICR and operational reasons, mostly as patients were not followed beyond investigator declared PD. This is a further sign of open-label bias. The discrepancies between PFS by INV and by BICR are mostly due to INV PFS time being longer than BICR PFS time. It can be assumed that these discrepancies are mainly related to the fact that no tumour assessment following investigator-assessed PD was planned according to the study protocol, which increases the rate of inconsistency. This is considered a major limitation, preventing any observations of BICR PD later than INV PD, as well as of any PD (whether investigator or BICR-assessed) after the start of new anticancer therapies. Despite these shortcomings it was accepted to present the primary endpoint PFS_{INV} in section 5.1 of the SmPC.

Albeit patients were enrolled based on a biomarker with an FRα expression in at least 75% of viable tumour cells with staining intensity level 2 or 3, the majority of patients treated with MIRV did not respond. However, the **key secondary ORR endpoint** was met, as MIRV outperformed ICC (ORR 42.3% vs 15.9%, p<0.0001), both in CR (5.3% vs 0%) and PR (37% vs 15.9%).

ORR by BICR was 36.1% in the MIRV arm vs 14.6% in the ICC arm. Thus the difference between arms was smaller, although consistent with INV assessment. This concerns both PR (29.1% vs 12.8% in the MIRV arm and the ICC arm respectively) and CR (7.0% in the MIRV arm and 1.8% in the ICC arm).

Median DOR (95% CI) per INV was longer in the MIRV arm (6.77 months; 5.62, 8.31) compared to the ICC arm (4.47 months; 4.17, 5.82). However, median DOR (95% CI) per BICR was longer with ICC (7.36 months; 4.27, 16.16) than with MIRV arm (6.93 months; 5.59, 9.40).

The study met the **key secondary endpoint of OS** as the median OS with MIRV was 16.46 (14.46, 24.57) months and 12.75 (10.91, 14.36) months with ICC (HR 0.67), meaning a 3.71 months OS benefit. The K-M for OS separate early. An OS update with a 27 October 2023 cut-off was provided during the evaluation. At this cut-off date, 55.9% of patients in the MIRV arm and 66.4% of patients in the ICC arm have died (39.6% and 50.4% at the initial submission, respectively), while 78 patients in the MIRV arm are in survival follow-up or on treatment (10 patients still on treatment), and in ICC arm 46 patients in follow-up (of which one patient is still on treatment). OS result is impacted by the bias due to early drop out, related to the open label design. However, even when applying conservative scenarios on the impact of early censoring, a detrimental effect on OS is not considered plausible.

The proportions of patients receiving new anticancer therapies were similar between the two arms (52% for the MIRV arm, 55.8% for the ICC arm).

The **key secondary endpoint, EORTC QLQ-OV28 abdominal / GI** was not met, as there was no significant difference at week 8/9 for improvement between arms.

Median (95% CI) PFS2 by INV was longer in the MIRV arm than in the ICC (11.04 months (9.36, 12.45) and 8.05 months (6.74, 9.36), respectively). There is no PFS2 data by BICR.

Additional analyses were presented for patients with dose reduction to 5 mg/kg and to 4 mg/kg AIBW (data not shown). Their relevance is reduced by the small numbers (54 patients with dose reduced to 5 mg/kg AIBW and 20 patients with dose reduced to 4mg/kg AIBW). No clear signals for detrimental effects from dose reductions were seen. However, these must be interpreted with caution as it is not known, when the reductions were made and how long the patient continued with a reduced dose.

Regarding subgroup analyses for PFS_{INV} and number of prior lines, the strongest benefit is seen after 1 prior line (HR 0.44), while after 2 lines HR is 0.68 and after 3 lines HR is 0.71. No relevant differences have been observed in distinct age groups. With primary platinum free interval (PFI) and most recent PFI, longer times are related to stronger efficacy (>6 months HR 0.63 and >3 months HR 0.61, respectively). A notable benefit is seen in the BRCAmt subgroup (HR 0.33). For patients without prior PARPi maintenance, the HR for PFS_{INV} is 0.74, while with prior PARPi maintenance the HR is 0.58. This could be related to the BRCA1/2 and HRD status. Patients without and with prior bevacizumab had a similar benefit from MIRV compared to ICC (HRs of 0.66 and 0.64, respectively).

PFS subgroup analyses by BICR (sensitivity analysis) were overall consistent with the primary analysis.

In general subgroup analyses for ORR_{INV} demonstrated consistent trends favouring MIRV over ICC. Only the number of prior lines is clearly related to ORR (difference in ORR after 1 line 39%, 2 lines 28.6%, and 3 lines 20.6%).

For subgroup analyses for OS, overall, there is more uncertainty in the subgroup analyses for OS than for PFS due to the lower number of events.

The MIRASOL study did not include patients with >3 prior lines and this is reflected in the indication. "High grade serous' was included in section 4.1 of the SmPC and is consistent with the pivotal study population.

Overall, despite the uncertainties and deficiencies discussed above, the study met its primary endpoint (PFS_{INV}) and key secondary endpoint (ORR_{IN}), and a statistically and clinically significant OS benefit

was observed in patients with advanced platinum resistant EOC which is considered important. Platinum resistant EOC is an aggressive disease and available treatments have limited efficacy. Albeit permanent cure with MIRV is not possible, these results are clinically relevant for the patients.

- **Supportive study: SORAYA (IMGN853-0417)**

This single arm study including 106 patients provides some support to the efficacy claims for the Elahere MAA but limited to ORR and DOR. The enrolment criteria define an almost identical patient population to MIRASOL (advanced PROC, after 1-3 prior lines). The most notable difference is the mandatory requirement for prior bevacizumab exposure. The primary endpoint was ORR_{INV} and the key secondary DOR_{INV}.

The primary endpoint ORR_{INV} was 32.4% with 34 responders in the 105 population. ORR by BICR contains 95 patients, with 30 responders and an ORR of 31.6%. Responses were similar by INV and BICR with 4.8% and 5.3% for CR and 27.6% and 26.3% for PR, respectively.

The key secondary endpoint DOR_{INV} is based on 34 patients, with the median DOR of 5.9 months indicating that treatment with MIRV is not exceptional.

As SORAYA does not bring added value to the efficacy claims, its results are not described in the SmPC.

- **Supportive study: FORWARD 1 (IMGN853-0403)**

A phase 3 RCT of MIRV vs SOC is an appropriate design and the open label setting unavoidable. However, a 1:1 allocation would have been favoured over the 2:1 ratio. For advanced EOC, 1-3 lines of prior therapy were allowed, which adds heterogeneity. The development of platinum resistance varies between patients and from the clinical point of view, allowing flexibility in prior lines is useful. The enrolment criteria are overall acceptable, but make the population different from patients treated in every day clinical practices. Patients were selected with FRα expression but with different criteria than in the MIRASOL and SORAYA studies, with minimum expression level allowed $\geqslant$50% of tumour cells with any FRα membrane staining visible at $\leqslant$10X microscope objective. Patients with FRα expression of 50- 74% of tumour cells were considered to have a medium level, while those with a FRα expression of $\geqslant$75% of tumour cells were considered to have a high-level expression. The trial was modified with 8 global amendments, including a change from 2-stage phase 2 study to a phase 3 study. These amendments could have affected the study integrity and results.

There were no unexpected findings in the demographic and baseline characteristics expect the lower proportion with prior exposure to PARPi (17%), probably related to the fact that the trial started enrolment in 2016.

The primary endpoint PFS_{BICR} did not reach statistical significance in the ITT population nor in the FRα high population (n=218). In the ITT population there were more PD events in the MIRV arm than in the ICC arm (65% vs 53%), while deaths were evenly distributed. The mPFS times by BICR in the ITT population were equal (4.14 months in the MIRV arm, 4.44 months in the ICC arm, HR 0.981). In FRα high population the difference in median PFS by BICR times was short (1.5 months) but favoured the MIRV arm (4.76 months vs 3.25 months, HR 0.693).

Key secondary endpoint ORR_{BICR} in ITT population and FRα high population was higher in the MIRV arm (22% and 24%) than in ICC arm (12% and 10%), respectively.

For key secondary endpoint OS, at the primary analysis, median OS in ITT was 16.43 months with MIRV and 14.03 months with ICC (HR 0.815). For the FRα high population median OS was not reached with MIRV and was 11.76 months with ICC (HR 0.618). With longer F-U, the median OS was 15.57

months with MIRV and 13.93 months with ICC in the ITT population (HR 0.855), while 17.31 months with MIRV and 12.02 months with ICC in FRα high population (HR 0.706).

Overall, the results were negative in the ITT population but suggested a higher benefit in patients with high FRα expression, justifying the conduct of the MIRASOL study in a FRα high population.

- **Supportive study FIH (IMGN853-0401)**

The main objectives of this trial with a dose escalation and a dose expansion part were to establish the MTD and RP2D. MTD and RP2D of Schedule A (Q3W) was determined to be 6 mg/kg AIBW. MTD of Schedule B (QW) was determined to be 2.0 mg/kg AIBW. 6 mg/kg AIBW IV once every 3 weeks was declared the MTD/RP2D for the expansion cohorts.

The study enrolled 206 patients with FRα-positive tumours, including 113 patients with EOC treated in the expansion cohorts. The majority (85%) of 113 patients with EOC in the expansion cohorts had platinum-resistant disease, 50% had received 1-3 prior systemic therapies and 50% had ≥4 lines, while 68% had prior bevacizumab. As the trial had no comparator arm, the time-to-event endpoints cannot be evaluated. In the 113 patient EOC population in expansion cohorts the ORR was 30%. In the 27-patient population with FR alpha high (≥75% by PS2+ scoring) and 1-3 prior lines the ORR was 44%. In a 39-patient population with >3 prior lines and FR alpha expression medium or high, the ORR was 10% (4 patients). Overall, the populations are small, highly selected with multiple enrolment criteria, and heterogeneous. The results can be seen as hypothesis generating, while their value for the B/R assessment is negligible.

- In vitro biomarker test for patient selection for efficacy

MIRV is a targeted agent with a monoclonal antibody against FRα, and accurate selection of patients with the FRα biomarker is fundamental. FRα has limited expression in normal tissues. IHC studies have demonstrated FRα overexpression particularly in serous and endometrioid ovarian cancers and serous and endometrioid endometrial cancers. According to the ESMO guideline on newly diagnosed and relapsed epithelial ovarian cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up – supplementary material, 60-100% of ovarian cancers overexpress FRα.

The same assay format and staining protocol (VENTANA FOLR1, FOLR1-2.1) were used in clinical trials for prospective enrolment of the patients, but with different scoring methods (10X in FORWARD 1, PS2+ in SORAYA, MIRASOL, and FIH). VENTANA FOLR1 (FOLR1-2.1) has been approved by the FDA.

In the EOC expansion cohorts of the FIH study, patients were required to have ≥25% FRα positivity in tumour cells with the PS2+ scoring. FORWARD 1 failed after enrolling patients with ≥50% FRα expression with the 10X scoring. According to the applicant's exploratory post hoc rescoring analysis with PS2+ some samples were misclassified with the 10X scoring. With PS2+ rescoring the population with FR alpha ≥75% had a median PFS_{BICR} of 5.6 months with MIRV vs 3.2 months with ICC, HR 0.549. Thus, the rationale in using the PS2+ scoring and raising the bar of FRα expression to ≥75% can be followed.

In the pivotal study MIRASOL (study 0416), the PS2+ scoring and the bar of at least 75% were used. Sub-group analyses demonstrated the predictive nature of FR alpha level on efficacy. Despite central assessment 25% of patients were charted to have FR alpha expression exactly as 75%, likely due to the fact that the scoring pathologists were not obliged to provide data beyond binary assessment, making these results unreliable for efficacy analyses. The remaining sub-groups are small, and limitations of the immunohistochemical scoring methodology should be considered. For PFSINV, the HR ranges from 0.47 (FR alpha ≥95%) to 0.86 (FR alpha >75%, ≤85%). However, in the FR alpha >75%, ≤85% category the time difference in median PFS is only 0.33 months. For OS, HR was 0.4 for

patients with FR alpha ≥95%, while there is no effect in FR alpha >85%, <95% (HR 1.02). Thus, in line with results from previous studies, FR alpha expression seems predictive of PFS. Further, there is a benefit of MIRV across all expression levels, though, it appears minimal in comparison to ICC in patients with FR alpha ≥75%, <85%. However, it should be noted that the reliability of the subgroup analyses are impacted by the scoring method and the small size of the subgroups. Importantly, no sign of detrimental effect as compared to ICC was observed in any of the provided analyses.

- **Analyses performed across studies**

An integrated summary of efficacy from ITT populations of MIRASOL and SORAYA, with 333 patients, who received MIRV, had FRα high (≥75%) and were enrolled after 1-3 prior lines was submitted. The applicant did not include results from the failed FORWARD 1, which enrolled patients with a lower cut-off for FRα and a different scoring method. As the pooling includes considerable sources of bias, these results cannot be considered to establish the efficacy of Elahere.

Patient and healthcare provider engagement

A methodology of engaging with patient organisations at the start of evaluation of new MAAs has been agreed by CHMP (for more details see the dedicated process and FAQs document: https://www.ema.europa.eu/en/documents/other/chmp-early-contact-patient-and-healthcare-professional-organisations-process-and-faqs_en.pdf). In this context the CHMP invited a healthcare professional society as well as a patient organisation to share their perspectives regarding the assessment of mirvetuximab soravtansine for the applied indication on behalf of its members. The response from EORTC and OvaCare confirmed the view that there is a substantial need for better treatment options particularly for recurrences in platinum resistant disease.

2.6.7. Conclusions on the clinical efficacy

The MIRASOL study met its primary endpoint $PFS_{INV,}$ however the PFS time gain was only 1.6 months with MIRV compared with ICC (5.62 vs. 3.98 months). The key secondary endpoint OS was also met: the median OS with MIRV was 16.46 (14.46, 24.57) months and 12.75 (10.91, 14.36) months with ICC, meaning a 3.71 month OS benefit in favor of MIRV. These results are clinically relevant, as advanced platinum-resistant ovarian cancer is a lethal disease, in which currently available chemotherapies offer limited efficacy.

To conclude, the efficacy of MIRV as monotherapy, despite the uncertainties and deficiencies highlighted in the discussion, is considered established 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.

2.6.8. Clinical safety

Table 63: (Pooled) Safety Analysis Populations

Group	Analysis Population	Number of Patients
All Patients (6 mg/kg AIBW Q3W)	All patients (EOC and endometrial) who received MIRV 6 mg/kg AIBW Q3W (Studies 0401, 0403, 0416, 0417) - Patients in expansion cohorts of Study IMGN853-0401 (n = 137) o EOC Patients (Cohorts 1, 3, and 5) (n = 113) o Endometrial Patients (Cohort 2) (n = 24) - Patients who received MIRV 6 mg/kg AIBW Q3W in Study IMGN853-0403 (n = 245) o Phase 3 portion (n = 243) o Stage 1 (n = 2) - 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 who received 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) o Phase 3 portion (n = 243) o Stage 1 (n = 2) - 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 in study 0416 who received MIRV 6 mg/kg AIBW Q3W	218
0416 IC Chemo[a]	All patients in safety population in Study 0416 who received IC Chemo (Pac, PLD, Topo)	207

Abbreviations: AIBW = adjusted ideal body weight; EOC = epithelial ovarian cancer, IC Chemo = investigator's choice chemotherapy; IV = intravenously; MIRV = mirvetuximab soravtansine; Pac = paclitaxel; PLD = pegylated liposomal doxorubicin; Q3W = every 3 weeks; Topo = topotecan.

[a] IC Chemo: Pac (80 mg/m^2 administered weekly within a 4-week cycle), PLD (40 mg/m^2 administered every 4 weeks), or 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).

Patient exposure

Table 64: Duration of exposure

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]				

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)
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; Top (Q4W): (last dose date – first dose date + 14) / 7; Top (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

The safety of MIRV has been evaluated in a population consisting of 706 patients, who received at least 1 dose of single-agent MIRV at 6 mg/kg AIBW Q3W in four clinical studies (=All patients). Of these patients 682 (97%) had the intended indication FRα-positive platinum resistant EOC and comprise the primary analysis population (=EOC patients).

Regarding demographics and baseline characteristics, in the primary analysis population, the median age was 63.0 years (range: 32 to 89 years), with 56% of the patients ≤ 64 years and 44% of patients ≥ 65 years. The median baseline weight was 66.0 kg (range: 36 to 126 kg). 56% of the patients had ECOG of 0, and 44% an ECOG of 1.

Regarding prior systemic therapies, in the primary analysis population, 41 % had received 3 prior therapies, 35% 2 prior therapies, and 16 % 1 prior therapies. In the study 0416, the history of prior cancer therapies was in general well balanced across the MIRV arm and the IC Chemotherapy arm. It is however noted that platinum therapy was the last line of treatment for 66% of the MIRV subjects versus 77% for the IC Chemotherapy subjects.

The number of patients who received ≥ 4 prior lines of cancer treatment was very limited (11 patients), and thus, no conclusions could be drawn regarding the safety of MIRV in these patients. This is considered acceptable as the indication is restricted to patients who have received 1 to 3 prior systemic treatment regimens.

The median duration of exposure for patients in the primary analysis population was 4.4 months (range: 1; 30), corresponding 6.0 cycles (range: 1; 44). The follow-up was until 30 days (28 days for study 0401) after the patient's last study drug, or until an adverse event had resolved or stabilized, or an outcome had been reached, whichever came first.

Adverse events

Overview of treatment-emergent adverse events (TEAEs) is presented in the table below.

Table 65: Overview of Treatment-emergent Adverse Events

Characteristic n (%)	**All Patients MIRV (6 mg/kg AIBW Q3W) (N = 706) n (%)**	**EOC Patients MIRV (6 mg/kg AIBW Q3W) (N = 682) n (%)**	**Study 0416 MIRV (6 mg/kg AIBW Q3W) (N = 218) n (%)**	**Study 0416 IC Chemotherapy[a] (N = 207) n (%)**
Patients experiencing ≥ 1 TEAE	696 (99)	672 (99)	210 (96)	194 (94)
≥ Grade 3	337 (48)	325 (48)	91 (42)	112 (54)
Related	641 (91)	619 (91)	188 (86)	167 (81)
≥ Grade 3 and related	182 (26)	175 (26)	53 (24)	77 (37)
SAEs	214 (30)	203 (30)	52 (24)	68 (33)
≥ Grade 3	172 (24)	163 (24)	44 (20)	59 (29)
Related	82 (12)	77 (11)	20 (9)	16 (8)
≥ Grade 3 and related	51 (7)	47 (7)	16 (7)	16 (8)
TEAEs leading to discontinuation	87 (12)	84 (12)	20 (9)	33 (16)
≥ Grade 3	49 (7)	48 (7)	10 (5)	22 (11)
Related	51 (7)	49 (7)	14 (6)	19 (9)
≥ Grade 3 and related	21 (3)	21 (3)	5 (2)	11 (5)
TEAEs leading to dose reduction or delay	351 (50)	340 (50)	130 (60)	121 (58)
TEAEs leading to dose reduction	183 (26)	179 (26)	74 (34)	50 (24)
≥ Grade 3	66 (9)	63 (9)	27 (12)	23 (11)
Related	171 (24)	167 (24)	67 (31)	47 (23)
≥ Grade 3 and related	61 (9)	58 (9)	23 (11)	21 (10)
TEAEs leading to dose delay/dose held	321 (45)	310 (45)	117 (54)	111 (54)
≥ Grade 3	117 (17)	111 (16)	44 (20)	69 (33)
Related	271 (38)	263 (39)	99 (45)	86 (42)
≥ Grade 3 and related	79 (11)	76 (11)	34 (16)	54 (26)
TEAEs leading to death	16 (2)	13 (2)	5 (2)	5 (2)
Related	2 (< 1)	2 (< 1)	1 (< 1)	1 (< 1)

Most common TEAEs

The most common TEAEs by SOC and PT are presented in the below table.

Table 66: TEAEs Occurring in ≥ 20% of Patients in Any Analysis Population by SOC and PT

System Organ Class Preferred Term	**All Patients MIRV (6 mg/kg AIBW Q3W) (N = 706) n (%)**	**EOC Patients MIRV (6 mg/kg AIBW Q3W) (N = 682) n (%)**	**Study 0416 MIRV (6 mg/kg AIBW Q3W) (N = 218) n (%)**	**Study 0416 IC Chemotherapy[a] (N = 207) n (%)**
Patients with TEAEs	696 (99)	672 (99)	210 (96)	194 (94)
Gastrointestinal disorders	559 (79)	540 (79)	153 (70)	137 (66)
Nausea	289 (41)	279 (41)	58 (27)	60 (29)
Diarrhoea	272 (39)	263 (39)	64 (29)	36 (17)
Abdominal pain	209 (30)	202 (30)	66 (30)	31 (15)
Constipation	178 (25)	175 (26)	59 (27)	40 (19)
Vomiting	164 (23)	159 (23)	39 (18)	37 (18)
General disorders and administration site conditions	428 (61)	413 (61)	122 (56)	114 (55)
Fatigue	248 (35)	236 (35)	66 (30)	52 (25)
Asthenia	124 (18)	122 (18)	42 (19)	35 (17)
Eye disorders	417 (59)	405 (59)	122 (56)	18 (9)
Vision blurred	301 (43)	294 (43)	89 (41)	5 (2)
Keratopathy	201 (28)	199 (29)	70 (32)	0
Dry eye	185 (26)	181 (27)	61 (28)	5 (2)
Nervous system disorders	390 (55)	376 (55)	115 (53)	70 (34)
Neuropathy peripheral	136 (19)	134 (20)	47 (22)	30 (14)
Metabolism and nutrition disorders	300 (42)	287 (42)	71 (33)	74 (36)
Decreased Appetite	157 (22)	149 (22)	39 (18)	28 (14)
Musculoskeletal and connective tissue disorders	286 (41)	279 (41)	74 (34)	51 (25)
Respiratory, thoracic, and mediastinal disorders	260 (37)	250 (37)	63 (29)	60 (29)
Investigations	252 (36)	239 (35)	60 (28)	47 (23)
Infections and infestations	237 (34)	231 (34)	63 (29)	56 (27)
Blood and lymphatic system disorders	176 (25)	170 (25)	46 (21)	105 (51)
Anaemia	82 (12)	80 (12)	21 (10)	71 (34)
Neutropenia	65 (9)	64 (9)	24 (11)	59 (29)
Skin and subcutaneous tissue disorders	132 (19)	131 (19)	35 (16)	76 (37)

The most common TEAEs ≥ Grade 3 occurring in ≥ 5% of patients in any analysis population by SOC and PT are presented in the below table.

Table 67: Grade 3 or Higher TEAEs Occurring in ≥ 5% of Patients in Any Analysis Population by SOC and PT

System Organ Class Preferred Term	All Patients MIRV (6 mg/kg AIBW Q3W) (N = 706) n (%)	EOC Patients MIRV (6 mg/kg AIBW Q3W) (N = 682) n (%)	Study 0416 MIRV (6 mg/kg AIBW Q3W) (N = 218) n (%)	Study 0416 IC Chemotherapy[a] (N = 207) n (%)
Patients with ≥ Grade 3 TEAEs	337 (48)	325 (48)	91 (42)	112 (54)
Gastrointestinal disorders	130 (18)	124 (18)	28 (13)	31 (15)
Eye disorders	76 (11)	75 (11)	30 (14)	0
Vision blurred	32 (5)	32 (5)	17 (8)	0
Keratopathy	32 (5)	31 (5)	20 (9)	0
Metabolism and nutrition disorders	52 (7)	47 (7)	9 (4)	10 (5)
General disorders and administration site conditions	38 (5)	35 (5)	10 (5)	22 (11)
Fatigue	19 (3)	17 (2)	5 (2)	11 (5)
Respiratory, thoracic, and mediastinal disorders	38 (5)	34 (5)	9 (4)	8 (4)
Nervous system disorders	34 (5)	31 (5)	11 (5)	9 (4)
Infections and infestations	34 (5)	30 (4)	10 (5)	13 (6)
Investigations	30 (4)	29 (4)	4 (2)	17 (8)
Blood and lymphatic system disorders	22 (3)	21 (3)	6 (3)	51 (25)
Anaemia	11 (2)	10 (1)	2 (< 1)	21 (10)
Neutropenia	5 (< 1)	5 (< 1)	2 (< 1)	36 (17)
Thrombocytopenia	5 (< 1)	4 (< 1)	2 (< 1)	13 (6)

The most frequently reported ≥ Grade 3 study drug-related TEAEs occurring in ≥ 1% of patients in any analysis population by SOC and PT is shown in the below table.

Table 68: Grade 3 or Higher Study Drug-Related TEAEs Occurring in ≥ 1% of Patients in Any Analysis Population by SOC and PT

System Organ Class Preferred Term	**All Patients MIRV (6 mg/kg AIBW Q3W) (N = 706) n (%)**	**EOC Patients MIRV (6 mg/kg AIBW Q3W) (N = 682) n (%)**	**Study 0416 MIRV (6 mg/kg AIBW Q3W) (N = 217) n (%)**	**Study 0416 IC Chemotherapy[a] (N = 207) n (%)**
Patients with related ≥ Grade 3 TEAEs	182 (26)	175 (26)	53 (24)	77 (37)
Eye disorders	60 (8)	59 (9)	26 (12)	0
Keratopathy	31 (4)	30 (4)	19 (9)	0
Vision blurred	28 (4)	28 (4)	16 (7)	0
Dry eye	12 (2)	12 (2)	7 (3)	0
Cataract	11 (2)	11 (2)	3 (1)	0
Visual acuity reduced	11 (2)	11 (2)	7 (3)	0
Keratitis	5 (< 1)	5 (< 1)	3 (1)	0
Gastrointestinal disorders	37 (5)	33 (5)	9 (4)	8 (4)
Diarrhoea	16 (2)	13 (2)	3 (1)	1 (< 1)
Nausea	9 (1)	9 (1)	2 (< 1)	2 (< 1)
Vomiting	10 (1)	9 (1)	2 (< 1)	0
Abdominal pain	8 (1)	7 (1)	3 (1)	1 (< 1)
General disorders and administration site conditions	22 (3)	21 (3)	4 (2)	13 (6)
Fatigue	12 (2)	11 (2)	2 (< 1)	8 (4)
Nervous system disorders	22 (3)	21 (3)	9 (4)	8 (4)
Neuropathy peripheral	7 (< 1)	7 (1)	3 (1)	4 (2)
Peripheral sensory neuropathy	7 (< 1)	7 (1)	2 (< 1)	2 (< 1)
Investigations	20 (3)	20 (3)	1 (< 1)	13 (6)
Gamma-glutamyltransferase increased	7 (< 1)	7 (1)	0	0
White blood cell count decreased	0	0	0	10 (5)
Metabolism and nutrition disorders	19 (3)	17 (2)	5 (2)	5 (2)
Blood and lymphatic system disorders	15 (2)	14 (2)	4 (2)	46 (22)
Anaemia	6 (< 1)	5 (< 1)	1 (< 1)	18 (9)
Neutropenia	5 (< 1)	5 (< 1)	2 (< 1)	35 (17)
Thrombocytopenia	4 (< 1)	3 (< 1)	1 (< 1)	13 (6)
Skin and subcutaneous tissue disorders	1 (< 1)	1 (< 1)	0	4 (2)
Respiratory, thoracic, and mediastinal disorders	9 (1)	9 (1)	1 (< 1)	0

Adverse reactions

Pooled data from 4 studies in the primary analysis population (N = 682) were used to evaluate the safety profile of MIRV and identify adverse reactions. This population represents all patients treated

with MIRV monotherapy at the proposed dose of 6 mg/kg AIBW IV for epithelial ovarian cancer (intended population).

The adverse reaction frequencies from clinical trials are based on all-causality AE frequencies, for which, after thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility as recommended in the SmPC guideline (https://health.ec.europa.eu/document/download/6a043dea-7d0f-4252-947b-cef58f53d37e_en).

Objective criteria were applied to the data for AEs to screen for potential ADRs, which were then subject to clinical review. Based on the analysis, the ADRs, as summarised in the ADR table below were identified for MIRV on the primary analysis population. Furthermore, all AEs for which a causal relationship to the MIRV treatment has been established are now included in the ADR table.

Table 69: ADRs by system organ class; DCO: 06-03-2023

	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)		0416 IC Chemo (N=207)	
System Organ Class Adverse Reaction	All grades n (%)	Grade 3 or 4 n (%)	All grades n (%)	Grade 3 or 4 n (%)	All grades n (%)	Grade 3 or 4 n (%)	All grades n (%)	Grade 3 or 4 n (%)
Gastrointestinal disorders	539 (76)	85 (12)	520 (76)	80 (12)	147 (67)	19 (9)	132 (64)	17 (8)
Nausea	289 (41)	14 (2)	279 (41)	14 (2)	58 (27)	4 (2)	60 (29)	4 (2)
Diarrhoea	272 (39)	21 (3)	263 (39)	18 (3)	64 (29)	3 (1)	36 (17)	1 (<1)
Abdominal pain	257 (36)	28 (4)	250 (37)	27 (4)	74 (34)	6 (3)	48 (23)	4 (2)
Constipation	178 (25)	4 (<1)	175 (26)	4 (<1)	59 (27)	0	40 (19)	2 (<1)
Vomiting	164 (23)	20 (3)	159 (23)	19 (3)	39 (18)	6 (3)	37 (18)	3 (1)
Abdominal distension	67 (9)	2 (<1)	66 (10)	2 (<1)	14 (6)	1 (<1)	12 (6)	0
Gastroeosophageal reflux disease	42 (6)	1 (<1)	42 (6)	1 (<1)	12 (6)	0	6 (3)	2 (<1)
Dyspepsia	42 (6)	0	41 (6)	0	8 (4)	0	4 (2)	0
Ascites	36 (5)	16 (2)	35 (5)	15 (2)	9 (4)	4 (2)	11 (5)	4 (2)
Stomatitis	28 (4)	1 (<1)	28 (4)	1 (<1)	7 (3)	0	23 (11)	1 (<1)
Eye disorders	408 (58)	75 (11)	397 (58)	74 (11)	120 (55)	30 (14)	10 (5)	0
Blurred vision event	333 (47)	37 (5)	325 (48)	37 (5)	98 (45)	19 (9)	6 (3)	0
Keratopathy	253 (36)	39 (6)	248 (36)	38 (6)	80 (37)	23 (11)	0	0
Dry eye	186 (26)	13 (2)	182 (27)	13 (2)	61 (28)	7 (3)	5 (2)	0
Cataract	107 (15)	28 (4)	106 (16)	28 (4)	34 (16)	7 (3)	1 (<1)	0
Photophobia	97 (14)	3 (<1)	97 (14)	3 (<1)	39 (18)	1 (<1)	1 (<1)	0
Eye pain	68 (10)	3 (<1)	68 (10)	3 (<1)	20 (9)	0	1 (<1)	0
Ocular discomfort	43 (6)	0	42 (6)	0	7 (3)	0	1 (<1)	0
Nervous system disorders	365 (52)	24 (3)	351 (51)	21 (3)	107 (49)	8 (4)	66 (32)	8 (4)
Peripheral neuropathy	254 (36)	21 (3)	248 (36)	18 (3)	81 (37)	8 (4)	47 (23)	8 (4)
Headache	133 (19)	3 (<1)	127 (19)	3 (<1)	31 (14)	0	20 (10)	0
Dysguesia	48 (7)	0	47 (7)	0	11 (5)	0	10 (5)	0
Dizziness	46 (7)	0	40 (6)	0	9 (4)	0	8 (4)	0
General disorders and administration site conditions	280 (40)	21 (3)	268 (39)	19 (3)	75 (34)	6 (3)	61 (29)	12 (6)
Fatigue	248 (35)	19 (3)	236 (35)	17 (2)	66 (30)	5 (2)	52 (25)	11 (5)
Pyrexia	62 (9)	2 (<1)	59 (9)	2 (<1)	14 (6)	1 (<1)	12 (6)	1 (<1)
Musculoskeletal and connective tissue disorders	244 (35)	6 (<1)	238 (35)	6 (<1)	66 (30)	1 (<1)	39 (19)	4 (2)
Arthralgia	111 (16)	2 (<1)	109 (16)	2 (<1)	32 (15)	0	11 (5)	0
Back pain	69 (10)	2 (<1)	67 (10)	2 (<1)	20 (9)	1 (<1)	17 (8)	3 (1)
Myalgia	68 (10)	1 (<1)	66 (10)	1 (<1)	20 (9)	0	7 (3)	1 (<1)
Pain in extremity	46 (7)	1 (<1)	45 (7)	1 (<1)	13 (6)	0	11 (5)	0

Muscle spasms	43 (6)	0	43 (6)	0	9 (4)	0	9 (4)	0
Metabolism and nutrition disorders	249 (35)	28 (4)	237 (35)	26 (4)	53 (24)	5 (2)	53 (26)	5 (2)
Decreased appetite	157 (22)	12 (2)	149 (22)	11 (2)	39 (18)	3 (1)	28 (14)	2 (<1)
Hypomagnesaemia	86 (12)	2 (<1)	78 (11)	2 (<1)	8 (4)	0	18 (9)	0
Hypokalaemia	68 (10)	9 (1)	62 (9)	8 (1)	14 (6)	1 (<1)	14 (7)	3 (1)
Dehydration	40 (6)	12 (2)	34 (5)	10 (1)	8 (4)	1 (<1)	1 (<1)	0
Investigations	193 (27)	20 (3)	183 (27)	20 (3)	45 (21)	1 (<1)	22 (11)	0
Aspartate aminotransferase increased	116 (16)	8 (1)	111 (16)	8 (1)	24 (11)	1 (<1)	9 (4)	0
Alanine aminotransferase increased	93 (13)	6 (<1)	90 (13)	6 (<1)	19 (9)	1 (<1)	9 (4)	0
Weight decreased	60 (8)	1 (<1)	55 (8)	1 (<1)	19 (9)	0	7 (3)	0
Blood alkaline phosphatase increased	46 (7)	3 (<1)	46 (7)	3 (<1)	9 (4)	0	4 (2)	0
Gamma-glutamyltransferase increased	28 (4)	8 (1)	28 (4)	8 (1)	7 (3)	0	2 (<1)	0
Respiratory, thoracic and mediastinal disorders	183 (26)	15 (2)	176 (26)	13 (2)	41 (19)	3 (1)	35 (17)	6 (3)
Cough	87 (12)	0	85 (12)	0	17 (8)	0	14 (7)	0
Dyspnoea	81 (11)	7 (<1)	79 (12)	7 (1)	14 (6)	2 (<1)	27 (13)	6 (3)
Pneumonitis	75 (11)	10 (1)	70 (10)	8 (1)	21 (10)	1 (<1)	1 (<1)	0
Blood and lymphatic system disorders	169 (24)	19 (3)	164 (24)	18 (3)	45 (21)	6 (3)	102 (49)	50 (24)
Anaemia	82 (12)	11 (2)	80 (12)	10 (1)	21 (10)	2 (<1)	71 (34)	21 (10)

	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)		0416 IC Chemo (N=207)	
System Organ Class Adverse Reaction	All grades n (%)	Grade 3 or 4 n (%)	All grades n (%)	Grade 3 or 4 n (%)	All grades n (%)	Grade 3 or 4 n (%)	All grades n (%)	Grade 3 or 4 n (%)
Thrombocytopenia	72 (10)	5 (<1)	69 (10)	4 (<1)	16 (7)	2 (<1)	33 (16)	13 (6)
Neutropenia	65 (9)	5 (<1)	64 (9)	5 (<1)	24 (11)	2 (<1)	59 (29)	36 (17)
Infections and infestations	76 (11)	10 (1)	71 (10)	7 (1)	16 (7)	2 (<1)	16 (8)	0
Urinary tract infection	76 (11)	10 (1)	71 (10)	7 (1)	16 (7)	2 (<1)	16 (8)	0
Psychiatric disorders	48 (7)	0	46 (7)	0	12 (6)	0	6 (3)	0
Insomnia	48 (7)	0	46 (7)	0	12 (6)	0	6 (3)	0
Vascular disorders	41 (6)	11 (2)	39 (6)	10 (1)	11 (5)	4 (2)	8 (4)	0
Hypertension	41 (6)	11 (2)	39 (6)	10 (1)	11 (5)	4 (2)	8 (4)	0
Skin and subcutaneous tissue disorders	28 (4)	0	28 (4)	0	8 (4)	0	6 (3)	0
Pruritis	28 (4)	0	28 (4)	0	8 (4)	0	6 (3)	0

Injury, poisoning and procedural complications	18 (3)	2 (<1)	17 (2)	2 (<1)	5 (2)	0	9 (4)	1 (<1)
Infusion related reaction/Hypersensitivity	18 (3)	2 (<1)	17 (2)	2 (<1)	5 (2)	0	9 (4)	1 (<1)
Hepatobiliary disorders	13 (2)	2 (<1)	12 (2)	1 (<1)	2 (<1)	0	0	0
Hyperbilirubinaemia	13 (2)	2 (<1)	12 (2)	1 (<1)	2 (<1)	0	0	0

IC Chemo: Paclitaxel (PAC; 80 mg/m² administered weekly [QW] within a 4-week cycle; pegylated liposomal doxorubicin (PLD; 40 mg/m² administered every 4 weeks [Q4W]; topotecan (TOPO; 4 mg/m² administered either on Days 1, 8 or 15 of a 4 week cycle [Q4W] or for 5 consecutive days at 1.25 mg/m² Days 1-5 every 3 weeks [Q3W]).
Coding was performed using MedDRA 24.0.
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 date for study IMGN853-0401: 10FEB2018; IMGN853-0403: 18MAR2020; IMGN853-0417: 22DEC2022; IMGN853-0416: 06MAR2023

Adverse events of special interest

AEs of special interest, which can be based on MIRV's mechanism of action, included ocular TEAEs and pneumonitis. Additional potential AEs of interest were peripheral neuropathy since MIRV is a DM4 (payload) tubulin-directed compound, and infusion-related reactions (IRRs) as MIRV is an antibody-drug conjugate.

Ocular AEs

Ocular AEs related to keratopathy, including visual impairment, have been reported with ADCs containing tubulin-directed payloads.

Patients with any active or chronic corneal disorders by medical history were excluded from the studies. This toxicity of MIRV was largely observed in study 0416 while the incidence of ocular AEs in the IC Chemo arm was very low, as well as severity.

The frequency and severity of ocular TEAEs by PT in ≥ 5% of patients are shown in the below table.

Table 70: Ocular TEAEs by PT and Maximum CTCAE Grade in ≥ 5% of Patients (All Analysis Populations)

Preferred Term Maximum CTCAE Grade	**All Patients MIRV (6 mg/kg AIBW Q3W) (N = 706) n (%)**	**EOC Patients MIRV (6 mg/kg AIBW Q3W) (N = 682) n (%)**	**Pooled Analysis Study 0417 and Study 0416 (6 mg/kg AIBW Q3W) (N = 324) n (%)**	**Study 0416 MIRV (6 mg/kg AIBW Q3W) (N = 218) n (%)**	**Study 0416 IC Chemotherapy[a] (N = 207) n (%)**
Patients with any TEAEs, n (%)					
All grades	417 (59)	405 (59)	185 (57)	122 (56)	18 (9)
⩾ Grade 3	76 (11)	75 (11)	45 (14)	30 (14)	0
Visual blurred, n (%)					
All grades	301 (43)	294 (43)	137 (42)	89 (41)	5 (2)
⩾ Grade 3	32 (5)	32 (5)	25 (8)	17 (8)	0

Preferred Term Maximum CTCAE Grade	**All Patients MIRV (6 mg/kg AIBW Q3W) (N = 706) n (%)**	**EOC Patients MIRV (6 mg/kg AIBW Q3W) (N = 682) n (%)**	**Pooled Analysis Study 0417 and Study 0416 (6 mg/kg AIBW Q3W) (N = 324) n (%)**	**Study 0416 MIRV (6 mg/kg AIBW Q3W) (N = 218) n (%)**	**Study 0416 IC Chemotherapy[a] (N = 207) n (%)**
Keratopathy, n (%)					
All grades	201 (28)	199 (29)	105 (32)	70 (32)	0
⩾ Grade 3	32 (5)	31 (5)	28 (9)	20 (9)	0
Dry eye, n (%)					
All grades	185 (26)	181 (27)	91 (28)	61 (28)	5 (2)
⩾ Grade 3	12 (2)	12 (2)	9 (3)	7 (3)	0
Cataract, n (%)					
All grades	104 (15)	103 (15)	53 (16)	32 (15)	1 (< 1)
⩾ Grade 3	28 (4)	28 (4)	12 (4)	7 (3)	0
Photophobia, n (%)					
All grades	97 (14)	97 (14)	56 (17)	39 (18)	1 (< 1)
⩾ Grade 3	3 (< 1)	3 (< 1)	1 (< 1)	1 (< 1)	0
Visual acuity reduced, n (%)					
All grades	87 (12)	87 (13)	30 (9)	26 (12)	0
⩾ Grade 3	11 (2)	11 (2)	7 (2)	7 (3)	0
Eye pain, n (%)					
All grades	68 (10)	68 (10)	29 (9)	20 (9)	1 (< 1)
⩾ Grade 3	3 (< 1)	3 (< 1)	0	0	0
Keratitis, n (%)					
All grades	39 (6)	37 (5)	16 (5)	11 (5)	0
⩾ Grade 3	6 (< 1)	6 (< 1)	5 (2)	3 (1)	0
Punctate keratitis, n (%)					
All grades	32 (5)	31 (5)	16 (5)	7 (3)	0
⩾ Grade 3	1 (< 1)	1 (< 1)	1 (< 1)	1 (< 1)	0
Vitreous floaters, n (%)					
All grades	32 (5)	30 (4)	14 (4)	11 (5)	2 (< 1)
⩾ Grade 3	0	0	0	0	0

The median time to first onset for ocular TEAEs for the EOC population was 5.14 weeks (0.1 to 68.6 weeks). Ocular adverse reactions improved in most cases either completely (53%) or partially (38%). There was no documented improvement of any ocular TEAE in 36 (9%) of patients. Amongst all patients, the final grade for patients with no documented improvement in blurred vision was Grade 3 for 2 patients and the final grade for patients with no documented improvement in cataract was Grade 3 for 7 patients and Grade 4 for one patient. Amongst these 8 patients with no documented improvement in cataracts Grade 3 or 4, 6/8 (75%) had documented cataracts (Grade 1) ongoing at baseline. 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. Most patients did not require dose modifications, but dose was delayed in 24%,

dose was reduced in 15%, dose was not given in 4% and infusion was interrupted in < 1%. The ocular event profile and the mitigation steps resulted in a discontinuation rate of 1%.

Pneumonitis

Frequency and severity of pneumonitis TEAEs are summarized in the below table.

Table 71: Pneumonitis TEAEs by PT and Maximum CTCAE Grade

Preferred Term and Grade	All Patients MIRV (6 mg/kg AIBW Q3W) (N = 706) n (%)	EOC Patients MIRV (6 mg/kg AIBW Q3W) (N = 682) n (%)	Study 0416 MIRV (6 mg/kg AIBW Q3W) (N = 218) n (%)	Study 0416 IC Chemotherapy[a] (N = 207) n (%)
Patients with pneumonitis (grouped term), 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

Abbreviations: AIBW = adjusted ideal body weight; EOC = epithelial ovarian cancer; MIRV = mirvetuximab soravtansine; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PT = Preferred Term; Q3W = every 3 weeks; Q4W = every 4 weeks; SOC = System Organ Class; TEAE = treatment-emergent adverse event.

[a] IC Chemo: paclitaxel (80 mg/m^2 administered weekly within a 4-week cycle), pegylated liposomal doxorubicin (40 mg/m^2 administered Q4W), or topotecan (4 mg/m^2 administered either on Days 1, 8, or 15 Q4W or for 5 consecutive days at 1.25 mg/m^2 Days 1-5 Q3W).

Note: Coding was performed using MedDRA (Medical Dictionary for Regulatory Activities), Version 24.0, and NCI-CTCAE, Version 5.0.

Note: Pneumonitis includes pneumonitis, interstitial lung disease, pulmonary fibrosis, respiratory failure, organizing pneumonia, and organizing pneumonia.

Note: When counting events, each event is counted once for each adverse event entered into the electronic case report form. For the remaining frequencies, each patient is counted once, with the worst grade for each Preferred Term.

Data cut-off date for study IMGN853-0401: 10FEB2018; IMGN853-0403: 18MAR2020; IMGN853-0417: 22DEC2022; IMGN853-0416: 06MAR2023

In the primary safety population and in the study 0416 MIRV group, pneumonitis was reported in 10% of patients, while in the IC Chemo group the incidence was < 1%. Because in study 0403 the majority of pneumonitis events were ≤ Grade 2 in severity (88%) with no Grade 4 or 5 pneumonitis events, the AESI designation for pneumonitis was removed in study 0417 and in pivotal study 0416. In study 0416 indeed most of the reported pneumonitis TEAEs were of ≤ Grade 2 in severity in patients treated with MIRV, and Grade 3 or higher events occurred in 2 (< 1%) patients compared with 0 patient in the IC Chemo group. However, TEAEs of Grade 5 respiratory failure were observed in 2 patients (< 1%) and occurred in study 0417 and pivotal study 0416, and one TEAE of Grade 5 respiratory failure (study 0417) was considered related to study drug. The median time to onset of pneumonitis was 18.1 weeks (range 1.6 to 97.0). Pneumonitis resulted in mirvetuximab soravtansine dose delays in 3%, dose reductions in 1% and permanent discontinuation in 3% of patients. Pneumonitis was the most common study drug-related SAE by PT (4%). Consequently, the risk of pneumonitis and severe respiratory failure can be linked to MIRV.

The median time to first onset of pneumonitis TEAEs was 21 weeks (3.1 to 49.1 weeks) for patients treated with MIRV in the pivotal study 0416, and the time to onset was 6 weeks for the 1 patient who had a pneumonitis TEAE in the IC Chemo arm.*Peripheral neuropathy TEAEs*

Peripheral neuropathy is a known AE associated with cytotoxic agents that target tubulin. It has been reported with anti-tubulin chemotherapies as well as with ADCs containing tubulin-directed payloads.

The mechanism behind peripheral neuropathy is hypothesised to be peripheral axonopathy induced by free payload released in the systemic circulation.

The median time to first onset for the peripheral neuropathy TEAEs was 5.86 weeks (0.1 to 126.7) in the primary analysis population.

Among patients in the primary analysis population (N = 682), a total of 248 (36%) patients had at least 1 reported peripheral neuropathy TEAE of any grade, most of which were ≤ Grade 2 (230 patients, 34%). A total of 18 (3%) patients reported peripheral neuropathy TEAEs ≥ Grade 3 in severity. No Grade 4 or Grade 5 TEAEs were observed in patients in the primary analysis group. Overall, patients in the MIRV analysis group reported more peripheral neuropathy TEAEs of all grades compared with patients in the IC Chemo analysis group: 81 (37%) patients vs 47 (23%) patients, respectively. TEAEs ≥ Grade 3 were similar between both analysis groups.

The peripheral neuropathy TEAEs in 248 patients treated with MIRV completely resolved in 58 patients (23%) and partially improved in 30 patients (12%). 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.

Peripheral neuropathy resulted in mirvetuximab soravtansine dose delays in 2%, dose reductions in 4%, and led to permanent discontinuation in <1% of patients.

In section 4.4 of the SmPC, a warning is included 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. In the primary safety population, no action was taken for 210 patients (31%), dose was delayed or not given for 5 patients (< 1%), dose was reduced for 28 patients (4%), and was dose permanently discontinued for 5 patients (< 1%). Most (160 patients, 65%) did not have documented improvement. Three of the 160 patients who did not have documented improvement had Grade 3 peripheral neuropathy.

Serious adverse event/deaths/other significant events

Serious adverse events

The table below shows the most frequently reported treatment-emergent SAEs occurring in ≥ 1% of patients in any analysis population by PT.

Table 72: SAEs Occurring in ≥ 1% of Patients in Any Analysis Population by SOC and PTSystem Organ Class

Preferred Term	**All Patients MIRV (6 mg/kg AIBW Q3W) (N = 706) n (%)**	**EOC Patients MIRV (6 mg/kg AIBW Q3W) (N = 682) n (%)**	**Study 0416 MIRV (6 mg/kg AIBW Q3W) (N = 218) n (%)**	**Study 0416 IC Chemotherapy[a] (N = 207) n (%)**
Patients with SAEs	214 (30)	203 (30)	52 (24)	68 (33)

Preferred Term	**All Patients MIRV (6 mg/kg AIBW Q3W) (N = 706) n (%)**	**EOC Patients MIRV (6 mg/kg AIBW Q3W) (N = 682) n (%)**	**Study 0416 MIRV (6 mg/kg AIBW Q3W) (N = 218) n (%)**	**Study 0416 IC Chemotherapy[a] (N = 207) n (%)**
Gastrointestinal disorders	101 (14)	96 (14)	25 (11)	27 (13)
Small intestinal obstruction	23 (3)	23 (3)	4 (2)	10 (5)
Intestinal obstruction	19 (3)	19 (3)	5 (2)	4 (2)
Abdominal pain	13 (2)	13 (2)	6 (3)	1 (< 1)
Ascites	11 (2)	10 (1)	4 (2)	2 (< 1)
Vomiting	11 (2)	10 (1)	3 (1)	2 (< 1)
Constipation	9 (1)	8 (1)	1 (< 1)	1 (< 1)
Large intestinal obstruction	8 (1)	6 (< 1)	1 (< 1)	1 (< 1)
Respiratory, thoracic, and mediastinal disorders	60 (8)	57 (8)	12 (6)	6 (3)
Pneumonitis	26 (4)	25 (4)	1 (< 1)	0
Pleural effusion	15 (2)	15 (2)	6 (3)	0
Dyspnoea	4 (< 1)	4 (< 1)	2 (< 1)	3 (1)
Infections and infestations	38 (5)	35 (5)	9 (4)	13 (6)
General disorders and administration site conditions	19 (3)	18 (3)	10 (5)	7 (3)
General physical health deterioration	4 (< 1)	4 (< 1)	3 (1)	2 (< 1)
Metabolism and nutrition disorders	15 (2)	15 (2)	1 (< 1)	5 (2)
Dehydration	9 (1)	9 (1)	1 (< 1)	0
Injury, poisoning and procedural complications	9 (1)	8 (1)	2 (< 1)	2 (< 1)
Nervous system disorders	8 (1)	8 (1)	2 (< 1)	1 (< 1)
Blood and lymphatic system disorders	5 (< 1)	4 (< 1)	2 (< 1)	9 (4)
Thrombocytopenia	3 (< 1)	2 (< 1)	2 (< 1)	3 (1)
Neutropenia	0	0	0	5 (2)
Investigations	0	0	0	3 (1)

SAEs were reported less for the MIRV group compared with the IC Chemo group, 24% vs 33% respectively. Overall, a greater proportion of patients treated with MIRV had SAEs of pleural effusion compared with patients treated with IC Chemo (6 vs 0 patients, respectively). A greater proportion of patients treated with IC Chemo had SAEs of neutropenia compared with those treated with MIRV (0 vs 5 patients, respectively).

Drug-related SAEs

Among patients in the primary analysis population (N = 682), a total of 77 (11%) patients had at least 1 reported study drug-related SAE. The most common study drug-related SAEs by SOC were Respiratory, thoracic, and mediastinal disorders (5%); Gastrointestinal disorders (2%); and General disorders and administration site conditions (1%). The most common study drug-related SAE by PT was pneumonitis (4%). All other study drug-related SAEs occurred in < 1% of patients.

In the pivotal Study 0416, a total of 20 (9%) patients treated with MIRV experienced study drug-related SAEs, with the most common SAEs of any grade by SOC occurring in Gastrointestinal disorders (7 patients, 3%). The most common study drug-related SAEs by PT were abdominal pain (3 patients, 1%) and vomiting (2 patients, < 1%). The frequency of study drug-related SAEs was similar between treatment groups.

In the pivotal study 0416, treatment-related Gastrointestinal Disorder SAEs occurred in 7 patients (3%) treated with MIRV and in 2 patients (< 1%) treated with IC Chemo. Two deaths in the MIRV arm were due to gastrointestinal disorders 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.

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, additional antiemetics may be considered thereafter as needed.

Deaths

In the primary analysis population, a total of 29 (4.3%) patients died during treatment and safety follow-up period. This includes deaths due to AEs in 9 (1.3%) patients, progressive disease in 19 (2.8%) patients, and 'other' [palliative sedation] in 1 (0.1%) patient. A total of 283 (41.5%) patients died more than 30 days after the last dose, primarily due to PD. Also in the primary analysis population, 13 (2%) patients died due to TEAEs. Six deaths occurred due to gastrointestinal TEAEs including 2 events of intestinal obstruction, and single events of ascites, large intestinal obstruction, small intestinal obstruction, intestinal perforation, and subileus, all of which were attributed to disease progression. Other fatal TEAEs were cardiac arrest and respiratory failure (2 patients each, < 1%); and cardiopulmonary failure, sepsis, neutropenic sepsis, and dyspnea (1 patient each, < 1%). The applicant clarified that the reason that there are two different numbers, 9 (1.3%) Deaths due to AEs and 13 (2%) died due to TEAEs, is because there are four patients who had an adverse event with the outcome of 'Fatal' but the Investigator reported 'Disease progression' as the overall reason for death reported on the Death CRF. These discrepancies are common in that the AEs reported were a direct result of the underlying progressive disease.

In the pivotal study 0416, among patients treated with MIRV, 9 (4.1%) patients died within 30 days of the last dose. The primary cause of death was disease progression (6 patients, 2.8%) and AE (3 patients, 1.4%). Of the patients treated with IC Chemo, 11 (5.3%) patients died within 30 days of the last dose. The primary causes of death were disease progression (7 patients, 3.4%) and AE (3 patients, 1.4%). Death during survival follow-up was lower among patients in the MIRV group (36.2%) compared with the IC Chemo group (48.3%).

Deaths causally related to the medicinal product

There were 2 fatal AEs considered related to study drug in the primary analysis population. The first was an 86-year-old patient who died due to respiratory failure (study 0417), and the second fatal AE was neutropenic sepsis in a 75-year-old patient (study 0416). The patient with fatal respiratory failure had an advanced ovarian cancer including involvement in the lung complicated by diffuse alveolar

damage. Based on a comprehensive review of information available for the case of neutropenic sepsis in the setting of disease progression, including medical history, prior events, concomitant medications, mechanism of action of MIRV, the applicant considered that there was, however, no strong evidence to support a causal association, and neutropenic sepsis was not considered to be an ADR. This can be considered acceptable, especially because neutropenia as such is listed as a common ADR in the tabulated list of adverse events in SmPC section 4.8

Other significant events

Premedication was introduced in study 0401 and based on the clinical experience in the Phase 1 it was required in studies 0403, 0417, and 0416 prior to each dose of MIRV to reduce the risk of infusion relates reactions (IRRs). This included a corticosteroid, antihistamine, and antipyretic at least 30 minutes before study drug administration for all patients, and consideration of corticosteroids 1 day before study drug administration in patients who had previously experienced an IRR. With these measures, the risk of IRRs was low.

Among patients in the primary analysis population (N = 682), 4 patients (< 1%) experienced Grade 3 events IRR or hypersensitivity events. No Grade 4 or 5 IRR events were reported. No events of IRR lead to study drug discontinuation.

Overall, TEAEs of IRR were similar between MIRV and IC Chemo. However, a greater proportion of patients treated with paclitaxel were observed to experience IRR TEAEs compared with any other IC Chemo treatment group (21%). Throughout the clinical studies IRR or hypersensitivity TEAEs to MIRV were not life-threatening.

Use of premedications (corticosteroids, antihistamines, and antipyretics) at least 30 minutes prior to infusion to reduce the incidence and severity of IRRs is recommended in section 4.2 of the SmPC. For patients who experienced an IRR Grade ≥2, additional premedications including corticosteroids should be considered the day prior to MIRV administration. Dose modifications include interrupting the infusion, administering supportive treatment, reducing the infusion rate, or permanently discontinuing treatment depending on severity grade.

Laboratory findings

Haematology and clinical chemistry

Remarkable changes in haematology or clinical chemistry parameters occurred infrequently. For the primary analysis population (N=682), the incidences of haematology laboratory abnormalities 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. In study 0416, a greater proportion of patients treated with IC Chemo reported neutropenia (29% vs 11%) and anaemia (34% vs 10%) compared with those treated with MIRV. Anaemia, thrombocytopenia, and neutropenia are included as ADRs in section 4.8 of the SmPC.

Regarding chemistry, in the primary analysis population, there was 1 patient each with a worst post-baseline Grade 4 laboratory value for hyperkalemia (0.1%) and hypomagnesemia (0.2%). The incidences of maximum post-baseline values of Grade 3 severity in ≥ 5 patients included 17 (2.5%) patients with hypokalemia, 11 (1.7%) patients with hypomagnesemia, and 6 (0.9%) patients with hypoalbuminemia. Thrombocytopenia SAEs occurred in 2 patients, and in one patient the SAE was considered related to MIRV treatment. Thrombocytopenia TEAEs led to dose reduction or delay in 18 patients (3%) treated with MIRV and led to treatment discontinuation in 9 patients (1%). No deaths

occurred due to thrombocytopenia TEAEs. Overall, MIRV is associated with relatively low myelosuppression compared with other cytotoxic chemotherapies.

Thrombocytopenia is included as and ADR in section 4.8 of the SmPC. 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.

Liver function tests

In the primary analysis population (N = 682), 9 (1.3%) patients had Grade 3 aspartate aminotransferase (AST) values, 14 (2.1%) patients had Grade 3 alanine aminotransferase (ALT) values, 3 (0.4%) patients had Grade 3 total bilirubin values, and 5 (0.7%) patients had Grade 3 ALP values.

For patients in the primary analysis population, analysis of liver function test results reported 81 (12.1%) patients with post-baseline concurrent ALT or AST > 3 × upper limit of normal (ULN), 15 (2.3%) patients with post-baseline total bilirubin levels (TBL) > 1.5 × ULN, and 179 (26.9%) patients with ALP > 1.5 × ULN. No patient had a concurrent (AST or ALT) > 3 × ULN and TBL > 3 × ULN and TBL > 1.5 × ULN occurred in 4 (0.6%) patients. Concurrent (AST or ALT) > 3 × ULN and ALP > 3 × ULN and ALP < 2 × ULN and TBL $\geq$ 2 $\times$ ULN did not occur in any patients.

No patient met the Hy's Law criteria.

No clinically relevant changes were observed over time for mean liver function tests, including parameters for AST, ALT, or blood bilirubin, and ALP parameters. Slight increases in values were seen at most of the treatment cycles. 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%). No hepatic enzyme elevation TEAEs led to treatment discontinuation or death.

In the pivotal study 0416, clinically significant liver function test results were similar between the MIRV group and the IC Chemo group.

Hyperkalaemia

Concerning the cardiac risk, the applicant undertook a review of clinical safety data specifically related to hyperkalaemia and cardiac events. Based on the comprehensive analysis, there was no evidence that the few events of elevated potassium level did result in cardiac adverse events.

Best corrected visual acuity and interocular pressure

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. Since BCVA was not collected in study 0401, the 113 patients from this study are not included in the primary analysis population for this parameter. Accordingly the number of patients in the primary analysis population in the context of BCVA examination is 569. According to the applicant, in the primary analysis population (N = 569), 496 patients had documentation of baseline BCVA, and 180 (53%) patients had end of treatment (EOT) and/or 30-day follow-up visit BCVA.

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). At the EOT/30-day follow-up, 13% (21/162 patients) had ≥ 3 lines of worsening in BCVA at last follow-up.

In pivotal study 0416, 6 (10%) patients had a EOT/30-day BCVA shift noted as ≥ 3 lines. 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/30-day examination. No patient had BCVA of 20/200 or worse at the last follow-up.

In the primary analysis population (N = 569), 347/569 had both baseline and post-baseline intraocular pressure (IOP) assessments.

Less than 1% of patients with baseline IOP ≤ 22 mmHg had final IOP > 22 mmHg. Values in study 0416 were similar to the primary analysis population.

Safety in special populations

Age

There were no observed trends in the proportion of patients experiencing TEAEs between age groups in the primary analysis population. TEAEs stratified by age were consistent with the overall TEAE. However, in the pivotal study 0416, fewer patients aged 18 to 64 years who were treated with MIRV reported diarrhoea and asthenia TEAEs than patients ≥ 65 years of age (20% vs 40% and 12% vs 27%, respectively). This difference can be seen slightly also in the primary analysis population. The AE profile in patients ≥ 85 years is difficult to evaluate, because only 4 patients in the primary safety group and 1 patient in the 0416 MIRV group belonged to this age group.

Patient geography

Overall TEAEs by SOC reported by geographic regions for the primary analysis population (N = 682) are similar, with the exception of Middle East and Africa, which had only 3 patients with higher frequency of TEAEs compared with the other regions.

Hepatic status

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 ≤ 3.0 × ULN; serum bilirubin ≤ 1.5 × ULN (patients with documented diagnosis of Gilbert syndrome were eligible if TBL < 3.0 × ULN); and serum albumin ≥ 2 g/dL.

So far, hepatic status did not affect the safety profile. Use of MIRV in patients with moderate or severe hepatic impairment has not been studied. Use of MIRV in patients with moderate hepatic impairment is currently included as missing information in the RMP and will be further characterised in study IMGN853-0425, a category 3 study in the RMP (MEA).

In section 5.2 of the SmPC, it is stated 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 no dosage 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 in section 4.2 of the SmPC it is stated that MIRV should be avoided in patients with moderate to severe hepatic impairment (TBL > 1.5 ULN with any AST).

Weight

TEAEs stratified by weight for all analysis populations were similar to those reported for all analysis populations for overall TEAEs. Overall, no specific trend was noted for the TEAEs by baseline body weight. However, population PK analysis indicated that exposure to S-methyl-DM4 increases with increasing AIBW, and exposure-response analysis indicated that higher C_{max} of S-methyl-DM4 was

associated with higher incidence of serious adverse events. The applicant conducted a subgroup analysis of SAEs by AIBW weight divisions in the upper and lower quartiles. Small numerical differences existed between the lower quartiles and the upper quartile, which were primarily reflected in a small increase in the SOC of Respiratory, thoracic, and mediastinal disorders under the PT of Pneumonitis (3% related SAEs in the <54kg and 54-65kg groups and 6% in the >65kg group).

Pregnancy and breastfeeding

Based on its mechanism of action, MIRV can cause embryo-foetal harm when administered to a pregnant woman because it contains a genotoxic compound (DM4) and affects actively dividing cells. In section 4.6 of the SmPC it is recommended that patients of childbearing potential must agree to use effective contraception during treatment with MIRV and for 7 months after the last dose.

Human immunoglobulin G (IgG) is known to cross the placental barrier; therefore, mirvetuximab soravtansine has the potential to be transmitted from the pregnant patient to the developing foetus. There are no available human data on mirvetuximab soravtansine use in pregnant patients to inform a drug-associated risk. No reproductive or developmental animal toxicity studies were conducted with mirvetuximab soravtansine.

Administration of Elahere to pregnant patients is not recommended, and patients should be informed of the potential risks 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 Elahere or within 7 months following the last dose, close monitoring is recommended.

No formal studies have been performed to assess the potential for transfer of MIRV or its metabolites into human breast milk, the effects on the breastfed infant, or the effects on milk production; however, a risk to the newborn/infant cannot be excluded as human immunoglobulin G (IgG) is known to pass on in breast milk. MIRV should not be used during breastfeeding and for 1 month after the last dose.

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 risk to the foetus. No recommendation for contraception for males is provided, but this is considered acceptable, as primary peritoneal serous carcinomas are extremely rare in males.

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

Fertility studies have not been conducted with mirvetuximab soravtansine or DM4. There are no data on the effect of Elahere on human fertility. However, given the mechanism of action of Elahere leads to microtubule disruption and death of rapidly dividing cells, there is the potential for drug-related fertility effects.

ADRs in special populations

The TEAE profile did not change significantly with age (up to 85 years), patient geography, hepatic status (only mild hepatic impairment included) or weight. This makes it reasonable to conclude, that also the ADR profile is unaffected of these intrinsic factors.

Table 73: AEs by age rangeMedDRA Terms

	Primary Analysis Population				Study 0416 IC Comparator			
	Age <65 n (%) N=379	**Age 65-74 n (%) N=229**	**Age 75-84 n (%) N=70**	**Age 85+ n (%) N=4**	**Age <65 n (%) N=119**	**Age 65-74 n (%) N=73**	**Age 75-84 n (%) N=14**	**Age 85+ n (%) N=1**
Total AEs	371 (98%)	228 (>99%)	69 (>99%)	4 (100%)	110 (92%)	69 (95%)	14 (100%)	1 (100%)
Serious AEs – Total	110 (29%)	72 (31%)	19 (27%)	2 (50%)	35 (29%)	27 (37%)	6 (43%)	0
- Fatal	8 (2%)	5 (2%)	2 (3%)	2 (50%)	2 (2%)	4 (6%)	1 (7%)	0
- Hospitalization / prolong existing hospitalization	88 (23%)	57 (25%)	14 (20%)	0	33 (28%)	21 (29%)	5 (36%)	0
- Life-threatening	0	0	1 (1%)	0	0	1 (1%)	0	0
- Disability/incapacity	0	2 (1%)	0	0	0	0	0	0
- Other (medically significant)	14 (4%)	8 (4%)	1 (1%)	0	0	1 (1%)	0	0
AE leading to drop-out	44 (12%)	(28) 12%	10 (14%)	2 (50%)	13 (11%)	16 (22%)	4 (29%)	0
Psychiatric disorders	54 (14%)	30 (13%)	13 (19%)	0	7(6%)	4(5%)	2(14%)	0
Nervous system disorders	212 (56%)	120 (52%)	43 (61%)	1 (25%)	41 (34%)	25 (34%)	3 (21%)	1 (100%)
Accidents and injuries	24 (6%)	23 (10%)	9 (13%)	0	4 (3%)	4 (6%)	1 (7%)	0
Cardiac disorders	19 (5%)	20 (9%)	0	0	6 (5%)	4 (5%)	2 (14%)	1 (100%)
Vascular disorders	48 (13%)	36 (16%)	8 (11%)	1 (25%)	13 (11%)	6 (8%)	2 (14%)	1 (100%)
Cerebrovascular disorders	0	0	0	0	0	1 (1%)	0	0
Infections and infestations	131 (35%)	74 (32%)	26 (37%)	0	30 (25%)	21 (29%)	4 (29%	1 (100%)
Anticholinergic syndrome	0	0	0	0	0	0	0	0
Quality of life decreased	0	0	0	0	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	31 (8%)	26 (11%)	12 (17%)	0	7 (6%)	4 (6%)	0	0
<other AE appearing more frequently in older patients>								
Diarrhoea	133 (35%)	101 (44%)	29 (41%)	0	18 (15%)	15 (21%)	2 (14%)	1 (100%)
Constipation	85 (22%)	65 (28%)	24 (34%)	1 (25%)	21 (18%)	17 (23%)	2 (14%)	0

Fatigue	122 (32%)	87 (38%)	26 (37%)	1 (25%)	30 (25%)	19 (26%)	2 (14%)	1 (100%)
Asthenia	57 (15%)	45 (20%)	20 (29%)	0	18 (15%)	12 (16%)	5 (36%)	0

Table 74: AE by special population by using the patients in the primary analysis population (N = 682)

	Active				**Comparator**			
MedDRA Terms	Hepatically impaired* n (%)	Renally impaired* n (%)	Pregnant n (%)	Other n (%)	Hepatically impaired* n (%)	Renally impaired* n (%)	Pregnant n (%)	Other n (%)
Total AEs	28 (100%)	108 (98%)	N/A	N/A	10 (100%)	43 (92%)	N/A	N/A
Serious AEs – Total	11 (39%)	33 (30%)	N/A	N/A	7 (70%)	23 (49%)	N/A	N/A
- Fatal	1 (4%)	4 (4%)	N/A	N/A	1 (10%)	2 (4%)	N/A	N/A
- Hospitalization / prolong existing hospitalization	7 (25%)	27 (25%)	N/A	N/A	6 (60%)	20 (43%)	N/A	N/A
- Life-threatening	0	0	N/A	N/A	0	1 (2%)	N/A	N/A
- Disability / incapacity	0	0	N/A	N/A	0	0	N/A	N/A
- Other (medically significant)	3 (11%)	2 (2%)	N/A	N/A	0	0	N/A	N/A
AE leading to drop-out	0	3 (3%)	N/A	N/A	5 (50%)	4 (9%)	N/A	N/A

Immunological events

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Two electrochemiluminescence (ECL)-based assays were developed and validated for the detection of anti-drug antibody (ADAs) in human plasma samples, and an assay was validated for the detection of neutralising antibody (NAb) in human plasma.

In the primary analysis 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. 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.

There were no significant differences identified in safety outcomes between seronegative and ADA-positive patients. In the primary analysis population (N=682), among the 626 patients with ADA evaluable samples, the percentage of patients with TEAEs ≥ Grade 3 was 47% for seronegative patients, 54% for ADA positive patients categorised as treatment-emergent, 20% for treatment-enhanced, and 35% for treatment-unaffected. The percentage of patients with SAEs was 31% for seronegative patients, 25% for patients with treatment-emergent ADAs, 20% for patients with treatment-enhanced ADAs, and 10% for patients with treatment-unaffected ADAs.

ADAs do not seem to increase the incidence of TEAEs or SAEs. However, a greater percentage of patients with treatment-emergent ADAs had TEAEs that led to study drug discontinuation (23%)

compared with seronegative patients (12%). Also, 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. 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. However, a greater percentage of patients with treatment-emergent ADAs had IRRs (25%) compared with seronegative patients (7%), and two of the 12 discontinuations among patients with treatment-emergent ADAs were due to SAEs of IRR.

The incidence of NAb was low, and therefore, the impact of NAb on safety or efficacy could not be established. There was no apparent impact of ADAs identified on MIRV clearance or exposure, and 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. Regarding specifically IRR, data do not suggest an increased risk for patients with a seropositive status.

Safety related to drug-drug interactions and other interactions

No clinical drug-drug interaction studies have been conducted. The applicant evaluated the potential effects of concomitantly taken CYP3A4 and P-gP inhibitors on exposure to MIRV, DM4, and S methyl-DM4 in population PK analysis. However, the data are too limited to draw firm conclusions or include information on DDI in the SmPC. Concomitant use of strong CYP4A4 inhibitors may increase exposure to DM4, this is addressed in section 5.2 of the SmPC.

Discontinuation due to adverse events

Discontinuation due to adverse events

TEAEs leading to discontinuation of study drug by SOC and PT for all analysis populations are shown in the below table.

Table 75: TEAEs Leading to Discontinuation by SOC and PT in ≥ 1% in Patients

System Organ Class Preferred Term	**All Patients MIRV (6 mg/kg AIBW Q3W) (N = 706) n (%)**	**EOC Patients MIRV (6 mg/kg AIBW Q3W) (N = 682) n (%)**	**Study 0416 MIRV (6 mg/kg AIBW Q3W) (N = 218) n (%)**	**Study 0416 IC Chemotherapy[a] (N = 207) n (%)**
Patients with TEAEs leading to discontinuation	87 (12)	84 (12)	20 (9)	33 (16)
Gastrointestinal disorders	27 (4)	25 (4)	3 (1)	9 (4)
Respiratory, thoracic, and mediastinal disorders	25 (4)	23 (3)	7 (3)	6 (3)
Pneumonitis	16 (2)	15 (2)	3 (1)	0

System Organ Class Preferred Term	**All Patients MIRV (6 mg/kg AIBW Q3W) (N = 706) n (%)**	**EOC Patients MIRV (6 mg/kg AIBW Q3W) (N = 682) n (%)**	**Study 0416 MIRV (6 mg/kg AIBW Q3W) (N = 218) n (%)**	**Study 0416 IC Chemotherapy[a] (N = 207) n (%)**
Blood and lymphatic system disorders	10 (1)	10 (1)	2 (< 1)	6 (3)
Thrombocytopenia	9 (1)	9 (1)	1 (< 1)	3 (1)
Nervous system disorders	10 (1)	9 (1)	5 (2)	6 (3)
Neuropathy peripheral	1 (< 1)	0	0	4 (2)
Eye disorders	8 (1)	8 (1)	4 (2)	0
Vision blurred	5 (< 1)	5 (< 1)	3 (1)	0
General disorders and administration site conditions	5 (< 1)	5 (< 1)	1 (< 1)	5 (2)
Fatigue	1 (< 1)	1 (< 1)	0	3 (1)
Infections and infestations	4 (< 1)	4 (< 1)	1 (< 1)	3 (1)
Investigations	2 (< 1)	2 (< 1)	0	3 (1)

In the primary analysis population (N = 682), a total of 84 (12%) patients had at least 1 reported TEAE leading to discontinuation of study drug. Forty-eight (7%) patients had ≥ 3 Grade TEAEs that lead to discontinuation. Study drug-related AEs leading to discontinuation were lower in the MIRV group (6%) than in the IC Chemo group (9%).

The most common TEAEs leading to discontinuation of study drug by SOC occurring in ≥ 1% of patients were Gastrointestinal disorders (4%); Respiratory, thoracic, and mediastinal disorders (4%); Blood and lymphatic system disorders (1%); Nervous system disorders (1%); and Eye disorders (1%). The most common TEAEs leading to discontinuation of study drug were pneumonitis (2%) and thrombocytopenia (1%). In the pivotal study 0416, the most common TEAEs leading to discontinuation of study drug were pneumonitis and vision blurred (1%) and pleural effusion and keratopathy (each, < 1%). All other TEAEs leading to discontinuation of study drug occurred in single patients.

Even though ocular TEAEs were very common in MIRV treated patients, only less than 1% of patients discontinued due to ocular TEAEs. Discontinuations due to pneumonitis, thrombocytopenia and peripheral neuropathy were also low (2%, 1% and < 1% respectively).

TEAEs leading to dose reduction or dose delay of study drug

The below table shows the most frequently reported TEAEs leading to dose reduction or dose delay of study drug occurring in patients in any analysis population by SOC and PT.

Table 76: TEAEs Leading to Dose Reduction or Dose Delay in ≥ 1% of Patients By SOC and PT

System Organ Class Preferred Term	**All Patients MIRV (6 mg/kg AIBW Q3W) (N = 706) n (%)**	**EOC Patients MIRV (6 mg/kg AIBW Q3W) (N = 682) n (%)**	**Study 0416 MIRV (6 mg/kg AIBW Q3W) (N = 218) n (%)**	**Study 0416 IC Chemotherapy[a] (N = 207) n (%)**
Patients with TEAEs leading to dose reduction or dose delay	332 (47)	321 (47)	121 (56)	93 (45)
Eye disorders	179 (25)	174 (26)	69 (32)	0
Vision blurred	120 (17)	117 (17)	42 (19)	0
Keratopathy	69 (10)	68 (10)	33 (15)	0
Dry eye	35 (5)	35 (5)	16 (7)	0
Keratitis	24 (3)	24 (4)	8 (4)	0
Cataract	21 (3)	21 (3)	8 (4)	0
Visual acuity reduced	21 (3)	21 (3)	16 (7)	0
Photophobia	16 (2)	16 (2)	11 (5)	0
Eye pain	12 (2)	12 (2)	6 (3)	0
Punctate keratitis	9 (1)	9 (1)	4 (2)	0
Blood and lymphatic system disorders	52 (7)	51 (7)	16 (7)	42 (20)
Neutropenia	34 (5)	34 (5)	11 (5)	31 (15)
Thrombocytopenia	19 (3)	18 (3)	6 (3)	13 (6)
Anaemia	3 (< 1)	3 (< 1)	0	9 (4)
Gastrointestinal disorders	42 (6)	41 (6)	15 (7)	13 (6)
Diarrhoea	11 (2)	11 (2)	4 (2)	3 (1)
Abdominal pain	7 (< 1)	7 (1)	2 (< 1)	1 (< 1)
Vomiting	6 (< 1)	6 (< 1)	4 (2)	3 (1)
Small intestinal obstruction	4 (< 1)	4 (< 1)	1 (< 1)	3 (1)
Nervous system disorders	36 (5)	35 (5)	16 (7)	19 (9)
Neuropathy peripheral	19 (3)	19 (3)	9 (4)	12 (6)
Peripheral sensory neuropathy	11 (2)	11 (2)	5 (2)	4 (2)
Respiratory, thoracic, and mediastinal disorders	35 (5)	35 (5)	13 (6)	3 (1)
Pneumonitis	18 (3)	18 (3)	8 (4)	0
Infections and infestations	28 (4)	26 (4)	12 (6)	11 (5)
COVID-19	6 (< 1)	6 (< 1)	4 (2)	5 (2)
General disorders and administration site conditions	25 (4)	25 (4)	10 (5)	13 (6)
Fatigue	8 (1)	8 (1)	3 (1)	4 (2)
Asthenia	6 (< 1)	6 (< 1)	3 (1)	3 (1)
Pyrexia	6 (< 1)	6 (< 1)	3 (1)	1 (< 1)
Investigations	13 (2)	13 (2)	3 (1)	7 (3)
Weight decreased	5 (< 1)	5 (< 1)	3 (1)	1 (< 1)
White blood cell count decreased	1 (< 1)	1 (< 1)	1 (< 1)	3 (1)
Blood creatinine increased	0	0	0	3 (1)
Metabolism and nutrition disorders	14 (2)	13 (2)	5 (2)	5 (2)

System Organ Class Preferred Term	All Patients MIRV (6 mg/kg AIBW Q3W) (N = 706) n (%)	EOC Patients MIRV (6 mg/kg AIBW Q3W) (N = 682) n (%)	Study 0416 MIRV (6 mg/kg AIBW Q3W) (N = 218) n (%)	Study 0416 IC Chemotherapy[a] (N = 207) n (%)
Decreased appetite	7 (< 1)	7 (1)	2 (< 1)	1 (< 1)
Musculoskeletal and connective tissue disorders	7 (< 1)	7 (1)	3 (1)	2 (< 1)
Skin and subcutaneous tissue disorders	1 (< 1)	1 (< 1)	0	6 (3)

Post marketing experience

The Food and Drug Administration (FDA) granted on 14 November 2022 accelerated approval for mirvetuximab soravtansine-gynx (Elahere) followed by full approval on 22 March 2024.

Cumulatively, 717 patients have been exposed to Elahere as of 13 May 2023. According to the applicant, no significant new safety data were identified that would change the safety profile of Elahere.

2.6.9. Discussion on clinical safety

Exposure

The safety of MIRV has been evaluated in a population consisting of 706 patients, who received at least 1 dose of single-agent MIRV at 6 mg/kg AIBW Q3W in four clinical studies. Of these patients 682 (97%) had the intended indication EOC and comprise the primary analysis population. The number of subjects can be considered sufficient for evaluation of clinical safety.

Subjects with > Grade 1 peripheral neuropathy, corneal disorders or active ocular conditions requiring ongoing treatment/monitoring, clinically significant cardiac disease or history of non-infectious interstitial lung disease including non-infectious pneumonitis were excluded from clinical trials. This is understood considering the safety profile of the treatment. In the primary analysis population, median age was 63 years and median weight was 66.0 kg, patients were predominantly white (84%) and had ECOG status 0 or 1. Within the pivotal study 0416, the two arms were in general well balanced at baseline. Overall, the population was consistent with the fact that most of the patients were at an advanced stage in clinical practice. Additionally, the clinical program was largely conducted in the United States, Canada and Europe, which does not raise concern about the generalisation of results to the European population.

The median duration of exposure for patients in the primary analysis population was 4.4 months (range: 1; 44), corresponding to 6.0 cycles. In the pivotal study 0416, the exposure to treatment was longer in the MIRV arm than in the IC Chemotherapy arm: 5 months and 3 months respectively. Likewise, the number of cycles was higher in the MIRV arm (7.0) compared to the IC Chemo arm (3.0). However, the relative dose intensity was similar. In open studies until the cut-off date of 6 March 2023, there have been 237 patients with long-term data ≥6 months and 67 patients with long-term data ≥12 months exposed to the proposed dose range. Overall, the extent of the exposure appears sufficient considering the disease and the poor prognosis of these patients. The follow-up of adverse events in clinical studies was until 30 days (28 days for study 0401) after the patient's last study drug, or until an adverse event had resolved or stabilized, or an outcome had been reached, whichever came first. This follow-up is conventional for cancer clinical studies and can be considered

sufficient for evaluation of the safety in the intended population. The number of patients who received ≥ 4 prior lines of cancer treatment was very limited (11 patients), and thus, no conclusions could be drawn regarding the safety of MIRV in these patients. This is acceptable as the indication is restricted to patients who received 1 to 3 prior systemic treatment regimens.

Adverse events

Among other TEAEs, eye disorders were very typical for MIRV. This was the clearest difference when compared to IC Chemo. On the other hand, MIRV was less myelosuppressive than IC Chemo.

In the primary analysis population, 99% of the patients experienced an AEs, 91% study drug-related AEs, and 26% related AEs ≥ Grade 3. Additionally, 30% of the patients reported at least 1 SAE, 11% a study drug-related SAE, and 7% ≥ Grade 3 and related SAE.The most common TEAEs by SOC in the primary analysis group (N = 682) were Gastrointestinal disorders (79%), General disorders and administration site conditions (61%), Eye disorders (59%), Nervous system disorders (55%), Metabolism and nutrition disorders (42%), Musculoskeletal and connective tissue disorders (41%), Respiratory, thoracic, and mediastinal disorders (37%), Investigations (35%), Infections and infestations (34%), and Blood and lymphatic system disorders (25%). The most common TEAEs by PT in the primary analysis group occurring in ≥ 20% of patients were vision blurred (43%), nausea (41%), diarrhea (39%), fatigue (35%), abdominal pain (30%), keratopathy (29%), dry eye (27%), constipation (26%), vomiting (23%), decreased appetite (22%), and peripheral neuropathy (20%).

The proportion of patients who experienced all grade TEAEs of any causality was similar between MIRV (96%) and IC Chemo (94%) treatment groups. However, fewer patients treated with MIRV experienced TEAEs ≥ Grade 3 in severity (irrespective of causality), 42% and 54%, respectively.

The most common SOCs with ≥ Grade 3 TEAEs in the primary analysis population (N = 682) were Gastrointestinal disorders (18%); Eye disorders (11%); Metabolism disorders (7%); and General disorders and administration site conditions, Nervous system disorders, and Respiratory, thoracic, and mediastinal disorders (5% each).

The most common TEAEs ≥ Grade 3 by PT were vision blurred and keratopathy (5% each). The most common gastrointestinal TEAEs ≥ Grade 3 by PT were abdominal pain (4%, 25 subjects), small intestinal obstruction (3%, 23), vomiting (3%, 19), diarrhoea (3%, 18), intestinal obstruction (3%,18), ascites (2%, 15), nausea (2%, 14), large intestinal obstruction (<1%, 6), constipation (<1%, 4) and intestinal perforation (<1%, 4). Of note, some kind of intestinal obstruction was a quite common TEAE ≥ Grade 3, as 6,9% (47 patients) in the primary analysis population had intestinal obstruction. However, intestinal obstruction was not more common in the 0416 MIRV arm than in the 0416 IC Chemo arm.

Of the grade 3 or higher TEAEs, patients treated with MIRV reported events within the Eye disorders SOC more frequently (14% vs 0%) than IC Chemo, with the largest disparities in PTs of keratopathy (9% vs 0%) and vision blurred (8% vs 0%). On the other hand, fewer patients treated with MIRV reported events within the SOC of Blood and lymphatic system disorders compared with IC Chemo (3% vs 25%), with the largest differences in neutropenia (< 1% vs 17%) and anaemia (< 1% vs 10%).

In toxicity studies, dermal observations at the injection site and other areas of skin (broken, dry, scaly, or discoloured skin, or scabs, sores, or scars in skin) were reported. Of note, skin and subcutaneous tissue disorders were experienced by 19% of the patients in the primary safety population, but these disorders were more common in patients treated by IC Chemo, 37%. Only 1 patient (1/682) in the primary analysis population had a ≥Grade 3 disorder, while in the IC Chemo treated population there were 6 patients (6/207). There were <1% (6/682) of MIRV treated patients experiencing a photosensitivity reaction, while none (0/207) in the IC Chemo treated patients.

Adverse drug reactions

Pooled data from 4 studies in the primary analysis population (N = 682) were used to evaluate the safety profile of MIRV and to select the adverse reactions for section 4.8 of the SmPC. This population represents all patients treated with MIRV monotherapy at the proposed dose of 6 mg/kg AIBW IV for epithelial ovarian cancer (intended population).

The adverse drug reaction frequencies from clinical trials were based on all-causality AE frequencies, as recommended in the Guideline on summary of product characteristic. Objective criteria were applied to the data for AEs to screen for potential ADRs, which were then subject to clinical review. Based on the analysis, the ADRs, as summarised in the ADR table were identified for MIRV on the primary analysis population. Furthermore, all AEs for which a causal relationship to the MIRV treatment has been established and included in section 4.8 of the SmPC.

Adverse events of special interest

AEs of special interest included ocular TEAEs and pneumonitis. Additional potential AEs of interest included peripheral neuropathy and infusion-related reactions (IRRs).

Ocular AEs

Ocular AEs related to keratopathy, including visual impairment, have been reported with ADCs containing tubulin-directed payloads. The pathogenesis of mirvetuximab soravtansine–induced keratopathy is not completely clear, but the absence of FRα on the cornea suggests these effects are indirect. According to the applicant, these dose-dependent, transient changes in refraction resulting in blurred vision resolve with normal corneal epithelial cell replacement (10-14 days). As already mentioned, patients with any active or chronic corneal disorders by medical history were excluded from the studies. Ocular toxicity of MIRV were largely observed in study 0416 while the incidence of ocular AEs in the IC Chemo arm was very low, as well as severity. Toxicity of the ocular surface is of concern and can largely impact the quality of life of the patients. Moreover, further complications could lead to corneal ulceration and threaten the vision. However, the effects observed with MIRV were mostly low grade and reversible, consistent with the physiology of the corneal epithelium, and the effects have not resulted in the ulcers, erosions, and perforations, which have been seen in other ADCs containing tubulin-directed payloads.

In clinical studies with MIRV, 405 of 682 patients (59%) developed ocular adverse reactions, which were mostly mild or moderate severity, but 75 patients (11%) had a severe (≥ Grade 3) ocular adverse reaction and 2 patients (< 1%) experienced a total of 3 Grade 4 events (i.e. keratopathy and cataract). The median time to first onset for ocular TEAEs for the EOC population was 5.14 weeks (0.1 to 68.6 weeks). The most common adverse reactions were vision blurred in 43% of patients and keratopathy in 29% of patients. In the primary analysis population (N=682), ocular adverse reactions improved in most cases either completely (53%) or partially (38%). There was no documented improvement of any ocular TEAE in 36 (9%) of patients. Amongst all patients, the final grade for patients with no documented improvement in blurred vision was Grade 3 for 2 patients and the final grade for patients with no documented improvement in cataract was Grade 3 for 7 patients and Grade 4 for one patient. Amongst these 8 patients with no documented improvement in cataracts Grade 3 or 4, 6/8 (75%) had documented cataracts (Grade 1) ongoing at baseline.

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. Most patients did not require dose modifications, but dose was delayed in 24%, dose was reduced in 15%, dose was not given in 4% and infusion was interrupted in < 1%. The ocular event profile and the mitigation steps resulted in a discontinuation rate of 1%.

Ocular disorder has been identified as an important identified risk in the RMP and this risk will be mitigated in clinical practice using routine risk minimisation measures including guidance in the SmPC and PIL. Section 4.2 of the SmPC advises healthcare professionals that an ophthalmic exam including visual acuity and slit lamp exam should be conducted before the initiation of Elahere 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. The treating physician should review the patient's ophthalmic examination report before dosing and determine the dose of Elahere based on the severity of findings in the most severely affected eye. Additionally, in section 4.4 of the SmPC it is stated that mirvetuximab soravtansine can cause severe ocular adverse reactions, including visual impairment (predominantly blurred vision), keratopathy (corneal disorders), dry eye, photophobia, and eye pain. Patients should be referred to an eye care professional for an ophthalmic exam before initiation of mirvetuximab soravtansine. 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. If ocular symptoms develop, an ophthalmic exam should be conducted, the patient's ophthalmic report should be reviewed and the dose of mirvetuximab soravtansine may be modified based on the severity of the findings. The guidance in the SmPC can be considered adequate.

In the intended SmPC as well, healthcare professionals will be recommended that patients should be advised to avoid use of contact lenses during treatment with MIRV unless directed by a healthcare professional. Healthcare professionals are advised to monitor patients for ocular disorders and to refer the patient to an eye care professional for an ophthalmic examination if a patient develops ocular symptoms of any grade or for any new or worsening ocular signs and symptoms. . Healthcare professionals will also be advised that Elahere may have moderate influence on the ability to drive and use machines. If patients experience visual disturbances, peripheral neuropathy, fatigue, or dizziness during treatment with mirvetuximab soravtansine, they should be instructed not to drive or use machines until complete resolution of symptoms is confirmed.

Treatment with MIRV should be withheld, reduced or permanently discontinued based on severity and persistence of ocular adverse reactions.

In Section 4.2 of the SmPC the following recommendations are included: 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 Elahere, unless the patient's eye care professional determines that the risks outweigh the benefits of such therapy. 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 Elahere (see Table 3). Patients should be advised to wait at least 15 minutes after ophthalmic topical steroid administration before instilling lubricating eye drops. Intraocular pressure should be checked frequently during treatment with ophthalmic topical steroids. Lubricating eye drops: Patients should be instructed to use lubricating eye drops throughout treatment with Elahere.

In section 4.4 of the SmPC, the following recommendation for ocular disorders are included: Use of lubricating eye drops during treatment with mirvetuximab soravtansine is recommended. In patients who develop ≥Grade 2 corneal adverse reactions, ophthalmic topical steroids are recommended for subsequent cycles of mirvetuximab soravtansine (see Section 4.2).

The guidance in the intended SmPC concerning ocular disorders can be considered adequate.

Pneumonitis

Some but not all ADCs are recognised to cause pneumonitis, but the exact mechanism is unknown. Pneumonitis or drug-induced ILD is one of the important causes of treatment-related AEs and mortality

in patients receiving ADCs, with an incidence range of 1% to 15.8% (Yong WP, Teo FS, Teo LL, et al., 2022). A systematic review and meta-analysis of ADCs in 169 clinical trials found that respiratory diseases (pneumonitis, 12.4% incidence) were the most common cause of treatment-related death in patients treated with ADCs (Zhu Y, Liu K, Wang K, et al., 2023). Therefore, the risk of pneumonitis is particularly of concerns given the risk life-threatening event which could potentially lead to death.

In the primary safety population and in the Study 0416 MIRV group, pneumonitis was reported in 10% of patients, while in the IC Chemo group the incidence was < 1%. In study 0416, most of the reported pneumonitis TEAEs were of ≤ Grade 2 in severity in patients treated with MIRV. In total, 0.9% (6/682) of patients had Grade 3 pneumonitis (grouped terms), and 0.2% (1/682) a Grade 4 event. Two patients (0.3%) died due to respiratory failure. One patient (0.2%) died due to respiratory failure in the setting of Grade 2 pneumonitis and lung metastases confirmed at autopsy. One patient (0.2%) died due to respiratory failure of unknown aetiology without concurrent pneumonitis.

The median time to first onset of pneumonitis TEAEs was 21 weeks (3.1 to 49.1 weeks) for patients treated with MIRV in the pivotal study 0416, and the time to onset was 6 weeks for the 1 patient who had a pneumonitis TEAE in the IC Chemo arm.

MIRV was permanently discontinued in 18 patients (3%). Pneumonitis was the most common study drug-related SAE by PT (4%). Consequently, the risk of pneumonitis and severe respiratory failure can be linked to MIRV.

The median time to onset of pneumonitis was 18.1 weeks (range 1.6 to 97.0). Pneumonitis resulted in mirvetuximab soravtansine dose delays in 3%, dose reductions in 1% and permanent discontinuation in 3% of patients. Pneumonitis was the most common study drug-related SAE by PT (4%). Consequently, the risk of pneumonitis and severe respiratory failure can be linked to MIRV.

In section 4.4 of the SmPC, a warning is included 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. 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. The guidelines in the SmPC concerning pneumonitis can be considered adequate.

Peripheral neuropathy is a known AE associated with cytotoxic agents that target tubulin. It has been reported with anti-tubulin chemotherapies as well as with ADCs containing tubulin-directed payloads. The mechanism behind peripheral neuropathy is hypothesised to be peripheral axonopathy induced by free payload released in the systemic circulation.

The median time to first onset for the peripheral neuropathy TEAEs was 5.9 weeks in the primary analysis population.36% of patients had at least 1 reported peripheral neuropathy TEAE, most of which were ≤ Grade 2 (34%) and 3% of patients reported peripheral neuropathy TEAEs ≥ Grade 3. No Grade 4 or Grade 5 TEAEs were observed. Overall patients in the MIRV analysis group reported more peripheral neuropathy TEAEs compared with the IC Chemo group: 37% vs 23%, but TEAEs ≥ Grade 3 were similar between both analysis groups.

The peripheral neuropathy TEAEs completely resolved in 23% and partially improved in 12%. There was no documented improvement in 65%, these patients were reported to have Grade 1 (42%), Grade 2 (22%), and Grade 3 (3 patients; 1%) peripheral neuropathy TEAEs at the final assessment. Based on the evaluation of potential predisposing baseline factors among those patients who had no documented improvement of peripheral neuropathy, no distinct differences in age, ECOG status, lines of therapy, type of therapy, stage at diagnosis, or time from first diagnosis to the date of the first dose of treatment with mirvetuximab soravtansine could be identified. However, 56% (32/57) of patients who

developed persistent Grade 2/3 peripheral neuropathy had pre-existing Grade 1 peripheral neuropathy prior to receiving mirvetuximab soravtansine, suggesting the most important predisposing factor for the development of Grade 2+ peripheral neuropathy is preexisting peripheral neuropathy.

Peripheral neuropathy resulted in mirvetuximab soravtansine dose delays in 2%, dose reductions in 4%, and led to permanent discontinuation in <1% of patients.

In section 4.4 of the SmPC, a warning is included to draw attention 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. In the primary safety population, no action was taken for 210 patients (31%), dose was delayed or not given for 5 patients (< 1%), dose was reduced for 28 patients (4%), and was dose permanently discontinued for 5 patients (< 1%). Most (160 patients, 65%) did not have documented improvement. Three of the 160 patients who did not have documented improvement had Grade 3 peripheral neuropathy.

Serious adverse events

In the primary analysis population, 30% of patients had at least 1 reported SAE. SAEs of ≥ Grade 3 occurred in 24% of patients. The most common SAEs were pneumonitis (4%), small intestinal obstruction and intestinal obstruction (3% each), abdominal pain, and pleural effusion (2% each), and constipation, ascites, vomiting, and dehydration (1% each) and thrombocytopenia (‹1%). In study 0416, SAEs were reported less frequently for the MIRV group compared with the IC Chemo group, 24% vs 33% respectively. Overall, a greater proportion of patients treated with MIRV had SAEs of pleural effusion compared with patients treated with IC Chemo (6 vs 0 patients). A greater proportion of patients treated with IC Chemo had SAEs of neutropenia compared with those treated with MIRV (0 vs 5 patients).

Drug-related SAEs

In the primary analysis population, 11% of patients had at least 1 reported study drug-related SAE. The most common study drug-related SAEs by SOC were Respiratory, thoracic, and mediastinal disorders (5%); Gastrointestinal disorders (2%); and General disorders and administration site conditions (1%). The most common study drug-related SAE by PT was pneumonitis (4%). All other study drug-related SAEs occurred in < 1% of patients.

Deaths

In the primary analysis population, a total of 29 (4.3%) patients died during treatment and safety follow-up period. 13 (2%) patients died due to TEAEs. Six deaths occurred due to gastrointestinal TEAEs including 2 events of intestinal obstruction, and single events of ascites, large intestinal obstruction, small intestinal obstruction, intestinal perforation, and subileus, all of which were attributed to disease progression. Other fatal TEAEs were cardiac arrest and respiratory failure (2 patients each, < 1%); and cardiopulmonary failure, sepsis, neutropenic sepsis, and dyspnea (1 patient each, < 1%). Two of these fatal AEs were considered related to study drug, which were the respiratory failure and the neutropenic sepsis. Based on a comprehensive review of information available for the case of neutropenic sepsis in the setting of disease progression, including medical history, prior events, concomitant medications, mechanism of action of MIRV, no strong evidence support a causal association, and neutropenic sepsis is not considered to be an ADR. This is acceptable, also because neutropenia as such is listed as a common ADR in the tabulated list of adverse events in section 4.8 of the SmPC. In the pivotal study 0416, among patients treated with MIRV, 9 (4.1%) patients died within 30 days of the last dose. The primary cause of death was disease progression (6 patients, 2.8%) and

AE (3 patients, 1.4%). Of the patients treated with IC Chemo, 11 (5.3%) patients died within 30 days of the last dose. The primary causes of death were disease progression (7 patients, 3.4%) and AE (3 patients, 1.4%).

Other significant events

IRRs were not shown to be a significant problem with MIRV. This is at least partly due to premedication, which included corticosteroid, antihistamine, and antipyretic at least 30 minutes before study drug administration for all patients, and consideration of corticosteroids 1 day before study drug administration in patients who had previously experienced an IRR.

In the primary analysis population, < 1% experienced Grade 3 events IRR or hypersensitivity events. No Grade 4 or 5 IRR events were reported. No events of IRR lead to study drug discontinuation.

Overall, TEAEs of IRR were similar between MIRV and IC Chemo. Hypersensitivity TEAEs to MIRV were not life-threatening.

Also, the use of premedications recommended in section 4.2 of the SmPC is in line with use in the clinical studies. Dose modifications including interrupting the infusion, administering supportive treatment, reducing the infusion rate, or permanently discontinuing treatment depending on severity grade have been adequately reflected in the SmPC.

Laboratory findings

Thrombocytopenia SAEs occurred in 2 patients, and in 1 patient the SAE was considered related to MIRV treatment. Thrombocytopenia TEAEs led to dose reduction or delay in 3% of patients treated with MIRV and led to treatment discontinuation in 1%. No deaths occurred due to thrombocytopenia TEAEs.

Thrombocytopenia is included as an ADR in section 4.8 of the SmPC. 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.

Regarding chemistry, in the primary analysis population, there was 1 patient each with a worst post-baseline Grade 4 laboratory value for hyperkalemia (0.1%) and hypomagnesemia (0.2%). The incidences of maximum post-baseline values of Grade 3 severity in ≥ 5 patients included 17 (2.5%) patients with hypokalemia, 11 (1.7%) patients with hypomagnesemia, and 6 (0.9%) patients with hypoalbuminemia.

A review of clinical safety data specifically related to hyperkalaemia and cardiac events was conducted and did not show evidence that the few events of elevated potassium level did result in cardiac adverse events.

In the pivotal study 0416, clinically significant liver function test results were similar between the MIRV group and the IC Chemo group. In section 4.8 of the SmPC, elevations in hepatic enzymes as well as hyperbilirubinaemia are included as ADR. MIRV should be avoided in patients with moderate to severe hepatic impairment (TBL > 1.5 ULN with any AST) and no dosage 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). Use of MIRV in patients with moderate hepatic impairment is currently included as missing information in the RMP and is planned to be further characterised in study IMGN853-0425, a category 3 study in the RMP (**MEA**).

Safety in special populations

There were no observed trends in the proportion of patients experiencing TEAEs between age groups in the primary analysis population. TEAEs stratified by age were consistent with the overall TEAEs.

TEAEs stratified by weight for all analysis populations were similar to those reported for all analysis populations for overall TEAEs. Overall, no specific trend was noted for the TEAEs by baseline body weight. However, population PK analysis indicated that exposure to S-methyl-DM4 increases with increasing AIBW, and exposure-response analysis indicated that higher C_{max} of S-methyl-DM4 was associated with higher incidence of serious adverse events. A subgroup analysis of SAEs by AIBW weight divisions in the upper and lower quartiles was conducted. Small numerical differences existed between the lower quartiles and the upper quartile, which were primarily reflected in a small increase in the SOC of Respiratory, thoracic, and mediastinal disorders under the PT of Pneumonitis (3% related SAEs in the <54kg and 54-65kg groups and 6% in the >65kg group). Given the very small numbers it is difficult to draw conclusions, and no relationship with pneumonitis was found in the E-R model. No other differences either related or unrelated were noted.

Based on its mechanism of action, MIRV can cause embryo-foetal harm when administered to a pregnant woman because it contains a genotoxic compound (DM4) and affects actively dividing cells. Women of childbearing potential should agree to use effective contraception during treatment with MIRV and for 7 months after the last dose.

MIRV should not be used during breastfeeding and for 1 month after the last dose, because a risk to the newborn/infant cannot be excluded. Human immunoglobulin G (IgG) is known to pass on in breast milk.

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 risk to the foetus.

Relevant statements have been included in section 4.6 of the SmPC.

Immunogenicity

The incidence of NAb was low, and therefore, the impact of NAb on safety or efficacy could not be established. There was no apparent impact of ADAs identified on MIRV clearance or exposure, and 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. Regarding specifically IRR, data do not suggest an increased risk for patients with a seropositive status. The risk of immunogenicity will be minimised in clinical practice through increasing healthcare professional awareness via section 5.1 of the SmPC which states that ADA were commonly detected. No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed, however, data are still limited. Furthermore, the risk of IRRs will be minimised through the use of premedications (corticosteroids, antihistamines, and antipyretics) to reduce the incidence and severity of IRRs. Immunogenicity will continue to be monitored using routine pharmacovigilance activities.

Discontinuations due to adverse events

The rate of study drug-related TEAEs that led to discontinuation were slightly lower in the MIRV treated patients compared to IC Chemo treated patients, 6% and 9% respectively. The same applies to ≥ 3 grade events leading to discontinuation of MIRV or IC Chemotherapy, 2% and 5%.

Even though ocular TEAEs were very common in MIRV treated patients, only less than 1% of patients discontinued due to ocular TEAEs. Discontinuations due to pneumonitis, thrombocytopenia and peripheral neuropathy were also low (2%, 1% and < 1% respectively).

The most common reasons for discontinuations are described in section 4.8 of the SmPC: Permanent discontinuation due to an adverse reaction occurred in 12% of patients who received mirvetuximab soravtansine, including most commonly gastrointestinal disorders (4%), respiratory, thoracic, and

mediastinal disorders (3%), blood and lymphatic system disorders (1%), nervous system disorders (1%), and eye disorders (1%).

Altogether, the rate of discontinuations due to adverse events can be considered relatively low and smaller than for IC Chemo in the pivotal trial, which may indicate that the adverse events are often manageable.

TEAEs leading to dose reduction or dose delay of study drug

Dose reductions and dose delays due to TEAEs were very common in patients treated with MIRV. The most common reasons were ocular TEAEs. In the primary analysis population, 50% of patients had at least 1 reported TEAE leading to dose reduction or dose delay/held of study drug. The most common by SOC were Eye disorders (26%). Also, neutropenia (5%), neuropathy peripheral (3%), thrombocytopenia and pneumonitis (3% each) and diarrhoea and peripheral sensory neuropathy (2% each) led to dose reduction or dose delay of study drug. In study 0416, TEAEs leading to dose reduction or dose delay were experienced in higher frequency in patients treated with MIRV compared to ICC, 56% vs 45%. However, this remains difficult to interpret considering the differences in exposure.

2.6.10. Conclusions on the clinical safety

Overall, the safety database and the extend of the exposure are sufficiently comprehensive to characterise the safety profile of mirvetuximab soravtansine (MIRV) in patients with FRα-positive platinum-resistant EOC.

In the clinical safety profile of MIRV, ocular ARs are dominant, but most of them were mild, manageable and reversible. However, it is to note that ocular toxicity may likely impact the treatment burden of the patients. Extensive recommendations have been included in the SmPC (sections 4.2, 4.4 and 4.8).

Pneumonitis was the most common serious adverse reaaction, which is of importance given its life-threatening risk. Peripheral neuropathy was otherwise common and most of the patients with peripheral neuropathy recovered only partially. Gastrointestinal disorders were also common being in some cases serious and leading even to death in form of intestinal obstructions. However, fatal intestinal obstructions were considered attributed to progressive disease. Thrombocytopenia and neutropenia may lead to consequences but overall serious MIRV was shown to be less myelosuppressive than IC Chemo. Overall, the safety profile appeared acceptable in the context of the poor prognosis of the target population.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 77: 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

2.7.2. Pharmacovigilance plan

Table 78: On-going 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

2.7.3. Risk minimisation measures

Table 79: 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 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:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *None*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	• *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*

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.3 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 14.11.2022. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC and a request of translation exemption have been submitted by the applicant and have been found acceptable by the QRD Group for the following reasons:

The QRD Group would accept the omission of particulars and the translation exemption on the vial label. Some suggestions were made regarding streamlining the labelling text, e.g., to only state the route of administration once as 'Intravenous use after dilution'. The translation exemption of the outer carton was accepted by most Member States apart from Germany and Spain who would like the company to consider the use of multilingual labelling. The labelling text of the outer carton could be streamlined to gain more space and accommodate more languages: E-numbers could be used so they would only need to be stated once and the statement 'Keep out of the sight and reach of children' may be omitted on the outer carton since the product is to be used at hospital level (the statement should in any case appear grey-shaded in the Annex IIIA). The QRD Group also suggested the company to refer to the Appendix IV to ensure the correct use of the term Lot.

The particulars to be omitted as per the QRD Group decision described above will however be included in the Annexes published with the EPAR on EMA website, and translated in all languages but will appear in grey-shaded to show that they will not be included on the printed materials.

The labelling subject to translation exemption as per the QRD Group decision above will however be translated in all languages in the Annexes published with the EPAR on EMA website, but the printed materials will only be translated in the language(s) as agreed by the QRD Group.

2.9.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Elahere (mirvetuximab soravtansine) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The agreed indication reflecting the data evaluated is:

"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 (see section 4.2)."

3.1.2. Available therapies and unmet medical need

When platinum-based chemotherapy is not an option for recurrent ovarian cancer, ESMO guidelines recommend single-agent chemotherapy (weekly paclitaxel, PLD, topotecan and gemcitabine). Bevacizumab should be recommended in combination with weekly paclitaxel, PLD or topotecan in patients without contraindications to bevacizumab and not previously exposed to bevacizumab. Integrating palliative care early in the treatment is strongly recommended. The efficacy of single agent chemotherapies is limited and a significant unmet medical need prevails.

3.1.3. Main clinical studies

Study IMGN853-0416 (MIRASOL), a global, randomised, open label phase 3 study evaluated mirvetuximab soravtansine (MIRV) monotherapy against single agent chemotherapy according to investigator's choice (ICC) in patients with advanced platinum-resistant FRα positive ovarian, fallopian tube or primary peritoneal cancer.

FRα positivity was defined as ≥75% of viable tumour cells exhibiting level 2 (moderate) and/or 3 (strong) membrane staining intensity, analysed using the Ventana FOLR1 assay at central laboratories.

The investigator's choice chemotherapies were paclitaxel, pegylated liposomal doxorubicin, or topotecan, declared before randomisation.

At least 1 but no more than 3 prior systemic lines of anticancer therapy were required prior enrolment.

Randomisation (1:1) was stratified by number of prior lines of therapy (1 versus 2 versus 3) as well as investigator's choice chemotherapies (paclitaxel, pegylated liposomal doxorubicin, or topotecan).The primary endpoint was PFS_{INV}. The key secondary endpoints were ORR_{INV}, OS, and PRO by EORTC QLQ-OV28 Abdominal/GI Symptom Scale.

For MIRV, the dosing was 6 mg/kg AIBW Q3W and according to standard practice for ICC.

Supportive studies consist of the single arm trial SORAYA (n=106), the phase 3 FORWARD-1 trial comparing MIRV to SOC (n=366) and a first in human study (FIH) (n=206).

3.2. Favourable effects

At the data cut-off (DCO) date of 6 March 2023, the MIRASOL study met its primary endpoint PFS_{INV} with a HR 0.65 (95% CI 0.521, 0.808), p<0.0001, with median PFS of 5.62 months with MIRV vs 3.98 months with ICC.

Furthermore, the MIRASOL study met the key secondary endpoint of OS with a HR 0.67 (95% CI 0.504, 0.885, p = 0.0046), with median OS of 16.46 months in MIRV arm vs 12.75 months in ICC arm.

Finally, supportive studies showed consistent efficacy results in patients with PROC and FRα high expression.

3.3. Uncertainties and limitations about favourable effects

While the open label setting in the MIRASOL study was unavoidable, it has impacted the study results in a way which cannot be retrospectively repaired or fully quantified. Early drop out has resulted in informative censoring potentially impacting the study results. While the bias cannot be accurately

accounted for and the exact treatment effect estimate will not be known, it is important to note that extensive further analyses of PFS and OS do not indicate a detrimental effect of MIRV.

The choice of the primary endpoint (PFS_{INV}) was not optimal (OS would have been preferred) and the concordance between PFS_{INV} and PFS_{BICR} was low. However, OS as key secondary efficacy endpoint was statistically significant.

3.4. Unfavourable effects

AEs of special interest included ocular TEAEs, pneumonitis and peripheral neuropathy.

Fifty-nine (59) % of patients had at least 1 ocular TEAE, and ≥ Grade 3 severity ocular TEAE occurred in 11%. The most common ocular TEAEs were vision blurred (43%), keratopathy (29%), dry eye (27%), cataract (15%), photophobia (14%), visual acuity reduced (13%), eye pain (10%), and keratitis and punctate keratitis (5% each). A warning related to ocular disorders was included in section 4.4 of the SmPC and ocular disorders are listed as an important identified risk in the RMP.

Ten (10) % of patients had at least 1 pneumonitis TEAE and the most common related SAE was pneumonitis (4%).

Thirty-six (36) % of patients had at least 1 reported peripheral neuropathy TEAE, most of which were Grade 2.

Twelve (12) % of patients had at least 1 TEAE leading to discontinuation of study drug most commonly gastrointestinal (4%); respiratory, thoracic, and mediastinal disorders (3%); blood and lymphatic system disorders (1%); nervous system disorders (1%); and eye disorders (1%).

Fifty (50)% of patients had at least 1 TEAE leading to dose reduction or dose delay/held of study drug most commonly eye disorders (26%) and gastrointestinal disorders (6%).

3.5. Uncertainties and limitations about unfavourable effects

Subjects with > Grade 1 peripheral neuropathy, corneal disorders or active ocular conditions requiring ongoing treatment/monitoring, clinically significant cardiac disease or history of non-infectious interstitial lung disease including non-infectious pneumonitis were excluded from clinical trials.

Toxicity of the ocular surface is of concern and can largely impact the quality of life of the patients. Extensive warnings and precautions for use have been included in the product information in order to mitigate this risk.

Hepatic impairment may increase exposure to DM4 and/or S-methyl-DM4, which may predispose to adverse reactions caused by the cytotoxic moiety of MIRV. The applicant will conduct a clinical study a clinical study (IMGN853-0425; Hepatic impairment cohort), a category 3 study in the RMP to evaluate the safety and PK of MIRV, DM4, and S-methyl-DM4 in patients with moderate hepatic impairment (**MEA**).

3.6. Effects Table

Table 80: Effects Table for mirvetuximab soravtansine monotherapy in patients with advanced platinum-resistant FR alpha positive ovarian, fallopian tube or primary peritoneal cancer (data cut-off for primary analysis in MIRASOL: 06 March 2023).

Effect	Short Description	Unit	Mirvetuximab soravtansine (n=227)	Chemotherapy by INV choice* (n=226)	Uncertainties/ Strength of evidence
PFS, median	Based on investigator assessment per RECIST v1.1	Months 95% CI	5.62 (4.34, 5.95)	3.98 (2.86, 4.47)	Primary endpoint statistically significant HR 0.65 (0.521, 0.808) uncertainty: informative censoring
		HR (95% CI) p value	0.65 (0.521, 0.808) p<0.0001		
OS, median	Time from randomisation to death	Months 95% CI	16.46 (14.46, 24.57)	12.75 (10.91, 14.36)	Key secondary endpoint statistically significant HR 0.67 (0.504, 0.885) uncertainty: informative censoring, lack of follow up
		HR (95% CI) p value	0.67 (0.504, 0.885) p = 0.0046		
Eye disorders	All events	%	59	9	Eye disorders typical for MIRV. Mostly mild and reversible. Typical for ADCs containing tubulin-directed payloads.
	Vision blurred	%	43	2	
	Keratopathy	%	29	0	
	Dry eye	%	27	2	
Nervous system disorders	All events	%	55	34	
	Peripheral neuropathy		20	14	Known AESI associated with cytotoxic agents that target tubulin.
Respiratory, thoracic and mediastinal disorders	All events	%	37	29	
	Pneumonitis	%	9	<1	Mostly mild, but most common SAE (4%)

* Paclitaxel, pegylated liposomal doxorubicin, topotecan
Abbreviations: HR = hazard ratio, INV = investigator, PFS = progression free survival, ORR = overall response rate, OS = overall survival

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Patients with PROC have few therapeutic options, consisting mainly of single agent chemotherapies. These have only limited efficacy and can be associated to high burden of adverse events. Thus, an unmet medical need in this setting prevails.

The efficacy analyses of the MIRASOL study demonstrated statistically significant improvements in PFS (primary endpoint) and key secondary endpoints of ORR and OS, while not in the 3rd key secondary endpoint with PRO measure EORTC QLQ-OV28 (Abdominal/GI subscale). An improvement of 1.64 months in $mPFS_{INV}$ was observed (5.62 (95% CI, 4.34, 5.95) months in the MIRV arm and 3.98 (95%

CI, 2.86, 4.47) months in ICC arm, HR 0.65 (95% CI 0.521, 0.808), p<0.0001). However, due to uncertainties with regards to the observed results (e.g. more PFS events in the MIRV arm, more censored patients in the ICC arm, with a definition of censoring rules as per FDA guidelines) some uncertainty in the overall results remain. Importantly, no detrimental effects on efficacy were detected.

Median OS (95% CI), a key secondary endpoint, was 16.46 (95% CI, 14.46, 24.57) months and 12.75 (95% CI, 10.91, 14.36) months in the MIRV arm and in the ICC arm, respectively, leading to a 3.71 months benefit in OS. This result is of importance as it supports the observed benefit in the primary endpoint. In addition, ORR by INV and BICR were higher in the MIRV arm compared to the ICC arm, mainly observed as increases in PR.

Overall, the benefits of MIRV over ICC were demonstrated in the MIRASOL study for PROC patients with a high expression of FRα.

The safety profile of MIRV is well characterised in the target population. Ocular disorders dominate the clinical safety profile. Most of them are mild but patients need to be monitored actively and they also need prophylaxis and/or treatment for ocular adverse events to be manageable and reversible. This is an important safety issue affecting the treatment with MIRV, as it concerned 59% of patients. Ocular toxicity may likely impact the treatment burden of the patients. Pneumonitis, which was the most common drug-related SAE and can be life-threatening, is an important unfavourable effect for MIRV treated patients, but occurs only in 10% and usually in milder form. Peripheral neuropathy is common and patients should be monitored for signs and symptoms of neuropathy as most of the patients in the MIRASOL study recovered only partially or did not recover. Gastrointestinal disorders are common and also need premedication.

These important safety problems can be at least partly mitigated with dose modifications, premedications and monitoring of signs and symptoms as reflected in section 4.4 of the SmPC, but their weight in the treatment with MIRV is inevitable. However, discontinuations due to AEs were quite rare. These toxicities could be considered acceptable, when considering the incurable and aggressive nature of platinum-resistant advanced ovarian cancer.

Overall, treatment with a targeted agent can be considered an option for patients with FRα ≥75% expression with 2+/3+ membrane staining intensity.

3.7.2. Balance of benefits and risks

Albeit the PFS benefit observed in the MIRASOL study is short (1.6 months), an OS benefit was also reported (median OS 16.46 months with MIRV vs. 12.75 months with ICC). This is an important outcome for patients with an aggressive cancer, for whom current treatments offer limited efficacy. Despite uncertainties regarding the precise value of its increase, the median PFS as primary endpoint was improved compared to SOC. Thus, it is relevant for patients with PROC for whom available therapeutic options have modest activity. In addition, the biological rationale and patient selection are plausible for this targeted therapy.

The follow-up is sufficient to demonstrate clinically relevant benefit. Bias from the open label setting has a permanent impact on the study results and cannot be accurately quantified. However, advanced PROC has poor prognosis with scarce treatment options with limited efficacy and despite all the uncertainties, MIRV has shown PFS and OS benefits which are clinically significant.

The important safety concerns with MIRV include ocular disorders, pneumonitis, peripheral neuropathy and gastrointestinal disorders. While ocular disorders were typical for MIRV, it was less myelosuppressive than IC Chemo. The AEs appear in general manageable, with a limited incidence of discontinuation due to AEs. The safety profile is considered acceptable in view of the poor prognosis of

the target population. The safety database is considered sufficient, as well as the patient exposure to assess risk profile in the target population. Furthermore, the reported PFS and OS benefits outweigh the risks considering the poor prognosis of these patients.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall benefit/risk balance of Elahere is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Elahere is not similar to Zejula within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Elahere is favourable in the following indication:

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 (see section 4.2).

The CHMP therefore recommends the granting of the subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that mirvetuximab soravtansine is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).