SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

ELAHERE 5 mg/mL concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL of concentrate for solution for infusion contains 5 mg of mirvetuximab soravtansine. One vial contains 100 mg mirvetuximab soravtansine in 20 mL.

Mirvetuximab soravtansine is a FRα-directed antibody-drug conjugate (ADC). The ADC consists of an anti-FRα monoclonal antibody of IgG1 subtype produced using recombinant DNA technology in Chinese Hamster Ovary cells and attached via a cleavable linker (butanoic acid, 4-(2-pyridinyldithio)- 2-sulfo-1-(2,5-dioxo-1-pyrrolidinyl) ester) to a maytansinoid DM4, an anti-tubulin agent.

Mirvetuximab soravtansine contains an average of 3.4 DM4 payload molecules bound to the anti-FRα antibody.

Excipients with known effect

This medicinal product contains 2.11 mg of polysorbate 20 in each vial. For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate). Clear to slightly opalescent, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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).

4.2 Posology and method of administration

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

Patient selection

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:

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

For example, 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

Pre-medication

Pre-medication for infusion related reactions (IRRs), nausea, and vomiting

Administer the pre-medications in Table 1 prior to each infusion of ELAHERE to reduce the incidence and severity of IRRs, nausea, and vomiting.

Table 1: Pre-medication prior to each ELAHERE infusion

Pre-medication	Route of administration	Examples (or equivalent)	Administration time prior to ELAHERE infusion
Corticosteroid	intravenous	dexamethasone 10 mg	at least 30 minutes prior
Antihistamine	oral or intravenous	chlorphenamine 10 mg	
Antipyretic	oral or intravenous	paracetamol 500 mg to 1000 mg	
Antiemetic	oral or intravenous	5-HT_3 serotonin receptor antagonist or appropriate alternatives	before each dose and following the administration of other premedication

For patients experiencing nausea and/or vomiting, additional antiemetics may be considered thereafter as needed.

For patients who experience an IRR Grade ≥2, additional pre-medication with dexamethasone 8 mg two times a day (BID) (or equivalent) the day before ELAHERE administration should be considered.

Ophthalmic exam and pre-medication

Ophthalmic exam: 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.

Ophthalmic topical steroids: 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.

During treatment with ophthalmic topical steroids the measurement of intraocular pressure and an examination with slit lamp should be carried out regularly.

Lubricating eye drops: It is recommended to instruct patients to use lubricating eye drops throughout treatment with ELAHERE.

Dose modifications

Before the start of each cycle, the patient should be advised to report any new or worsening symptoms to the treating physician or qualified individual.

In patients who develop new or worsening ocular symptoms, an ophthalmic exam should be conducted before dosing. The treating physician should review the patient's ophthalmic examination report before dosing and determine the dose of ELAHERE based on the severity of findings in the most severely affected eye.

Table 2 and Table 3 provide dose reductions and modifications for adverse reactions. The schedule of administration should be maintained at a 3-week interval between the doses.

Table 2: Dose reduction schedule

	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 3: Dose modifications for adverse reactions

Adverse reaction	**Severity of adverse reaction***	**Dose modification**
Keratitis/keratopathy (see sections 4.4 and 4.8)	Non-confluent 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 to nonconfluent superficial keratitis/keratopathy or better or resolved, then maintain at same dose level. Consider dose reduction for patients with recurrent confluent keratitis/keratopathy despite best supportive care or in patients with ocular toxicity lasting longer than 14 days.
	Corneal ulcer or stromal opacity or best corrected distance visual acuity 6/60 or worse	Withhold dose until improved to nonconfluent superficial keratitis/keratopathy or better 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 if recurrent, lasts longer than 28 days, or at physician discretion.
Adverse reaction	**Severity of adverse reaction***	**Dose modification**
	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
	Grade 1	Maintain infusion rate

Infusion-related reactions/ hypersensitivity (see sections 4.4 and 4.8)	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 with dexamethasone 8 mg oral BID the day before infusion (or local equivalent) 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 after discharge from the infusion area. • Permanently discontinue
Haematological (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.

Special populations

Paediatric population

There is no relevant use of ELAHERE for the treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancer in the paediatric population (see section 5.1).

Elderly

No dose adjustment of ELAHERE is recommended in patients □65 years of age (see section 5.2).

Renal impairment

No dose adjustment of ELAHERE is recommended for patients with mild to moderate renal impairment (creatinine clearance [CLcr] 30 to <90 mL/min). ELAHERE has not been evaluated in patients with severe renal impairment (CLcr 15 to <30 mL/min) or end-stage renal disease and the potential need for dose adjustment in these patients cannot be determined (see section 5.2).

Hepatic impairment

No dose adjustment of ELAHERE is recommended for patients with mild hepatic impairment (total bilirubin ≤ upper limit of normal [ULN] and aspartate aminotransferase [AST] > ULN or total bilirubin >1 to 1.5 times ULN and any AST) (see section 5.2).

ELAHERE should be avoided in patients with moderate to severe hepatic impairment (total bilirubin >1.5 ULN with any AST).

Method of administration

ELAHERE is for intravenous infusion at a rate of 1 mg/min. If well tolerated after 30 minutes, the infusion rate can be increased to 3 mg/min. If well tolerated after 30 minutes at 3 mg/min, the infusion rate can be increased to 5 mg/min.

For incompatibilities, see section 6.2.

ELAHERE requires dilution with 5% glucose for intravenous infusion. For instructions on dilution of the medicinal product before administration, see section 6.6.

ELAHERE must be administered as an intravenous infusion only, using a 0.2 or 0.22 µm polyethersulfone (PES) in-line filter (see Special handling and disposal procedures in section 6.6).

Precautions to be taken before handling or administering the medicinal product

This medicinal product contains a cytotoxic component, which is covalently attached to the monoclonal antibody (see special handling and disposal procedures in section 6.6).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Ocular disorders

Mirvetuximab soravtansine can cause severe ocular adverse reactions, including visual impairment (predominantly blurred vision), keratopathy (corneal disorders), dry eye, photophobia, and eye pain (see sections 4.7 and 4.8).

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 (see section 4.2).

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 physician should monitor patients for ocular toxicity and withhold, reduce, or permanently discontinue mirvetuximab soravtansine based on the severity and persistence of ocular adverse reactions (see section 4.2).

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

Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in

patients treated with mirvetuximab soravtansine (see section 4.8).

Patients should be monitored for pulmonary signs and symptoms of pneumonitis, which may include hypoxia, cough, dyspnoea, or interstitial infiltrates on radiologic exams. Infectious, neoplastic, and other causes for such symptoms should be excluded through appropriate investigations.

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 (see section 4.2). Patients who are asymptomatic may continue dosing of mirvetuximab soravtansine with close monitoring.

Peripheral neuropathy

Peripheral neuropathy has occurred with mirveutximab soravtansine, including Grade ≥3 reactions

(see section 4.8).

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, mirvetuximab soravtansine dose should be withheld, reduced, or permanently discontinued based on the severity of peripheral neuropathy (see section 4.2).

Embryo-foetal toxicity

Based on its mechanism of action, mirvetuximab soravtansine could cause embryo-foetal harm when administered to a pregnant patient because it contains a genotoxic compound (DM4) and affects actively dividing cells.

Patients of childbearing potential should use effective contraception during treatment with mirvetuximab soravtansine and for 7 months after the last dose (see section 4.6).

Excipients with known effect

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

This medicinal product contains 2.11 mg of polysorbate 20 in each vial.

4.5 Interaction with other medicinal products and other forms of interaction

Clinical drug-drug interaction studies with ELAHERE have not been conducted.

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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

The pregnancy status in patients of childbearing potential should be verified prior to initiating mirvetuximab soravtansine treatment.

Patients of childbearing potential should use effective contraception during treatment with mirvetuximab soravtansine and for 7 months after the last dose.

Pregnancy

Based on its mechanism of action, mirvetuximab soravtansine can cause embryo-foetal harm when administered to a pregnant patient because it contains a genotoxic compound (DM4) and affects actively dividing cells (see sections 5.1 and 5.3). 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.

Breast-feeding

It is unknown whether mirvetuximab soravtansine/metabolites are excreted in human milk. A risk to the newborn/infant cannot be excluded as human immunoglobulin G (IgG) is known to pass on in breast milk. ELAHERE should not be used during breast-feeding and for 1 month after the last dose.

Fertility

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.

4.7 Effects on ability to drive and use machines

ELAHERE has 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.

4.8 Undesirable effects

Summary of safety profile

The most common adverse reactions with mirvetuximab soravtansine were blurred vision (43%), nausea (41%), diarrhoea (39%), fatigue (35%), abdominal pain (30%), keratopathy (29%), dry eye (27%), constipation (26%), vomiting (23%), decreased appetite (22%), peripheral neuropathy (20%), headache (19%), asthenia (18%), AST increased (16%), and arthralgia (16%).

The most commonly reported serious adverse reactions were pneumonitis (4%), small intestinal obstruction (3%), intestinal obstruction (3%), pleural effusion (2%), abdominal pain (2%), dehydration (1%), constipation (1%), nausea (1%), ascites (1%) and thrombocytopenia (<1%).

Adverse reactions that most commonly led to dose reduction or dose delay were blurred vision (17%), keratopathy (10%), dry eye (5%), neutropenia (5%), keratitis (4%), cataract (3%), visual acuity reduced (3%), thrombocytopenia (3%), peripheral neuropathy (3%), and pneumonitis (3%).

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%).

Tabulated list of adverse reactions

The frequencies of adverse reactions are based on pooled data from 4 clinical studies which included 682 patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer (collectively referenced as Epithelial Ovarian Cancer (EOC) treated with mirvetuximab soravtansine 6 mg/kg AIBW administered once every 3 weeks. The median duration of treatment with mirvetuximab soravtansine was 19.1 weeks (range: 3, 132 weeks).

The adverse reaction frequencies from clinical studies are based on all-cause adverse event frequencies, for which, after thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility.

Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); very rare (<1/10 000). Within each frequency grouping, where relevant, adverse reactions are presented in order of decreasing seriousness.

Table 4: Tabulated list of all grade adverse reactions in patients treated with mirvetuximab soravtansine in clinical studies

System Organ Class	Frequency category	Adverse reactions
Infections and infestations	Very common	Urinary tract infection
Blood and lymphatic system disorders	Very common	Anaemia, thrombocytopenia
	Common	Neutropenia
Metabolism and nutrition disorders	Very common	Decreased appetite, hypomagnesaemia
	Common	Hypokalaemia, dehydration
Psychiatric disorders	Common	Insomnia
Nervous system disorders	Very common	Peripheral neuropathy[1], headache,
	Common	Dysgeusia, dizziness
Eye disorders	Very common	Keratopathy[2], cataract[3], blurred vision event[4], photophobia, eye pain, dry eye[5]
	Common	Ocular discomfort[6]
Vascular disorders	Common	Hypertension
Respiratory, thoracic and mediastinal disorders	Very common	Pneumonitis[7], dyspnoea, cough

Gastrointestinal disorders	Very common	Diarrhoea, abdominal pain[8], constipation, abdominal distension, vomiting, nausea
	Common	Ascites, gastro-oesophageal reflux disease, stomatitis, dyspepsia
Hepatobiliary disorders	Common	Hyperbilirubinaemia
Skin and subcutaneous tissue disorders	Common	Pruritus
Musculoskeletal and connective tissue disorders	Very common	Arthralgia
	Common	Myalgia, back pain, pain in extremity, muscle spasms
General disorders and administration site conditions	Very common	Fatigue
	Common	Pyrexia
Investigations	Very common	Aspartate aminotransferase increased, alanine aminotransferase increased
	Common	Blood alkaline phosphatase increased, gamma-glutamyl transferase increased, weight decreased
Injury, poisoning and procedural complication	Common	Infusion related reaction/hypersensitivity[9]

[1] Peripheral neuropathy grouped term includes hypoaesthesia, neuropathy peripheral, neurotoxicity, paraesthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, and polyneuropathy (see section Description of selected adverse reactions).

[2] Keratopathy group term includes corneal cyst, corneal deposits, corneal disorder, corneal epithelial microcysts, corneal epithelium defect, corneal erosion, corneal opacity, corneal pigmentation, keratitis, keratitis interstitial, keratopathy, limbal stem cell deficiency, and punctate keratitis (see section Description of selected adverse reactions).

[3] Cataract grouped term includes cataract, cataract cortical, and cataract nuclear (see section Description of selected adverse reactions).

[4] Blurred vision event grouped term includes accommodation disorder, diplopia, hypermetropia, presbyopia, refraction disorder, vision blurred, visual impairment,

visual acuity reduced, and vitreous floaters (see section Description of selected adverse reactions).

[5] Dry eye grouped term includes dry eye and lacrimation decreased (see section Description of selected adverse reactions).

[6] Ocular discomfort grouped term includes eye irritation, eye pruritus, foreign body sensation in eye, and ocular discomfort (see section Description of selected adverse reactions).

[7] Pneumonitis group term includes interstitial lung disease, organising pneumonia, pneumonitis, pulmonary fibrosis, and respiratory failure (see section Description of selected adverse reactions).

[8] Abdominal pain grouped term includes abdominal discomfort, abdominal pain, abdominal pain lower, and abdominal pain upper.

[9] Infusion related reaction/hypersensitivity grouped term includes SMQ Hypersensitivity narrow and

flushing, erythema, erythema of eyelid.

Description of selected adverse reactions

Ocular disorders

Ocular adverse reactions (grouped terms) occurred in 59% of patients with EOC treated with mirvetuximab soravtansine. Eleven percent (11%) of patients experienced Grade 3 ocular adverse reactions and <1% experienced Grade 4 events. The most common ≥ Grade 3 ocular adverse reactions were blurred vision and keratopathy (both 5%, grouped terms) and cataract (4%).

The median time to onset for first ocular adverse reaction was 5.1 weeks (range: 0.1 to 68.6). Of the patients who experienced ocular events, 53% had complete resolution (Grade 0) and 38% had partial improvement (defined as a decrease in severity by one or more grades from the worst grade). At the last follow-up, 0.3% (2/682) patients had ≥ Grade 3 ocular adverse events (1 patient with Grade 3 decreased visual acuity and 1 patient with Grade 4 cataract).

Ocular adverse reactions led to dose delays in 24% of patients, and dose reductions in 15% of patients. Ocular adverse reactions led to permanent discontinuation of mirvetuximab soravtansine in 1% of patients.

Pneumonitis

Pneumonitis (grouped terms) occurred in 10% of patients with EOC treated with mirvetuximab soravtansine, including 0.9% (6/682) patients with Grade 3 events, and 0.2% (1/682) patient with 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 1 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 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.

Peripheral neuropathy

Peripheral neuropathy (grouped terms) occurred in 36% of patients with EOC treated with mirvetuximab soravtansine across clinical studies; 3% of patients experienced Grade 3 peripheral neuropathy.

The median time to onset of peripheral neuropathy was 5.9 weeks (range 0.1 to 126.7). Peripheral neuropathy resulted in mirvetuximab soravtansine dose delays in 2%, dose reductions in 4%, and led to permanent discontinuation in 0.7% of patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme: Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is no known treatment/antidote available for overdose of mirvetuximab soravtansine. In case of overdose, patients must be closely monitored for signs or symptoms of adverse reactions and appropriate symptomatic treatment initiated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents, monoclonal antibodies and antibody drug conjugates, other monoclonal antibodies and antibody drug conjugates.

ATC code: L01FX26

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.

Pharmacodynamic effects

Cardiac electrophysiology

At the approved recommended dose, mirvetuximab soravtansine did not cause mean increases >10 msec in the QTc interval based on the results of concentration-QTc analysis.

Clinical efficacy and safety

Study IMGN853-0416 (MIRASOL)

The efficacy and safety of mirvetuximab soravtansine were studied in Study IMGN853-0416, a multicentre, open-label, active-controlled, randomised, two-arm phase 3 study that enrolled platinum- resistant advanced high-grade serous epithelial ovarian, primary peritoneal or fallopian tube cancers patients whose tumours (including archival tissue) were FRα positive as determined by the FOLR1 (FOLR1-2.1) RxDx assay (≥75% of viable tumour cells with moderate (2) and/or strong (3) membrane staining intensity by immunohistochemistry (IHC)).

Platinum-resistant disease was defined as EOC that recurred within 6 months of the last dose of platinum.

The study excluded patients with primary platinum-refractory disease, patients with ECOG≥2 and patients with active or chronic corneal disorders, ocular conditions requiring ongoing treatment, Grade ≥2 peripheral neuropathy, or non-infectious ILD/pneumonitis.

Patients were randomised 1:1 to receive either ELAHERE 6 mg/kg AIBW IV (N=227) at Day 1 of each 3-week cycle or one of the following chemotherapies (N=226) as decided by the investigator prior to randomisation:

- Paclitaxel (Pac) 80 mg/m^2 administered once weekly within a 4-week cycle;
- Pegylated liposomal doxorubicin (PLD) 40 mg/m^2 administered once every 4 weeks;
- Topotecan (Topo) 4 mg/m^2 administered on Days 1, 8, and 15 every 4 weeks or for 5 consecutive days at 1.25 mg/m^2 from Days 1-5 of each 21-day cycle

Randomisation was stratified by number of prior lines of therapy (1 vs 2 vs 3) and by Investigator's choice of chemotherapy (IC Chemo) (Pac vs PLD vs Topo). Treatment was administered until disease progression, death, withdrawal of consent, or unacceptable toxicity.

The primary efficacy outcome measure was progression free survival (PFS) based on investigator assessment using RECIST 1.1 criteria. Objective response rate (ORR) and overall survival (OS) were key secondary efficacy outcome measures.

In total, 453 patients were randomised. The median age was 63 years (range: 29 to 88 years), and patients were predominantly white (66%; 12% Asian). Most patients (80%) had ovarian cancer of epithelial origin; 11% of the fallopian tube; 8% of primary peritoneal; all (100%) were of high-grade serous histology. Approximately half the patients (47%) received 3 prior systemic therapies, 39% had 2 prior lines, and 14% of patients had 1 prior line. The majority of patients received a prior poly ADP ribose polymerase (PARP) inhibitor (55%) and prior bevacizumab (62%). The platinum-free interval following the most recent line of therapy was ≤3 months in 41% of patients, and 3 to 6 months in 58% of patients. Fifty five percent (55%) of patients had an ECOG performance status of 0, and 44% had an ECOG of 1.

The primary analysis demonstrated a statistically significant improvement in PFS and OS for patients randomised to ELAHERE as compared with IC chemotherapy.

Table 5 summarises the efficacy results of study IMGN853-0416 (MIRASOL).

Table 5: Efficacy results of Study IMGN853-0416

Efficacy parameter	**ELAHERE N=227**	**IC chemotherapies N=226**
Progression-free survival (PFS) as assessed by investigator		
Number of events (%)	176 (77.5)	166 (73.5)
Median, months (95% CI)	5.62 (4.34, 5.95)	3.98 (2.86, 4.47)
Hazard ratio (95% CI)	0.65 (0.521, 0.808)	
p-value	<0.001	
Overall survival (OS)		
Number of events (%)	90 (39.6)	114 (50.4)
Median, months (95% CI)	16.46 (14.46, 24.57)	12.75 (10.91, 14.36)
Hazard ratio (95% CI)	0.67 (0.504, 0.885)	
p-value	0.0046*	

Data cut-off 06 March 2023.

*: pre-determined efficacy boundary = 0.01313, 2-sided (adjusted by observed number of deaths 204).

The Kaplan Meier curves for investigator-assessed PFS (median follow-up of 11.2 months) and OS (median follow-up of 13.1 months) are presented in Figure 1 and Figure 2.

Figure 1: Kaplan-Meier curve for progression-free survival by treatment arm in MIRASOL (intent to treat population)

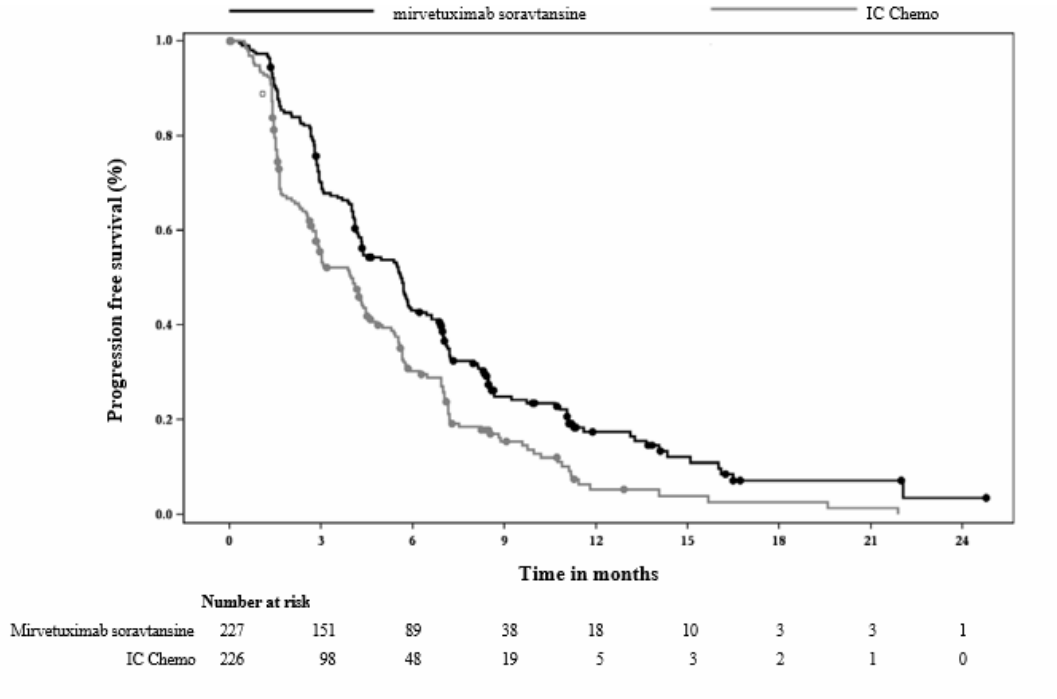
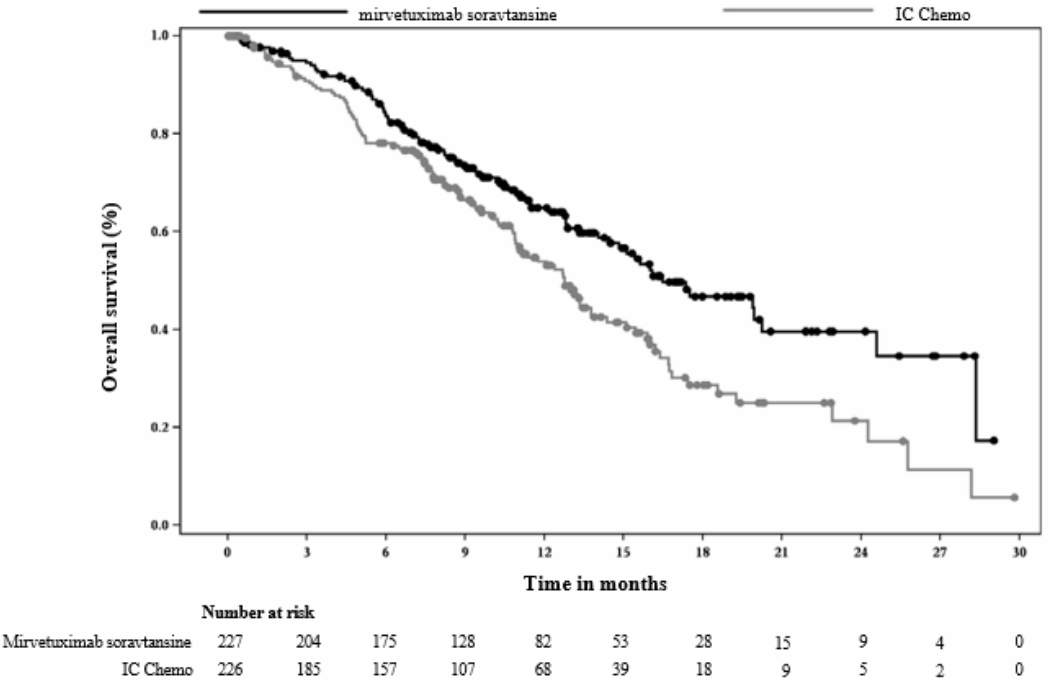


Figure 2: Kaplan-Meier curve for overall survival by treatment arm in MIRASOL (intent to treat population)



At an additional descriptive analysis with median follow-up of 20.3 months, OS results were consistent with the primary analysis.

Immunogenicity

Anti-drug antibodies (ADA) were commonly detected. No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed, however, data are still limited.

Paediatric population

The Medicines and Healthcare products Regulatory Agency has waived the obligation to submit the results of studies with ELAHERE in all subsets of the paediatric population in treatment of ovarian carcinoma, treatment of fallopian tube carcinoma, and treatment of peritoneal carcinoma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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.

Table 6 summarises the exposure parameters of mirvetuximab soravtansine, unconjugated DM4, and its metabolite S-methyl-DM4 following administration after the first cycle (3-weeks) of mirvetuximab soravtansine 6 mg/kg 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.

Table 6: Exposure parameters of mirvetuximab soravtansine, unconjugated DM4, and S-methyl DM4 after first treatment cycle of 6 mg/kg of mirvetuximab soravtansine

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

Cmax = maximum concentration, AUCtau = area under the concentration vs. time curve over the dosing interval (21 days).

Absorption

Mirvetuximab soravtansine is administered as an intravenous infusion. There have been no studies performed with other routes of administration.

Distribution

The mean (±SD) steady state volume of distribution of mirvetuximab soravtansine was 2.63 (±2.98) L. Human plasma protein binding of DM4 and S-methyl DM4 was >99%, in vitro.

Biotransformation

The monoclonal antibody portion of mirvetuximab soravtansine is expected to be metabolised into small peptides by catabolic pathways. Unconjugated DM4 and S-methyl-DM4 undergo metabolism by CYP3A4. In human plasma, DM4 and S-methyl DM4 were identified as the main circulating metabolites, accounting for approximately 0.4% and 1.4% of mirvetuximab soravtansine AUC, respectively.

Elimination

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) L/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.

Special populations

No clinically significant differences in the pharmacokinetics of mirvetuximab soravtansine were observed based on age (32 to 89 years), race (White, Black, or Asian), body weight (36 to 136 kg), mild hepatic impairment (total bilirubin ≤ULN and any AST >ULN or total bilirubin >1 to 1.5 times ULN and any AST), or mild to moderate renal impairment (CLcr ≥30 and <90 mL/min).

The pharmacokinetics of mirvetuximab soravtansine in patients with moderate to severe hepatic impairment (total bilirubin >1.5 ULN with any AST) or severe renal impairment (CLcr 15 to 30 mL/min) is unknown.

Drug interaction studies

In vitro studies

Cytochrome P450 (CYP) enzymes: Unconjugated DM4 is a time-dependent inhibitor of CYP3A4. Unconjugated DM4 and S-methyl DM4 are not direct inhibitors of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A. DM4 and S-methyl DM4 are not inducers of CYP1A2, CYP2B6, or CYP3A4.

Transporter systems: Unconjugated DM4 and S-methyl DM4 are substrates of P-gp but are not inhibitors of P-gp.

5.3 Preclinical safety data

Target organs identified with single-dose administration of mirvetuximab soravtansine in cynomolgus monkeys were limited to skin and cellular depletion of the bone marrow and lymphoid tissue. Repeat dosing in cynomolgus monkeys and Dutch-belted rabbits also indicated ophthalmic findings including corneal microcysts, pigmentation, attenuation and degeneration/necrosis of the corneal epithelium.

These findings were dose intensity (dose and schedule) dependent with fewer overall findings and recovery of those findings observed in the 3-week dosing schedule (the clinical dosing schedule).

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

DM4 and S-methyl DM4 were not mutagenic in the bacterial reverse mutation (Ames) assay. DM4 and S-methyl DM4 resulted in micronuclei in polychromatic erythrocytes.

No reproductive or developmental animal toxicity studies were conducted with mirvetuximab soravtansine.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glacial acetic acid (E260)

Sodium acetate (E262)

Sucrose

Polysorbate 20 (E432)

Water for injections

6.2 Incompatibilities

ELAHERE is incompatible with sodium chloride 9 mg/mL (0.9%) solution for infusion. This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

5 Years

Diluted solution

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.

From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of user.

6.4 Special precautions for storage

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.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

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.

Pack size of 1 vial.

6.6 Special precautions for disposal

ELAHERE is a cytotoxic medicinal product. Follow applicable special handling and disposal procedures.

Preparation

- Calculate the dose (mg) (based on the patient's AIBW), total volume (mL) of solution required, and the number of vials of ELAHERE needed (see section 4.2). More than one vial will be needed for a full dose.
- Remove the vials of ELAHERE from the refrigerator and allow to warm to room temperature.
- Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. ELAHERE is a clear to slightly opalescent, colourless solution.
- The medicinal product should not be used if the solution is discoloured or cloudy, or if foreign particulate matter is present.
- Gently swirl and inspect each vial prior to withdrawing the calculated dose volume of

ELAHERE for subsequent further dilution. Do not shake the vial.

- Using aseptic technique, withdraw the calculated dose volume of ELAHERE for subsequent further dilution. Each vial contains an overfill that allows withdrawal of the labelled amount.
- ELAHERE contains no preservatives and is intended for single dose only. Discard any unused solution remaining in the vial.

Dilution

- ELAHERE must be diluted prior to administration with 5% glucose to a final concentration of 1 mg/mL to 2 mg/mL.
- ELAHERE is not compatible with sodium chloride 9 mg/mL (0.9%) solution for infusion. ELAHERE must not be mixed with any other medicinal products or intravenous fluids. Determine the volume of 5% glucose required to achieve the final diluted active substance concentration. Either remove the excess 5% glucose from a pre-filled intravenous bag or add the calculated volume of 5% glucose to a sterile empty intravenous bag. Then add the calculated dose volume of ELAHERE to the intravenous bag.
- Gently mix the diluted solution by slowly inverting the bag several times to assure uniform

mixing. Do not shake or agitate.

- If the diluted infusion solution is not used immediately, store the solution in accordance with section 6.3. If refrigerated, allow the infusion bag to reach room temperature prior to administration. After refrigeration, administer diluted infusion solutions within 8 hours (including infusion time).
- Do not freeze the prepared infusion solution.

Administration

- Inspect the ELAHERE intravenous infusion bag visually for particulate matter and

discolouration prior to administration.

- Administer pre-medications prior to ELAHERE administration (see section 4.2).
- Administer ELAHERE as an intravenous infusion only, using a 0.2 or 0.22 µm polyethersulfone (PES) in-line filter. Do not substitute other membrane materials.
- Use of administration delivery devices containing Di-2-ethylhexyl phthalate (DEHP) should be avoided.
- Administer the initial dose as an intravenous infusion at the rate of 1 mg/min. If well tolerated after 30 minutes at 1 mg/min, the infusion rate can be increased to 3 mg/min. If well tolerated after 30 minutes at 3 mg/min, the infusion rate can be increased to 5 mg/min.
- If no infusion-related reactions occur with the previous dose, subsequent infusions should be started at the maximally tolerated rate and may be increased up to a maximum infusion rate of 5 mg/min, as tolerated.
- Following the infusion, flush the intravenous line with 5% glucose to ensure delivery of the full dose. Do not use any other intravenous fluids for flushing.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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SL6 4UB

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 41042/0100

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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