Australian Government
Department of Health, Disability and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Elahere

Active ingredient: Mirvetuximab soravtansine

Sponsor: AbbVie Pty Ltd

November 2026

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List of abbreviations

Abbreviation	Meaning
ADA	Anti-drug antibody/anti-drug antibodies
AE(s)	Adverse event(s)
AIBW	Adjusted ideal body weight
ARTG	Australian Register of Therapeutic Goods
ASA	Australia-specific annex
AUC	Area under the concentration time curve
$AUC_{0\text{-}d21}$	Area under the concentration time curve for days 0 to 21
BICR	Blinded independent central review
CI	Confidence interval
C_{max}	Maximum concentration
CMI	Consumer Medicines Information
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Trough concentration
CYP2C19	Cytochrome P450 isoenzyme C19
CYP2C9	Cytochrome P450 isoenzyme 2C9
CYP3A4	Cytochrome P450 isoenzyme 3A4
DLP	Data lock point
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EOC	Epithelial ovarian cancer
ESMO	European Society for Medical Oncology
EU	European Union
FDA	United States Food and Drug Administration
FRα	Folate receptor-alpha
HR	Hazard ratio
IC_{50}	Concentration that achieves 50% inhibition
ITT	Intent to treat
IV	Intravenous
NAbs	Neutralising antibodies
NCCN	National Comprehensive Cancer Network
ORR	Objective response rate

Abbreviation	Meaning
OS	Overall survival
PARP	Poly-ADP ribose polymerase
PFS	Progression free survival
PFS2	Progression free survival 2
P-gp	P-glycoprotein
PI	Product Information
PK	Pharmacokinetic(s)
PLD	Pegylated liposomal doxorubicin
PopPK	Population pharmacokinetic(s)
PROC	Platinum resistant ovarian cancer
PSUR(s)	Periodic safety update report(s)
RECIST	Response Evaluation Criteria in Solid Tumours
RMP	Risk management plan
TBW	Total body weight
TEAE(s)	Treatment emergent adverse event(s)
TGA	Therapeutic Goods Administration
TRAE(s)	Treatment related adverse event(s)

Product submission

Submission details

Type of submission:	New biological entity
Product name:	Elahere
Active ingredient:	Mirvetuximab soravtansine
Decision:	Approved
Date of decision:	17 November 2025
Date of entry onto ARTG:	19 February 2026
ARTG number:	472925
▼*Black Triangle Scheme*	Yes
for the current submission:	
Sponsor's name and address:	AbbVie Pty Ltd
	241 O'Riordan Street, Mascot NSW 2020
Dose form:	Concentrate solution
Strength:	100 mg/20 mL
Container:	Vial
Pack size:	One
Approved therapeutic use for the current submission:	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 of the Product Information).
Route of administration:	Intravenous infusion
Dosage:	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. For further information regarding dosage, such as dosage modifications to manage adverse reactions, refer to the Product Information.
Pregnancy category:	D Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health

professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Product background

This AusPAR describes the submission by AbbVie Pty Ltd (the sponsor) to register Elahere (mirvetuximab soravtansine) 100 mg/20 mL concentrate solution for intravenous infusion vial for the following proposed indication:[1]

> *Treatment of adult patients with folate receptor-alpha (FRα) positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received one to three prior systemic treatment regimens.*

Disease or condition

Ovarian cancer is the eighth most common cancer in women worldwide in terms of both incidence and mortality, accounting for approximately 323,603 new cases and 206,956 deaths in 2022.[2] According to the Australian Institute of Health and Welfare (AIHW), there is an estimate of 1,805 new cases of ovarian cancer and serous carcinomas of the fallopian tube in 2024, which will account for approximately 26% of the gynaecological cancers diagnosed.[3] In 2024, ovarian cancer and serous carcinomas of the fallopian tube is estimated to account for 1,070 deaths, which is estimated to be 48% of deaths from gynaecological cancer.[2]

Risk factors of ovarian cancer include family history of ovarian cancer, increasing age and mutation in one of several genes for example, breast cancer gene 1 (BRCA1) or breast cancer gene 2 (BRCA2). Epithelial ovarian cancer (EOC) may not cause early signs or symptoms. When signs or symptoms do appear, the cancer is often advanced. Signs and symptoms include pain, swelling, or a feeling of pressure in the abdomen or pelvis, urinary urgency or frequency, difficulty eating or feeling full, a lump in the pelvic area, and gastrointestinal problems such as gas, bloating, or constipation. These symptoms often go unrecognised, leading to delays in diagnosis.

Current treatment options

There are currently no specific guidelines in Australia which recommend therapies for EOC. As such, consensus-based treatment decisions follow the European Society of Medical Oncology (ESMO) or National Comprehensive Cancer Network (NCCN) guidelines. Standard first-line treatment for EOC is cytoreductive surgery in combination with platinum-based chemotherapy with or without bevacizumab, followed by bevacizumab with or without poly-ADP ribose polymerase (PARP) inhibitors (that is, olaparib or niraparib) as maintenance therapy. Most patients with advanced EOC relapse during or after treatment with platinum-containing

[1] This is the original indication proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered in the Australian Register of Therapeutic Goods.
[2] Heintz AP, et al. Carcinoma of the ovary. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. Int J Gynaecol Obstet. 2006;95 Suppl 1:S161-92.
[3] Australian Institute of Health and Welfare. Cancer data in Australia. Canberra, Australia: AIHW; 2024 [cited 2024 Aug 21]. Available from: https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia.

regimens. Disease recurring within 6 months of platinum-based chemotherapy is classified as platinum resistant ovarian cancer (PROC). Once patients develop PROC, their prognosis is poor.

Clinical rationale

When platinum-based chemotherapy is not an option for recurrent ovarian cancer, ESMO guidelines recommend single-agent chemotherapy (weekly paclitaxel, pegylated liposomal doxorubicin (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 there is a significant unmet medical need.

Regulatory status

Australian regulatory status

This product is considered a new biological entity for Australian regulatory purposes.

Elahere was granted TGA orphan designation for the treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancer on 20 November 2024.

This submission was submitted through the TGA's Comparable Overseas Regulator B (COR-B) process, using evaluation reports from the European Medicines Agency (EMA). The full dossier was submitted to the TGA.

International regulatory status

At the time the TGA considered this submission, a similar submission had been considered by other regulatory agencies. The following table summarises these submissions and provides the indications where approved.

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
European Union	28 September 2023	Approved on 15 November 2024	*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).*

Region	Submission date	Status	Approved indications
United States of America	28 March 2022 (accelerated approval) 5 October 2023 (full approval)	Approved on: 14 November 2022 (accelerated approval) 22 March 2024 (full approval)	*Elahere is a folate receptor alpha (FRα)-directed antibody and microtubule inhibitor conjugate indicated for the treatment of adult patients with FRα positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received one to three prior systemic treatment regimens. Select patients for therapy based on an FDA-approved test.*
Switzerland	31 October 2024	Under consideration	*Under consideration*
Puerto Rico	28 March 2022 (accelerated approval) 5 October 2023 (full approval)	Approved on: 14 November 2022 (accelerated approval) 22 March 2024 (full approval)	*Elahere is a folate receptor alpha (FRα)-directed antibody and microtubule inhibitor conjugate indicated for the treatment of adult patients with FRα positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received one to three prior systemic treatment regimens. Select patients for therapy based on an FDA-approved test.*
Israel	11 June 2023	Approved on 14 October 2024	*Elahere (mirvetuximab soravtansine) is indicated for the treatment of adult patients with folate alpha receptor (FRα) positive, platinum resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received one to three prior systemic treatment regimens.*

Region	Submission date	Status	Approved indications
China	14 September 2023 (conditional approval)	Approved on 22 November 2024 (conditional approval)	*Elahere is indicated for adult patients with platinum resistant epithelial ovarian, fallopian tube or primary peritoneal cancer who are folate receptor-alpha (FRα) positive and who have received one to three prior systemic therapies.* *The above indication is conditionally approved based on results of clinical surrogate endpoints, clinical endpoint data are not yet available, and the efficacy and safety are yet to be further confirmed postmarketing. The full approval of the above indications will depend on whether the clinical benefit of this product in the above population can be confirmed by ongoing, randomized, controlled confirmatory clinical trials.*
Macao	2 February 2024	Approved on 30 April 2024	*Elahere is indicated for the treatment of adult patients with folate receptor-alpha (FRα) positive, platinum resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received one to three prior systemic treatment regimens.*
Brazil	29 August 2024	Under consideration	*Under consideration*
Mexico	30 September 2024	Under consideration	*Under consideration*
United Arab Emirates	30 September 2024	Under consideration	*Under consideration*
Columbia	31 October 2024	Under consideration	*Under consideration*
Argentina	14 November 2024	Under consideration	*Under consideration*

Region	Submission date	Status	Approved indications
Saudi Arabia	24 November 2024	Under consideration	*Under consideration*

Registration timeline

This submission was evaluated under the standard prescription medicines registration process.

Table 2: Timeline for Submission PM-2024-05687-1-4

Description	Date
Designation (Orphan)	20 November 2024
Submission dossier accepted and first round evaluation commenced	31 January 2025
Evaluation completed	11 August 2025
Registration decision (Outcome)	17 November 2025
Registration in the ARTG completed	19 February 2026
Number of working days from submission dossier acceptance to registration decision*	144

* The COR-B process has a 175 working day evaluation and decision timeframe.

Assessment overview

A summary of the TGA's assessment for this submission is provided below.

This section is a TGA summary of wording used in TGA's evaluation report, which discussed numerous aspects of overseas evaluation reports and included some information that was commercial-in-confidence.

The following guideline was referred to by the Delegate as being relevant to this submission:

- EMA: ICH Topic S9 Guideline on Non-clinical Evaluation for Anticancer Pharmaceuticals (EMA/CHMP/ICH/646107/2008)

  TGA-adopted, effective date: May 2010

Quality evaluation summary

Mirvetuximab soravtansine is an antibody-drug conjugate composed of mirvetuximab, a recombinant, monoclonal immunoglobulin G1 antibody produced in Chinese hamster ovary cells that specifically binds to folate receptor-alpha (FRα), and DM4, a cytotoxic maytansine derivative and anti-mitotic agent that inhibits tubulin polymerisation and microtubule assembly resulting in G2-M cell cycle arrest and apoptosis.

The active ingredient was produced by chemical conjugation of the antibody and small molecule components. The antibody is produced by recombinant DNA technology, and the small molecule components are produced by chemical synthesis. Information about the manufacturing, storage and control facilities for the active substance has been provided in the dossier. Good Manufacturing Practice (GMP) compliance for the manufacturers has been demonstrated.

The overall quality of the active substance was demonstrated via adequate control of the starting material, control of critical steps and intermediates, process validation, extensive characterisation using orthogonal and state-of-the-art analytical methods, control of impurities and contaminants, generation of robust reference materials and batch analyses that covered multiple manufacturing campaigns.

Mirvetuximab soravtansine finished product, Elahere, is a concentrate solution for infusion presented at the concentration of 5 mg/mL or 100 mg/20 mL vial. The product is available in a vial with a rubber stopper and an aluminium seal fitted with a flip-off plastic cap. One vial of 20 mL contains 100 mg of mirvetuximab soravtansine, glacial acetic acid, sucrose and polysorbate 20 in a preservative-free acetate-buffered solution. The formulation development has been adequately described and the final formulation intended for marketing was used in the Phase III clinical trials.

The recommended storage condition is 5 years when stored at 5 ± 3 °C, protected from light.

The recommended shelf life and storage conditions for the diluted product are ambient temperature (18 to 25 °C) for no more than 8 hours (including infusion time), or under refrigeration at 2 to 8 °C for no more than 24 hours. After refrigeration, allow the diluted infusion solution to reach room temperature, administer within 8 hours (including infusion time).

There are no objections on quality grounds to the approval of Elahere.

Nonclinical evaluation summary

The submitted nonclinical dossier was in accordance with the relevant ICH guideline for the nonclinical assessment of anticancer pharmaceuticals (ICH S9). The overall quality of the nonclinical dossier was high. All pivotal safety related studies were Good Laboratory Practice (GLP) compliant.

In vitro, mirvetuximab soravtansine bound the FRα receptor with nanomolar affinity within expected clinical plasma concentrations. The conjugation of DM4 had no measurable impact on the binding affinity. S-methyl DM4 (active metabolite) displayed high cytotoxicity with half maximal inhibitory concentration (IC_{50}) values ranging from 1.1 to 32 pM. Mirvetuximab soravtansine also imparted cytotoxicity on FRα cells via bystander effect following lysosomal processing. *In vivo*, mirvetuximab soravtansine administration resulted in dose-related increase in anti-tumour activity in xenograft mouse models of ovarian carcinoma cells. However, only a partial regression of tumour growth was observed in most tested cell lines.

Mirvetuximab soravtansine only cross-reacted with human, cynomolgus and rhesus monkey FRα. The selected species for pharmacodynamic and toxicology studies were supported by the cross-reactivity data. No mirvetuximab soravtansine cross reactivity was noted with other members of the FRα family (FR-β, FR-γ or and FR-δ). Corneal keratopathy was noted in multiple animal studies despite the lack of corneal FRα expression, indicating a putative off-target mechanism mirvetuximab soravtansine treatment and corneal findings.

Safety pharmacology assessments conducted concurrently with repeat dose toxicity studies revealed no mirvetuximab soravtansine related cardiac, central nervous system or respiratory effects.

Overall, the pharmacokinetic profile in animals was qualitatively comparable to that of humans. mirvetuximab soravtansine was readily and rapidly distributed following intravenous (IV) administration. Distribution was primarily to the liver, bone marrow, lung, kidneys, and spleen. Distribution to eye was also noted; however, penetration into brain and spinal cord was

comparatively limited. The half-life of mirvetuximab soravtansine was slightly longer in rat compared with monkey or human. In monkeys and humans, the half-life for the DM4 conjugate was greater compared with the antibody component alone. Plasma protein binding of DM4 is very high for all species. Similarly, plasma protein binding of S-methyl DM4 was very high for human and rat, and high for monkey. Faecal and urinary excretion were the primary and secondary routes of DM4 or S-methyl DM4 excretion.

Based on *in vitro* studies, cytochrome P450 isoenzyme 3A4 (CYP3A4) (and to a lesser extent cytochrome P450 isoenzyme 2C9 (CYP2C9) and cytochrome P450 isoenzyme C19 (CYP2C19)) inhibitors could alter systemic exposure of DM4 and S-methyl DM4. DM4 and S-methyl DM4 were not direct inhibitors of human hepatic CYP enzymes. While DM4 and S-methyl DM4 were identified as substrates of P-glycoprotein (P-gp), it did not act as an inhibitor of P-gp.

Mirvetuximab soravtansine had a high order of acute oral toxicity in rats and dogs. Repeat-dose toxicity studies by the IV route were conducted in monkey. Additional repeat-dose toxicity studies were conducted in rabbit to evaluate ocular toxicity. Maximum exposures (area under the concentration time curve (AUC)) were low in both species. In the 10-week monkey study, major target organs for mirvetuximab soravtansine were skin, eye and haematopoietic system. Skin findings including broken skin, dry skin, discoloured skin, scaly skin, sores, scabs, abrasions, superficial dermal erosions, and ulcerative wounds. The haematology effects were consistent with decreased haematopoiesis. Ophthalmic findings included corneal keratopathy characterised by subtle multifocal subepithelial microcystic lesions. In rabbits, histopathological ocular findings included attenuation and degeneration (necrosis) of the corneal epithelium.

Neither DM4 nor S-methyl DM4 were genotoxic in bacterial mutagenesis assays; however, both compounds were genotoxic in *in vivo* rat micronucleus tests. No carcinogenicity studies were conducted with mirvetuximab soravtansine. No reproductive toxicity studies were conducted mirvetuximab soravtansine. DM4 was phototoxic in the in the neutral red uptake assay system.

Nonclinical conclusions

There are no major deficiencies in the nonclinical dossier. A minor deficiency is the absence of interaction assessment of DM4 and S-methyl-DM4 with transporters other than P-gp.

The primary pharmacology studies support the drug's use for the proposed indication.

Corneal keratopathy was noted in the monkey toxicity study at clinically equivalent maximum concentration (C_{max}) and AUC ratios, as well as an occurrence of corneal microcystic lesions. In the absence of corneal FRα, an off-target mechanistic link between mirvetuximab soravtansine treatment and corneal findings is likely.

There are no nonclinical objections to the registration of Elahere.

Clinical evaluation summary

Summary of clinical studies

The clinical dossier consisted of:

- One Phase I study
  - Study 0401, a Phase I, first in human study which evaluated the safety, tolerability and pharmacokinetics of mirvetuximab soravtansine in adults with ovarian cancer and other FOLR1-positive solid tumours.

- 3 Phase III studies
  - Study 0416 (MIRASOL), a global Phase III, randomised, open label, multicentre clinical trial designed to evaluate the efficacy, safety and patient reported outcomes of mirvetuximab soravtansine compared with investigator's choice single agent chemotherapies in patients who received prior systemic anticancer therapies.
  - Study 0417 (SORAYA), a Phase III single arm study of mirvetuximab soravtansine in platinum resistant, advanced high grade epithelial ovarian, primary peritoneal, or fallopian tube cancers with high folate receptor alpha expression.
  - Study 0403 (FORWARD 1), a Phase III, randomised, open label study which evaluated the safety and efficacy of mirvetuximab soravtansine compared with investigator's choice single agent chemotherapies in women with folate receptor α-positive advanced epithelial ovarian cancer, primary peritoneal cancer or fallopian tube cancer.

Pharmacology

Pharmacokinetics

Key pharmacokinetics (PK) findings included the following:

- Clinical PK data were collected in 4 clinical studies: Study 0401 and Study 0403 with dense PK sampling, and Study 0417 and Study 0416 with sparse sampling. There were no dedicated clinical pharmacology studies.
- The pharmacokinetics were characterised after patients were administered mirvetuximab soravtansine 0.161 mg/kg to 8.71 mg/kg adjusted ideal body weight (AIBW) doses. The recommended dose and regimen for Elahere is 6 mg/kg AIBW as an IV solution every 3 weeks (21-day cycle).
- Mirvetuximab soravtansine is administered as an IV solution and thus the bioavailability is 100%.
- Mirvetuximab soravtansine has a small volume of distribution, approximately 2.5 to 4 L. *In vitro* human plasma protein binding of DM4 and S-methyl-DM4 was > 99%.
- The elimination pathways of mirvetuximab soravtansine were not clinically investigated. The antibody component of mirvetuximab soravtansine has a molecular weight of approximately 146 kDa and renal filtration will be negligible. 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 (± standard deviation) total plasma clearance of mirvetuximab soravtansine, unconjugated DM4 and S-methyl-DM4 were 18.9 (± 9.8) mL/hour, 14.5 (± 4.5) L/hour and 5.3 (± 3.4) L/hour respectively and terminal phase half-lives 4.9 days, 2.8 days and 5.1 days respectively. Graphical exploratory analysis indicated no apparent association between anti-drug antibody (ADA) status and exposure to mirvetuximab soravtansine. It was concluded that because of the low occurrence of ADA (< 10% treatment-emergent and treatment-induced), the effect of these antibodies on the PK of mirvetuximab soravtansine is unknown.
- Metabolism: immunoglobulin G antibodies are mainly catabolised by lysosomal proteolysis and then eliminated or re-used by the body, which is assumed to be the case for mirvetuximab soravtansine.
- DM4 is released intra-cellularly when the antibody drug conjugate is catabolised by lysosomal proteolysis or extracellularly by deconjugation of the payload from the complex. DM4 is metabolised by a S-methyl transferase to S-methyl-DM4. Based on *in vitro* studies, both DM4 and S-methyl-DM4 are mainly metabolised by CYP3A4, and both are P-gp

substrates. Unconjugated DM4 and S-methyl-DM4 over mirvetuximab soravtansine ratios in Study 0403, based on molarity, were approximately 0.4% and 1.4%, respectively. DM4-sulfo-SPDB-lysine and DM4-sulfo-TBA were identified in human plasma in Study 0401 at trace levels. Metabolite excretion from 6 patients was characterised in Study 0403. Six metabolites were identified, and it was estimated that approximately 0.70% of all payload related materials were excreted in urine over 24 hours post infusion.

- Dose proportionality: in Study 0401, exposure to mirvetuximab soravtansine increased approximately proportionally over the dose range 3.3 to 7 mg/kg total body weight (TBW), which includes proposed dose of 6 mg/kg AIBW. At lower dose (0.15 to 0.5 mg/kg TBW), clearance was higher than following higher doses.
- Special populations: renal function: predicted exposure to mirvetuximab soravtansine, 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.
- Hepatic function: predicted exposure to mirvetuximab soravtansine, DM4, and S-methyl-DM4 was similar between patients with normal hepatic function (n = 589) and those with mild hepatic impairment (n = 101).
- Adjusted ideal body weight (AIBW): the range of AIBW (n = 758) was 38.7 to 96.7 kg. Population pharmacokinetic (PopPK) modelling revealed AIBW as a statistically significant covariate for mirvetuximab soravtansine clearance and central volume of distribution, both of which increased with increasing AIBW. Simulations indicated that with the proposed dose regimen AIBW and total body weight have limited effect on exposure to mirvetuximab soravtansine. Predicted exposure to DM4 and S-methyl-DM4 increase slightly with increasing AIBW.
- Although age was a statistically significant covariate for mirvetuximab soravtansine central volume of distribution, age had no relevant effect on predicted exposure parameters.

Pharmacodynamics

Key pharmacodynamic findings included the following:

- Pharmacodynamic endpoints were not evaluated in clinical studies.
- In the exposure-response analyses for efficacy and safety, individual exposure parameters following the first dose (C_{max}, trough concentration (C_{trough}), and area under the concentration time curve for days 0 to 21 ($AUC_{0\text{-}d21}$) for mirvetuximab soravtansine, DM4, and S-methyl-DM4) were predicted using the final PopPK model. Exposure-response analyses for efficacy indicated that lower mirvetuximab soravtansine C_{trough} and $AUC_{0\text{-}d21}$, with some baseline characteristics, were associated with shorter progression free survival (PFS) and overall survival (OS) and lower objective response rate (ORR) in pivotal Study 0416, whereas mirvetuximab soravtansine C_{max} and DM4 exposure metrics did not show significant association with efficacy endpoints. Exposure-response analyses for safety indicated that higher exposure to mirvetuximab soravtansine, 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; mirvetuximab soravtansine $AUC_{0\text{-}d21}$ 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 adverse events whereas mirvetuximab soravtansine and DM4 exposures were not.
- Exposure-response analyses results must be interpreted with caution as:
  - one mirvetuximab soravtansine dose level (6 mg/kg AIBW, every 3 weeks) was used in pivotal Study 0416, and there may be confounding factors that are associated with both

increased elimination of mirvetuximab soravtansine and with lower probability of therapeutic response.

  - 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 mirvetuximab soravtansine, DM4, and S-methyl-DM4 during the study. For example, 59.2% of patients in the pivotal Study 0416 had dose modification(s).
  - the PopPK model for DM4 and S-methyl-DM4 was structurally unidentifiable. Additional exposure-response analyses with observed DM4 and S-methyl-DM4 exposure parameters were conducted showing overall agreement with those obtained with predicted exposure parameters.

- Mirvetuximab soravtansine at the recommended dose has a low likelihood of proarrhythmic effects due to delayed repolarisation. The concentration QTc analyses did not evaluate the potential relationship between concentration of DM4 and S-methyl-DM4 and ΔQTc. This was not pursued as *in vitro* and *in vivo* studies did not indicate the need for further clinical study and safety results of the clinical studies did not raise cardiac concerns for mirvetuximab soravtansine.
- The proposed dose of 6 mg/kg AIBW, every 3 weeks was used for approximately 91% of patients in the dataset, including all randomised to mirvetuximab soravtansine in the pivotal Study 0416. Exposure-response analyses cannot determine whether this is the optimal posology, but the benefit/risk evaluation of the proposed dose can be performed based on the observed clinical data. Furthermore, results of PK analyses support the proposed AIBW based posology and proposed dose modifications are based on observed adverse reactions, which is considered acceptable.

Efficacy

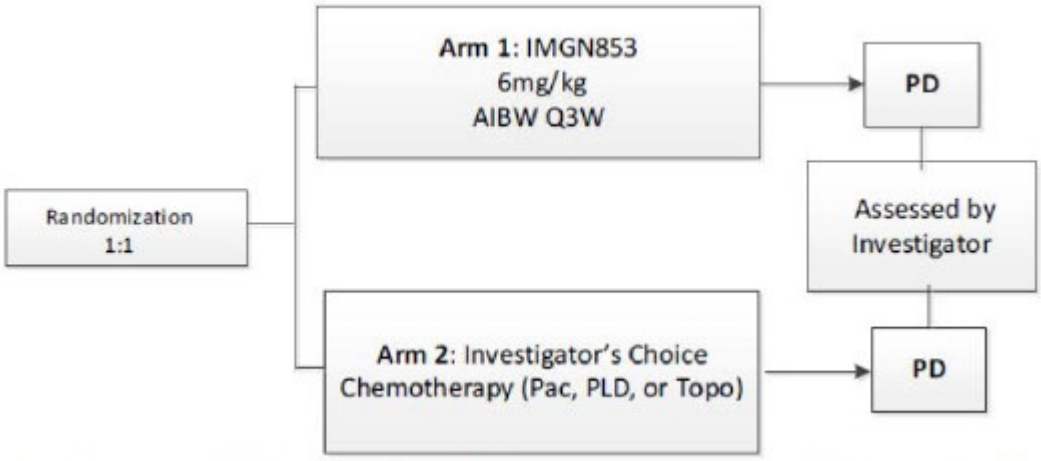
The pivotal data for efficacy comes from Study 0416 (MIRASOL). Supporting data from Study 0417 (single-arm study), Study 0401 (Phase I first in human study) and Study 0403 (Phase III) have also been evaluated.

Study 0416 (MIRASOL)

Design

The MIRASOL study is a global Phase III, randomised, open label, multicentre clinical trial evaluating the efficacy and safety of mirvetuximab soravtansine compared with investigator's choice single agent chemotherapies in patients with platinum resistant high grade serous ovarian cancer with Frα high expression who have received prior systemic anticancer therapies.

Figure 1: MIRASOL study design



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

Trial location

The study was conducted at 201 study centres globally located in North America, Middle East, Africa, Europe and Asia-Pacific (136 of which enrolled patients).

There were 7 patients randomised in an Australia site.

Diagnostic criteria

Study 0416 (MIRASOL) was a Phase III open label study with 1:1 allocation (stratified by number of prior lines of therapy (1 versus 2 versus 3); chemotherapy chosen prior to randomisation (paclitaxel versus pegylated liposomal doxorubicin (PLD) versus topotecan)).

Key inclusion criteria

- Female patients ≥ 18 years of age
- Confirmed diagnosis of high grade serous EOC, primary peritoneal cancer or fallopian tube cancer
- Patients must have had platinum resistant disease
- One to 3 prior lines of systemic therapy (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)
- Disease progression on or after most recent line of therapy
- FRα positive (that is, ≥ 75% of viable tumour cells with level 2 and/or 3 membrane staining; as per Ventana FOLR1 assay)
- Patients must have had at least one lesion that meets the definition of measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (radiologically measured by the investigator)
- Patients must have had an Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1
- Patients must have had adequate hematologic, liver, and kidney functions

Key exclusion criteria

- Histological types including: endometrioid, clear cell, mucinous, or sarcomatous histology, or mixed tumours containing any of the above histologies, or low-grade, borderline ovarian tumour
- Patients with primary platinum refractory disease
- Patients with prior wide field radiotherapy affecting at least 20% of the bone marrow
- Patients with > Grade 1 peripheral neuropathy per Common Terminology Criteria for Adverse Events (CTCAE)
- Patients with active or chronic corneal disorder, history of corneal transplant, or active ocular conditions requiring ongoing treatment/monitoring
- Patients with serious concurrent illness or clinically relevant active infection
- Patients with history of multiple sclerosis or other demyelinating disease and/or Lambert-Eaton syndrome (paraneoplastic syndrome)
- Patients with clinically significant cardiac disease
- Patients assigned to PLD stratum only:
  - Left ventricular ejection fraction below the institutional limit of normal as measured by echocardiography or multigated acquisition scan
- Patients with a history of hemorrhagic or ischemic stroke within 6 months prior to randomisation
- Patients with a history of cirrhotic liver disease (Child-Pugh Class B or C)
- Patients with previous non-infectious interstitial lung disease including non-infectious pneumonitis
- Patients with a history of other malignancy within 3 years prior to randomisation

Intervention

- Mirvetuximab soravtansine 6 mg/kg AIBW, every 3 weeks via IV infusion.

Comparator

- Chemotherapy, investigator/physician choice of:
  - Paclitaxel 80 mg/m^2 on Day 1, 8, 15 and 22 every 4 weeks
  - PLD 40 mg/m^2 every 4 weeks
  - Topotecan 4 mg/m^2 on Day 2, 8 and 15 every 4 weeks, or 1.25 mg/m^2 on Days 1 to 5 every 3 weeks

Primary endpoint

- To compare PFS of patients randomised to mirvetuximab soravtansine versus investigator's choice chemotherapy, as assessed by the investigator.

Key secondary endpoints

- To compare ORR of patients randomised to mirvetuximab soravtansine versus investigator's choice chemotherapy, as assessed by the investigator.

- To compare OS of patients randomised to mirvetuximab soravtansine versus investigator's choice chemotherapy.
- To compare the patient reported outcome European Organisation for Research and Treatment of Cancer (EORTC) QLQ-OV28 (abdominal/gastrointestinal symptom scale) assessment from patients randomised to mirvetuximab soravtansine versus investigator's choice chemotherapy.

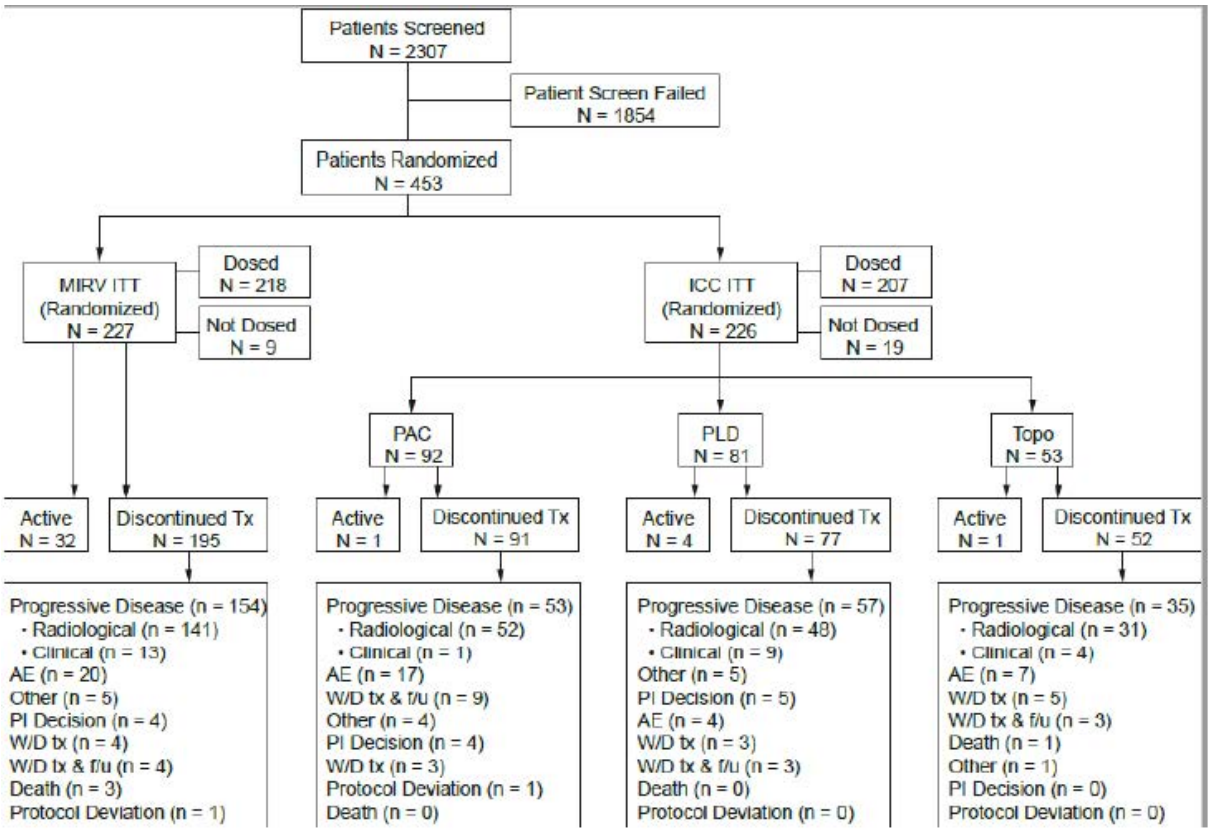
Other secondary endpoints

- To compare the safety and tolerability of mirvetuximab soravtansine and investigator's choice chemotherapy.
- To compare duration of response (DOR) in patients randomised to mirvetuximab soravtansine versus investigator's choice chemotherapy.
- To compare CA-125 response rate per Gynecologic Cancer Intergroup (GCIG) CA-125 criteria in patients randomised to mirvetuximab soravtansine versus investigator's choice chemotherapy.
- To compare the time to progression or death on the next line of treatment (PFS2) in patients randomised to mirvetuximab soravtansine versus investigator's choice chemotherapy.

Patient disposition

The participant flow is presented in Figure 2.

Figure 2: Participant flow in MIRASOL



Abbreviations: f/u = follow-up, N = number of patients, tx = treatment, W/D = withdrawal.

The patient disposition in the intent to treat (ITT) population is presented in Table 3.

Table 3: Patient disposition in intent to treat 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 (mirvetuximab soravtansine or investigator's choice chemotherapy).

[b] The Safety population is defined as all patients in ITT who received at least one dose of mirvetuximab soravtansine or investigator's choice chemotherapy.

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

Baseline characteristics

The patient demographics, disease history, and prior anticancer treatment were generally well balanced between treatment arms.

- median age = 63 years (mirvetuximab soravtansine 64 years; investigator's choice chemotherapy 62 years)
- White = 66% (mirvetuximab soravtansine 69%; investigator's choice chemotherapy 64%)
- ovarian cancer of epithelial origin = 80% (mirvetuximab soravtansine 80%; investigator's choice chemotherapy 81%)
- high-grade serous histology = 100%

- 2 prior systemic therapies = 39% (mirvetuximab soravtansine 40%; investigator's choice chemotherapy 39%)
- 3 prior systemic therapies = 47% (mirvetuximab soravtansine 48%; investigator's choice chemotherapy 46%)
- previous poly ADP-ribose polymerase (PARP) inhibitor = 55% (mirvetuximab soravtansine 55%; investigator's choice chemotherapy 56%)
- platinum free interval following most recent line of therapy ≤ 3 months = 41% (mirvetuximab soravtansine 39%; investigator's choice chemotherapy 44%), > 3 to 6 months = 58% (mirvetuximab soravtansine 61%; investigator's choice chemotherapy 55%)
- ECOG 0 = 55% (mirvetuximab soravtansine 57%; investigator's choice chemotherapy 53%)
- ECOG 1 = 44% (mirvetuximab soravtansine 43%; investigator's choice chemotherapy 45%)

Results

Progression free survival

The study met the primary efficacy endpoint (log-rank p < 0.0001) with a PFS hazard ratio (HR) of 0.65 (95% confidence interval (CI): 0.521, 0.808). In the ITT population, median investigator assessed PFS was 5.62 months (95% CI: 4.34, 5.95) in the mirvetuximab soravtansine arm versus 3.98 months (95% CI: 2.86, 4.47) in the investigator's choice chemotherapy arm.

Progression free survival by blinded independent central review (BICR) was evaluated as a sensitivity analysis, and results were concordant with the primary analysis performed by investigator assessment. The median BICR assessed PFS was 5.91 months (95% CI: 4.93, 6.97) in the mirvetuximab soravtansine arm and 4.34 months (95% CI: 3.52, 4.99) in the investigator's choice chemotherapy arm (HR = 0.72; 95% CI: 0.558, 0.920).

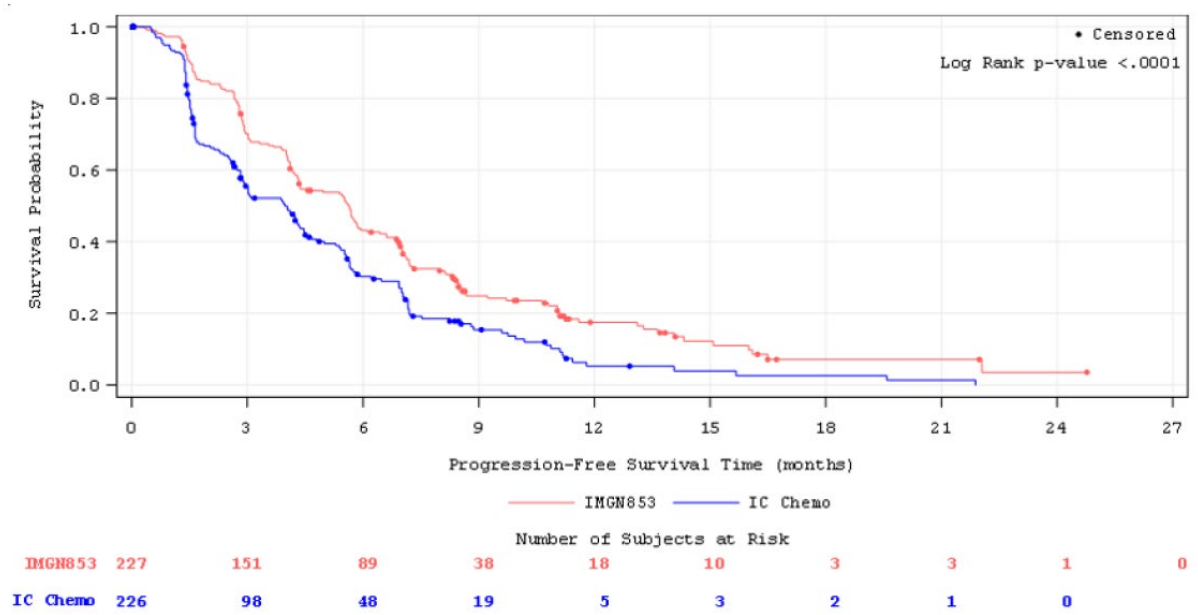
Table 4: Study 0416 summary of primary efficacy analysis

	Investigator-assessed		BICR-assessed	
Endpoints	**Mirvetuximab Soravtansine (N = 227)**	**IC Chemotherapy (N = 226)**	**Mirvetuximab Soravtansine (N = 227)**	**IC Chemotherapy (N = 226)**
Kaplan-Meier estimate PFS (months)				
Median (95% CI)	5.62 (4.34, 5.95)	3.98 (2.86, 4.47)	5.91 (4.93, 6.97)	4.34 (3.52, 4.99)
Hazard ratio and p-value				
Hazard ratio (95% CI)	0.65 (0.521, 0.808)		0.72 (0.558, 0.920)	
p-value	< 0.0001		0.0082	

Abbreviations: BICR = blinded independent central review, CI = confidence interval, IC = investigator's choice, ITT = intent to treat, N = number of participants, PFS = progression free survival.

Note: PFS is defined as the time from the date of first dose of mirvetuximab soravtansine until the date of progressive disease or death from any cause, whichever occurred first.

Figure 3: Study 0416 Kaplan-Meier plot for investigator assessed progression free survival intent to treat population



Abbreviations: IC = investigator's choice, ITT = intent to treat, IMGN853 = mirvetuximab soravtansine, PD = progressive disease, PFS = progression free survival.

Note: PFS is defined as the time from the date of first dose of mirvetuximab soravtansine until the date of PD or death from any cause, whichever occurred first.

Secondary endpoints

The key secondary ORR endpoint was met (mirvetuximab soravtansine 42.3% versus investigator's choice chemotherapy 15.9%, $p < 0.0001$). Objective response rate by BICR was 36.1% in the mirvetuximab soravtansine arm versus 14.6% in the investigator's choice chemotherapy arm. Median DOR (95% CI) per investigator was longer in the mirvetuximab soravtansine arm (6.77 months; 5.62, 8.31) compared to the investigator's choice chemotherapy arm (4.47 months; 4.17, 5.82). However, median DOR (95% CI) per BICR was longer with investigator's choice chemotherapy (7.36 months; 4.27, 16.16) than with mirvetuximab soravtansine (6.93 months; 5.59, 9.40).

The study met the key secondary endpoint of OS as the median OS with mirvetuximab soravtansine was 16.46 (95% CI: 14.46, 24.57) months and 12.75 (95% CI: 10.91, 14.36) months with investigator's choice chemotherapy (HR 0.67), meaning a 3.71-month OS benefit. This is impacted by the bias due to early drop out related to the open label design but even applying conservative scenarios on the impact of early censoring, a detrimental effect on OS is not considered plausible.

The key secondary endpoint of patient reported outcome was not met, as there was no significant difference at Week 8/9 for improvement between the mirvetuximab soravtansine and investigator's choice chemotherapy arms. Median (95% CI) time to second disease progression (PFS2) by investigator was longer in the mirvetuximab soravtansine arm than in the investigator's choice chemotherapy arm (11.04 months (9.36, 12.45) and 8.05 months (6.74, 9.36), respectively). Dose reduction numbers were small for meaningful analyses, but no clear detrimental effects were seen.

Overall, despite the uncertainties and deficiencies discussed above, the study met its primary endpoint (PFS by investigator) and key secondary endpoint (ORR by investigator), and a statistically and clinically significant OS benefit was observed in patients with advanced platinum resistant EOC; these results are clinically relevant for the patients.

Subgroup analysis

Subgroup analyses of PFS by investigator, PFS by BICR, ORR, OS and PFS2 were consistent with the overall population analysis.

Study 0417 (SORAYA)

The primary endpoint ORR by investigator was 32.4% with 34 responders in the 105 population. Objective response rate (ORR) by BICR contains 95 patients, with 30 responders and an ORR of 31.6%. The key secondary endpoint DOR by investigator is based on 34 patients, with the median DOR of 5.9 months. As SORAYA does not bring added value to the efficacy claims, its results were not described in the summary of product characteristics (EMA).

Study 0403 (FORWARD 1)

This is a Phase III open label, randomised controlled trial of mirvetuximab soravtansine versus investigator's choice chemotherapy randomised 2:1 in women with advanced EOC who had received one to 3 prior lines of therapy. This study included patients with FRα level ≥ 50% of tumour cells with staining visible at ≤ 10 times microscope objective. The trial was modified with 8 global amendments, including a change from a 2-stage Phase II study to a Phase III study. These amendments could have affected the study integrity and results. The primary endpoint, PFS by BICR. did not reach statistical significance in the ITT population nor in the FRα high population (n = 218). The median PFS times by BICR in the ITT population were equal (4.14 months in the mirvetuximab soravtansine arm, 4.44 months in the investigator's choice chemotherapy arm, HR 0.981). In FRα high population the difference in median PFS by BICR times was short (1.5 months) but favoured the mirvetuximab soravtansine arm (4.76 months versus 3.25 months, HR 0.693). Key secondary endpoint ORR by BICR in ITT population and FRα high population was 22% and 24% in the mirvetuximab soravtansine arm versus 12% and 10% in the investigator's choice chemotherapy arm respectively. With longer follow-up, the median OS was 15.57 months with mirvetuximab soravtansine and 13.93 months with investigator's choice chemotherapy in the ITT population (HR 0.855), while 17.31 months with mirvetuximab soravtansine and 12.02 months with investigator's choice chemotherapy 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.

Study 0401 (FIH)

This was a dose escalation and a dose expansion trial to establish the maximum tolerated dose and the recommended Phase II dose. Overall, the populations are small, highly selected with multiple enrolment criteria, and heterogeneous, results are hypothesis generating and their value for the benefit-risk assessment is negligible.

Analyses performed across studies

This was an integrated summary of efficacy from ITT populations of MIRASOL and SORAYA, with 333 patients, FRα ≥ 75%, enrolled after one to 3 lines of therapy; FORWARD 1 was not included. As the pooling includes considerable sources of bias, it was concluded these results could not be considered to establish the efficacy of Elahere.

Safety

Study 0416 (MIRASOL)

The median duration of exposure for patients in MIRASOL was longer for the mirvetuximab soravtansine arm compared with the investigator's choice chemotherapy arm (5.0 versus 3.0 months, respectively). The median relative dose intensity was similar between the populations (approximately 99%).

Treatment emergent adverse events

The overall incidence of treatment emergent adverse events (TEAEs) was similar between the two arms. The most common adverse events (AEs) in patients receiving mirvetuximab soravtansine were blurred vision, keratopathy, abdominal pain and fatigue. The incidence of TEAEs of Grade 3 to 5 was higher in patients in the investigator's choice chemotherapy arm (54.1% versus 41.7%).

Treatment related adverse events

There was a higher incidence of treatment related adverse events (TRAEs) reported in those in the mirvetuximab soravtansine arm than the investigator's choice chemotherapy arm (86% versus 81%).

Overall, there was one death due to a TRAE in the mirvetuximab soravtansine arm (neutropenic sepsis) and one death due to a TRAE in the investigator's choice chemotherapy arm (septic shock; patient received topotecan).

In the primary analysis population, 29 (4.3%) patients died during treatment and the safety follow-up period; 13 (2%) 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 sub-ileus, 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 dyspnoea (one patient each, < 1%). Two of these fatal AEs were considered related to study drug, which were the respiratory failure and the neutropenic sepsis. It is noted that the overseas regulator did not consider neutropenic sepsis to be an adverse drug reaction after a comprehensive review of the case.

Serious adverse events

The incidence of serious adverse events was higher in patients in the investigator's choice chemotherapy arm (33% versus 24%).

Dose interruptions, reductions and discontinuations due to adverse events

Treatment emergent adverse events leading to permanent discontinuation of the study drug were reported in 9.2% of patients in the mirvetuximab soravtansine arm (most commonly due to blurred vision; pneumonitis) versus 15.9% of patients in the investigator's choice chemotherapy arm (most commonly due to peripheral neuropathy; thrombocytopenia; fatigue). Treatment emergent adverse events leading to study drug dose interruption were similar in the two arms (53.7% in the mirvetuximab soravtansine arm versus 53.6% in the investigator's choice chemotherapy arm). Treatment related adverse events leading to study drug dose reduction were reported with a higher incidence in the mirvetuximab soravtansine arm (33.9% versus 24.2%).

Adverse events of special interest

Adverse events of special interest included peripheral neuropathy, alopecia, haematologic AEs, gastrointestinal AEs and ocular events.

Ocular adverse events

Ocular AEs related to keratopathy have been reported with tubulin-directed payloads. The pathogenesis of mirvetuximab soravtansine induced keratopathy is not clear but the absence of FRα on the cornea suggests an indirect effect, which (as per the sponsor) resolve with normal corneal epithelial cell replacement (10 to 14 days). 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 mirvetuximab soravtansine 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 antibody drug conjugates containing tubulin-directed payloads. In the primary analysis population 59% of patients developed ocular adverse reaction (mostly mild or moderate severity), 11% had ≥ Grade 3 adverse reactions and 2 patients (< 1%) experienced a total of 3 Grade 4 events (that is, keratopathy and cataract). The median time to first onset was 5.14 weeks (0.1 to 68.6 weeks) and the most common AEs were vision blurred (43%) and keratopathy (29%). Most patients had complete (53%) or partial (38%) improvement; 9% had no documented improvement with final Grade 3 blurred vision in 2 patients, cataract of Grade 3 in 7 patients and Grade 4 for one patient (6 out of 8 had documented Grade 1 cataracts 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. Doses were delayed in 24%, reduced in 15%, not given in 4% and infusion interrupted in < 1%, with discontinuation in 1% of patients. Baseline ophthalmic examination with a slit lamp and visual acuity are advised, if any new or worsening ocular symptoms develop prior to doses and if ≥ Grade 2 additional exams at a minimum of every other cycle or as clinically indicated until resolution to Baseline. The examination reports should be reviewed prior to dosing and regimen determined accordingly. The patient should be encouraged to report any eye symptoms. Patients should be advised to avoid contact lenses while on mirvetuximab soravtansine 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. Secondary prophylaxis with steroid eye drops is recommended if patients found to have ≥ Grade 2 corneal adverse reactions (keratopathy), unless the patient's eye care professional determines that the risks outweigh the benefits of such therapy, from day of infusion to day 7 of each cycle, and apply lubricating eye drops not less than 15 minutes after the steroid eye drop which they should use throughout treatment with Elahere. While on steroid eye drops, intraocular pressure must be monitored.

Pneumonitis

Some antibody drug conjugates are recognised to cause pneumonitis, but the exact mechanism is unknown. This risk is particularly of concern given the risk of life-threatening event which could potentially lead to death. In the primary safety population and Study 0416 mirvetuximab soravtansine arm, pneumonitis was reported in 10%, while in < 1% of the investigator's choice chemotherapy arm. In Study 0416, most were Grade 2 or less. 0.9% (6 out of 682 patients) had Grade 3 pneumonitis while 0.2% (1 out of 682) had a Grade 4 event. Two patients died due to respiratory failure: one in the setting of a Grade 2 pneumonitis and lung metastasis confirmed at autopsy, one patient due to respiratory failure of unknown aetiology without concurrent

pneumonitis. Median time to onset was 21 weeks (3.1 to 49.1) for mirvetuximab soravtansine arm patients in Study 0416. Mirvetuximab soravtansine was permanently discontinued in 18 patients (3%). Pneumonitis was the most common serious adverse event by preferred term (4%). The advice given for pneumonitis is to withhold treatment until ≤ Grade 1 and consider dose reduction for any patient who has persistent or recurrent Grade 2 pneumonitis and to permanently discontinue if Grade 3 or 4. Patients who are asymptomatic may continue dosing of mirvetuximab soravtansine with close monitoring.

Peripheral neuropathy

Peripheral neuropathy is a known AE with cytotoxic agents that target tubulin. The mechanism behind peripheral neuropathy is hypothesised to be peripheral axonopathy induced by free payload released in the systemic circulation. Median time to onset in the primary analysis population was 5.9 weeks. This was reported in 36% of patients, most ≤ Grade 2 (34%) and only 3% with ≥ Grade 3 (no Grade 4 or 5). Patients in the mirvetuximab soravtansine arm versus the investigator's choice chemotherapy arm reported more of this symptom (37% versus 23%) while ≥ Grade 3 were similar. This resolved in 23% and partially improved in 12%. Of the 65%, who did not improve, 42% had Grade 1, 22% Grade 2 and 1% Grade 3 at final assessment. A total of 56% (32 out of 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. This caused dose delays in 2%, dose reductions in 4% and permanent discontinuation of mirvetuximab soravtansine in < 1% of patients. For patients experiencing new or worsening peripheral neuropathy, the mirvetuximab soravtansine dose should be withheld, reduced, or permanently discontinued based on the severity of peripheral neuropathy.

Post-marketing data

On 14 November 2022, the United States Food and Drug Administration (FDA) granted accelerated approval of mirvetuximab soravtansine-gynx (Elahere) for adult patients with FRα-positive, platinum resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received one to 3 prior systemic treatment regimens. The sponsor states that cumulatively, 717 patients have been exposed to Elahere as of 13 May 2023, and that based on the currently available data to date, no significant new safety data were identified that would change the safety profile of Elahere, when used for its approved indication at the recommended dose and in the approved population.

Safety conclusion

The overseas regulator concluded that:

> *The safety database and the extent 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. Pneumonitis was highlighted as a common SAE [serious adverse event]; it can be life-threatening. Peripheral neuropathy was common and most recovered partially. GI disorders were common and, in some cases, serious and leading 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 MIRV was shown to be less myelosuppressive than ICC [investigator's choice chemotherapy]. Overall,*

the safety profile appeared acceptable in the context of the poor prognosis of the target population.

The TGA clinical evaluation agreed with the above safety assessment and conclusions.

Clinical conclusion

The overseas regulator concluded that:

Overall, the benefits of MIRV [mirvetuximab soravtansine] over ICC were demonstrated in the MIRASOL study for PROC patients with a high expression of FRα. The population also has an important unmet clinical need as this cancer is aggressive and treatment options and their efficacy in this population are limited. The PFS benefit is short (1.6 months over ICC) but an OS benefit was also reported (median OS 16.46 months with MIRV vs. 12.75 months with ICC). There are uncertainties due to the open label design and the bias cannot be accurately quantified. The safety profile of MIRV is well characterised in the target population. Ocular disorders are prevalent but are mostly mild and will require preventative and active monitoring and treatment to be manageable and reversible. Ocular toxicity may likely impact the treatment burden of the patients. Pneumonitis, 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 need premedication. It was less myelosuppressive than ICC. These important safety problems can be at least partly mitigated with dose modifications, premedications and monitoring of signs and symptoms. Overall, treatment with a targeted agent can be considered an option for patients with FRα ≥75% expression with 2+/3+ membrane staining intensity.

The TGA clinical evaluation agreed with the clinical benefit-risk balance as assessed by the overseas regulator.

Risk management plan

The sponsor has submitted European Union (EU) risk management plan (RMP) version 1.0 (dated 21 October 2024; data lock point (DLP) 06 March 2023) and Australia-specific annex (ASA) version 1.0 (dated December 2024) in support of this application.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 5. The TGA may request an updated RMP at any stage of a product's life cycle, during both the pre-approval and post-approval phases.

Table 5: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Ocular disorders	✓	–	✓	–
Important potential risks	None	–	–	–	–

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Missing information	Use in patients with moderate hepatic impairment	✓	✓[†]	✓	–

[†]Study IMGN853-0425

The above summary of safety concerns is acceptable from an RMP perspective.

Routine and additional pharmacovigilance activities are proposed. Additional pharmacovigilance includes a Phase II, open label study to further characterise the missing information 'use in patients with moderate hepatic impairment' and will include Australian patients. The pharmacovigilance plan is satisfactory.

Only routine risk minimisation activities have been proposed. This is the same approach approved in the EU. Routine risk minimisation is acceptable to manage the risks associated with this product given that the medicine is initiated and supervised by healthcare professionals experienced in the use of anticancer medicinal products.

The RMP evaluation recommended conditions of registration relating to the versions of the risk management plan, requirement for periodic safety update reports, and inclusion of the medicine in the Black Triangle Scheme.

Risk-benefit analysis

Delegate's considerations

Platinum resistant EOC is an aggressive disease, and available treatments have limited efficacy.

Proposed indication

At the commencement of the evaluation process, the sponsor proposed to register a new therapeutic entity 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, who have received one to three prior systemic treatment regimens.*

Following clinical evaluation, at the recommendation of the clinical evaluation, the sponsor amended the proposed indication to the following:

> *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.*

Benefits/uncertainties of benefit

The sponsor has provided adequate evidence of effectiveness to support registration of Elahere for the evaluated population.

Study 0416 MIRASOL met both the primary endpoint of PFS and key secondary endpoint of OS. The median OS was 16.5 months for mirvetuximab soravtansine and 12.8 months for investigator's choice chemotherapy, that is, a 3.7-month OS benefit.

Supportive studies showed consistent efficacy results.

Uncertainties

Histology

All patients evaluated in the pivotal Study 0416 MIRASOL (and supporting Study 0417) had a confirmed diagnosis of high grade serous EOC/PPC/fallopian tube cancer, per inclusion criteria. Other histologies were specifically excluded, including endometrioid, clear cell, mucinous, sarcomatous histology, mixed tumours containing any of these histologies, and, of note, low-grade or borderline ovarian tumour, and therefore efficacy of Elahere has not been established for the treatment of patients with EOC/FT/PPC of these other histological subtypes.

Overall survival as a secondary endpoint

Overall survival would have been the preferred primary endpoint, as recommended by the overseas regulator prior to commencement of the study. However, PFS (by investigator) was considered to be an acceptable primary endpoint, with OS included as a key secondary endpoint. Overall survival as a secondary efficacy endpoint was statistically significant.

Open label setting

An open label setting was unavoidable and acceptable in the context of the population under evaluation.

- Uneven distribution of patients who did not receive treatment (9 patients in the mirvetuximab soravtansine arm versus 19 in the investigator's choice chemotherapy arm) or who withdrew (8 in the mirvetuximab soravtansine arm versus 17 in the investigator's choice chemotherapy arm), presumably due to open label setting; thus, informative censoring impacts the PFS and OS analyses. Additional analyses were conducted to address the uneven distribution, 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 mirvetuximab soravtansine arm despite the primary analysis showing a benefit for mirvetuximab soravtansine. The proportions of patients censored for new anticancer therapy before progressive disease /death or without baseline or post-baseline assessment are higher in the investigator's choice chemotherapy 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.
- Open label bias can be demonstrated when considering the number of early dropouts in the comparator arm (13% by Week 6) and the low concordance between the investigator and BICR results. 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, although 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 benefit/risk profile can be considered positive.

Small absolute progression free survival gain

The time gain of PFS was only 1.6 months. Despite this, the efficacy based on the totality of evidence is clinically relevant. The Kaplan-Meier PFS curves show an early separation of curves.

An OS benefit was demonstrated for mirvetuximab soravtansine (median OS 16.5 months versus 12.8 months for investigator's choice chemotherapy).

Immunogenicity

The incidence of neutralising antibodies (NAbs) was low, and therefore, the impact of NAbs on efficacy or safety could not be established. There was no apparent impact of ADAs identified on mirvetuximab soravtansine 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 infusion related reactions, data do not suggest an increased risk for patients with a seropositive status. The Product Information (PI) should include a statement regarding the frequency of ADA detection. No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed however data are still limited.

The sponsor is expected to submit data post registration relating to ADAs/NAbs against mirvetuximab soravtansine antibodies as per an FDA post marketing commitment, in 2028.

Risks/uncertainties of risk

Based on the data provided by the sponsor, the safety profile has been established for Elahere. Ocular AEs are notable, but most were mild, manageable and reversible. As ocular toxicity is likely to impact on the treatment burden of patients, adequate details of ocular toxicity must be included in the PI.

Exposure

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 mirvetuximab soravtansine arm than in the investigator's choice chemotherapy arm: 5 months and 3 months respectively. Likewise, the number of cycles was higher in the mirvetuximab soravtansine arm (7.0) compared to the investigator's choice chemotherapy arm (3.0). However, the relative dose intensity was similar. Overall, the extent of the exposure appears sufficient considering the disease and the poor prognosis of these patients.

Greater than 3 lines of therapy

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 mirvetuximab soravtansine in these patients. This is acceptable as the proposed indication is restricted to patients who received 1 to 3 prior systemic treatment regimens.

Adverse events of special interest

Adverse events of special interest included ocular AEs, pneumonitis, peripheral neuropathy and infusion related reactions.

Ocular toxicities

A total of 59% of patients had at least one ocular TEAE, and ≥ Grade 3 severity ocular TEAE occurred in 11%. 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 mirvetuximab soravtansine 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 antibody drug conjugates containing tubulin-directed payloads. Ocular disorder has been

identified as an important identified risk in the RMP and this risk should be mitigated in clinical practice using routine risk minimisation measures including guidance in the PI.

Pneumonitis/interstitial lung disease

In Study 0416, in the mirvetuximab soravtansine arm, pneumonitis was reported in 10% of patients, while in the investigator's choice chemotherapy arm the incidence was < 1%. Most of the reported pneumonitis TEAEs were of ≤ Grade 2 in severity in patients treated with mirvetuximab soravtansine. In total, 0.9% (6 out of 682) of patients had Grade 3 pneumonitis (grouped terms), and 0.2% (1 out of 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 PI should contain a warning that severe, life-threatening, or fatal interstitial lung disease, including pneumonitis, can occur in patients treated with mirvetuximab soravtansine. Patients should be monitored for pulmonary signs and symptoms of pneumonitis. Mirvetuximab soravtansine 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. Mirvetuximab soravtansine should be permanently discontinued in all patients with Grade 3 or 4 pneumonitis. Patients who are asymptomatic may continue dosing of mirvetuximab soravtansine with close monitoring.

Peripheral neuropathy

Overall patients in the mirvetuximab soravtansine arm reported more peripheral neuropathy TEAEs compared to those in the investigator's choice chemotherapy arm: 37% versus 23%, but TEAEs ≥ Grade 3 were similar between both analysis groups. Peripheral neuropathy resulted in mirvetuximab soravtansine dose delays in 2%, dose reductions in 4%, and led to permanent discontinuation in < 1% of patients. The 'Special warnings and precautions for use' section of the PI should include a warning to draw attention to the risk of peripheral neuropathy with the use of mirvetuximab soravtansine, 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 mirvetuximab soravtansine dose should be withheld, reduced, or permanently discontinued based on the severity of peripheral neuropathy.

Infusion related reactions

See Immunogenicity section above.

Myelosuppression

Thrombocytopenia and neutropenia may lead to consequences in patients treated with mirvetuximab soravtansine. However, mirvetuximab soravtansine was seen to be less myelosuppressive than chemotherapy.

Embryo-fetal toxicity

Embryo-fetal toxicity is a risk that should be included under the 'Special warnings and precautions for use' section of the PI (it is noted that this has been added as per the latest version of the proposed PI).

Adjusted ideal body weight dosing

The proposed dosage by AIBW is unusual. Use of the formula outlined in the initial proposed PI is associated with the potential for miscalculation, leading to an incorrect administered dose. To

reduce such risks, an example of a patient's calculation should be included (it is noted that this has been amended as per the latest version of the proposed PI).

Overall, the safety profile appears to be acceptable in the context of the poor prognosis of the intended population.

Uncertainties

Patients with > Grade 1 peripheral neuropathy, corneal disorders, active ocular conditions, significant cardiac disease or interstitial lung disease

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 MIRASOL/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 PI in order to mitigate this risk.

Populations not evaluated

Mirvetuximab soravtansine has not been studied in patients with cirrhotic liver disease or those patients with moderate or severe hepatic impairment as per study exclusion criteria. Mirvetuximab soravtansine has not been studied in patients with severe or end-stage renal impairment as per study exclusion criteria.

Hepatic impairment may increase exposure to DM4 and/or S-methyl-DM4, which may predispose to adverse reactions caused by the cytotoxic moiety of mirvetuximab soravtansine. The sponsor is conducting a clinical study (Study IMGN853-0425; hepatic impairment cohort) to evaluate the safety and PK of mirvetuximab soravtansine, DM4, and S-methyl-DM4 in patients with moderate hepatic impairment.

Study IMGN853-0425 will further characterise the use of Elahere in patients with moderate hepatic impairment, while the use in patients with severe hepatic impairment is contraindicated. Final data from this study should be submitted to the TGA for evaluation as a condition of registration, in addition to the submission of a revised RMP.

The sponsor provided the following update on Study IMGN856-0425:

> *Study IMGN853-0425, entitled, "A randomized Phase 2, open-label study of MIRV [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" is active and open for enrolment with one patient enrolled as of 11 July 2025 (Randomized Phase 2 Cohort).*
>
> *The study consist of 2 cohorts and the primary objectives behind them are as follows:*
>
> - *The first cohort study will characterize the safety and efficacy of the alternative dosing schedule (once every 2 weeks, Q2W) and the US-approved dosing schedule (once every 3 weeks, Q3W).*
> - *The second cohort study will determine the starting dose of MIRV in patients with moderate hepatic impairment.*

Benefit/risk balance

Overall, the benefit-risk assessment for mirvetuximab soravtansine is favourable for the evaluated population.

Proposed action

The Delegate is supportive of the application to register the product on the ARTG, for 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.*

Assessment outcome

Based on a review of quality, safety, and efficacy, the TGA decided to register Elahere (mirvetuximab soravtansine) 100 mg/20 mL concentrate solution for intravenous infusion vial, indicated for:

> *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).*

Specific conditions of registration

- Elahere (mirvetuximab soravtansine) is to be included in the Black Triangle Scheme. The PI and CMI for Elahere must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date of first supply of the product.
- The Elahere EU-Risk Management Plan (RMP) (version 1.0, dated 21 October 2024, data lock point 06 March 2023), with Australia-Specific Annex (ASA) (version 1.0, dated December 2024), included with submission PM-2024-05687-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of the approval letter. Each report must be submitted within ninety calendar days of the data lock point for that report.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.
- Laboratory testing & compliance with Certified Product Details (CPD)

  i. All batches of Elahere supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

ii. When requested by the TGA, the sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the Product. Please note that outcomes of laboratory testing may be published on the TGA website.

- Certified Product Details

  The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM), in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

  A template for preparation of CPD for biological prescription medicines can be obtained from the TGA website

  [for the form] https://www.tga.gov.au/form/certified-product-details-cpdbiological-prescription-medicines

  [for the CPD guidance] https://www.tga.gov.au/guidance-7-certified-productdetails

- Conduct, and submit the final results for, an open label, non-randomised, dose escalation trial, with expansion in a sufficient number of patients, to determine an appropriate starting dose of mirvetuximab soravtansine in patients with moderate hepatic impairment, according to National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria, in the target patient population. Collect safety and pharmacokinetic information for mirvetuximab soravtansine, unconjugated DM4, and s-methyl DM4 from the trial and utilise this information to determine the appropriate starting dose of mirvetuximab soravtansine for this population.
- Complete, and submit the final analysis of, the ongoing clinical trial, Study 0416, entitled, “A 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 (MIRASOL),” including the pre-specified final overall survival analysis.
- Evaluate the effect of anti-mirvetuximab soravtansine antibodies and the effect of neutralising antibodies against mirvetuximab soravtansine on the efficacy, safety, and pharmacokinetics of mirvetuximab soravtansine. Submit an amended integrated summary of immunogenicity report with data from a sufficient number of patients in ongoing studies and future studies. Key efficacy endpoints should include overall response rate, progression free survival, and overall survival.

Product Information and Consumer Medicine Information

For the most recent Product Information (PI) and Consumer Medicine Information (CMI), please refer to the TGA PI/CMI search facility.

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Reference/Publication