NEW ZEALAND DATA SHEET

1. ELAHERE® 100mg/20mL concentrate solution for intravenous infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution contains 5 mg of mirvetuximab soravtansine. Each single-dose vial contains 100 mg mirvetuximab soravtansine in 20 mL solution.

Mirvetuximab soravtansine is a folate receptor alpha (FRα)-directed antibody-drug conjugate consisting of three components: 1) an anti-FRα monoclonal antibody of human immunoglobulin G (IgG)1 subtype 2) the small molecule anti-tubulin agent DM4 (a maytansine derivative) and 3) a linker, sulfo-SPDB (1-((2,5-dioxopyrrolidin-1-yl)oxy)-1-oxo-4-(pyridin-2-yldisulfanyl)butane-2-sulfonic acid) that covalently attaches DM4 to the mirvetuximab antibody.

Mirvetuximab soravtansine is produced by chemical conjugation of the antibody and small molecule components. The antibody is produced by mammalian (Chinese hamster ovary) cells, and the small molecule components are produced by chemical synthesis. An average of 3.4 molecules of DM4 are attached to each antibody molecule.

For the full list of excipients see **Section 6.1 List of excipients**.

3. PHARMACEUTICAL FORM

Concentrate solution for intravenous infusion single dose vial.

Elahere (mirvetuximab soravtansine) is supplied as a sterile, preservative-free, 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 epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received one to three prior systemic treatment regimens.

4.2 Dose and method of administration

Patient Selection

Eligible patients should have FRα tumour status defined as ≥75% viable tumour cells demonstrating moderate (2+) and/or strong (3+) membrane staining by immunohistochemistry (IHC), assessed by a validated test (see Section 5.1 Pharmacodynamic Properties – Clinical Studies).

Recommended 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. Dosing based on AIBW reduces exposure variability for patients who are either underweight or overweight.

The total dose of Elahere is calculated based on each patient's AIBW using the following formula:

AIBW = Ideal Body Weight (IBW [kg]) + 0.4*(Actual weight [kg] – IBW)

Female IBW [kg] = 0.9*height[cm] – 92

Premedication and Required Eye Care

Premedication

Administer the pre-medications in Table 1 prior to each infusion of Elahere to reduce the incidence and severity of infusion related reactions (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	diphenhydramine 25 mg to 50 mg	
Antipyretic	oral or intravenous	paracetamol 500 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, consider additional antiemetics as needed.

For patients who experience an IRR Grade ≥ 2, consider additional pre-medication with dexamethasone 8 mg BID (or equivalent) the day before Elahere administration.

Ophthalmic Examination and Premedication

Ophthalmic Examination: Conduct an ophthalmic exam including visual acuity and slit lamp exam prior to initiation of Elahere, and thereafter if a patient develops new or worsening ocular symptoms prior to the next dose.

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.

Administer steroid eye drops on the day of infusion and through the next 7 days of each subsequent cycle of Elahere (see Table 3).

Wait at least 10 minutes or as directed per local prescribing information after ophthalmic topical steroid administration before instilling lubricating eye drops.

Intraocular pressure should be checked frequently during treatment with ophthalmic topical steroids.

Lubricating eye drops: Instruct patients to use lubricating eye drops throughout treatment with Elahere.

Dose Modification

Table 2 provides dose reduction levels and Table 3 provides dosage modifications for Elahere due to adverse reactions.

In patients who develop new or worsening ocular symptoms, conduct an ophthalmic examination before dosing. Review the ophthalmic examination report and determine the dose of Elahere based on the severity of findings in the most severely affected eye.

Table 2. Dose Reduction Schedule

	Elahere dose levels
Starting dose	6 mg/kg AIBW once every 3 weeks (21-day cycle)
First dose reduction	5 mg/kg AIBW once every 3 weeks (21-day cycle)
Second dose reduction	4 mg/kg AIBW* once every 3 weeks (21-day cycle)

* 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	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 non-confluent 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	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.
	Grade 3 or 4	Permanently discontinue
Peripheral neuropathy	Grade 2	Withhold dose until Grade 1 or less, then reduce by one dose level.
	Grade 3 or 4	Permanently discontinue

Adverse reaction	Severity of adverse reaction*	Dose modification
Infusion-related reactions/ Hypersensitivity	Grade 1	Maintain infusion rate
	Grade 2	• Interrupt infusion and administer supportive treatment. • After recovery from symptoms, resume the infusion at 50% of the previous rate, and if no further symptoms appear, increase rate as appropriate until infusion is completed. • Administer additional pre-medication 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	Grade 3 or 4	Withhold dose until Grade 1 or less, then resume at one lower dose level.
Other adverse reactions	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.

Preparation and Administration

Elahere must be diluted by a healthcare professional and administrated as an intravenous infusion.

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. 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.
- Inspect the vials visually for particulate matter and discolouration prior to administration. Elahere is a clear to slightly opalescent, colourless solution. Do not use 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. Do not shake the vial.
- Using aseptic technique, withdraw the calculated dose volume of Elahere for subsequent dilution.
- Elahere contains no preservatives and is intended for single dose only. Product is for single use in one patient only. Discard any unused solution remaining in the vial.

Dilution

For instructions on dilution of Elahere before administration, see Section 6.6 Special Precautions for Disposal and Other Handling.

Administration

- If the prepared infusion solution was stored refrigerated (2°C to 8°C), allow the infusion bag to reach room temperature prior to administration. Administer diluted infusion solution within 8 hours (including infusion time).
- 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 Dose and method of administration - Premedication and Required Eye Care).
- Administer Elahere as an intravenous infusion only, using a 0.2 or 0.22µm polyethersulfone (PES) in-line filter. Do not substitute other membrane materials.
- Avoid use of administration delivery devices containing Di-2-ethylhexyl phthalate (DEHP).
- 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.

Dosing in Special Populations

Paediatrics

The safety and efficacy of mirvetuximab soravtansine in children less than 18 years of age have not been established.

Geriatric

No dosage adjustment of Elahere is recommended in patients ≥ 65 years of age (see Section 5.2 Pharmacokinetic Properties).

Renal Impairment

No dosage adjustment of Elahere is recommended for patients with mild to moderate renal impairment (creatine clearance [CrCl] 30 to 89 mL/min). The effect of severe renal impairment (CrCl 15 to < 30 mL/min) or end-stage renal disease on Elahere is unknown (see Section 5.2 Pharmacokinetic Properties).

Hepatic Impairment

No dosage adjustment of Elahere is recommended for patients with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin >1 to 1.5 times ULN and any AST) (see Section 5.2 Pharmacokinetic Properties).

Avoid use of Elahere in patients with moderate or severe hepatic impairment (total bilirubin > 1.5 ULN).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 List of Excipients.

4.4 Special warnings and precautions for use

Ocular Disorders

Elahere can cause severe ocular adverse reactions, including blurred vision, keratopathy (corneal disorders), dry eye, photophobia, and eye pain (see Section 4.8 Undesirable Effects).

Refer patients to an eye care professional for an ophthalmic examination before initiation of Elahere.

Before the start of each cycle, advise patients to report any new or worsening ocular symptoms to the treating physician or qualified individual.

If ocular symptoms develop, conduct an ophthalmic examination, review the ophthalmic report and modify the dose of Elahere as needed based on the severity of the findings (see Section 4.2 Dose and method of administration).

Use of lubricating eye drops during treatment with Elahere is recommended. Ophthalmic topical steroids are recommended in patients who develop Grade 2 corneal adverse reactions (see Section 4.2 Dose and method of administration).

Monitor patients for ocular toxicity and withhold, reduce, or permanently discontinue Elahere based on the severity and persistence of ocular adverse reactions (see Section 4.2 Dose and method of administration).

Advise patients to avoid use of contact lenses during treatment with Elahere unless directed by a healthcare professional.

Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with Elahere (see Section 4.8 Undesirable Effects).

Monitor patients 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.

Withhold Elahere for patients who develop persistent or recurrent Grade 2 pneumonitis until symptoms resolve to ≤ Grade 1 and consider dose reduction. Permanently discontinue Elahere in all patients with Grade 3 or 4 pneumonitis (see Section 4.2 Dose and method of

administration). Patients who are asymptomatic may continue dosing of Elahere with close monitoring.

Peripheral Neuropathy

Peripheral neuropathy has occurred with Elahere treatment, including Grade ≥ 3 reactions (see Section 4.8 Undesirable Effects).

Monitor patients 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, withhold dosage, dose reduce, or permanently discontinue Elahere based on the severity of peripheral neuropathy (see Section 4.2 Dose and method of administration).

4.5 Interaction with other medicines and other forms of interaction

No clinical studies evaluating the drug-drug interaction potential of mirvetuximab soravtansine have been conducted.

DM4 is a CYP3A4 substrate. Concomitant use of Elahere with strong CYP3A4 inhibitors may increase unconjugated DM4 exposure, which may increase the risk of Elahere adverse reactions. Closely monitor patients for adverse reactions with Elahere when used concomitantly with strong CYP3A4 inhibitors.

4.6 Fertility, pregnancy and lactation

Impairment of Fertility

Fertility studies have not been conducted with mirvetuximab soravtansine or DM4. There are no data on the effect of Elahere on human fertility.

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

Pregnancy

Based on its mechanism of action, mirvetuximab soravtansine can cause embryofetal harm when administered to a pregnant patient because it contains a genotoxic compound (DM4) and affects actively dividing cells (see Section 5.3 Preclinical safety data – Mutagenicity). 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.

Advise patients of the potential risk to a foetus. The pregnancy status in patients of childbearing potential should be verified prior to initiating treatment. Females of reproductive potential should use effective contraception during treatment with Elahere and for 7 months after the last dose. Patients who become pregnant must immediately contact their doctor.

Lactation

There are no data on the presence of mirvetuximab soravtansine in human milk or the effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with Elahere and for 1 month after the last dose.

4.7 Effects on ability to drive and use machines

No studies on the effects of mirvetuximab soravtansine on the ability to drive and use machines have been performed. Elahere may have moderate influence on the ability to drive and use machines. Patients may experience visual disturbances or peripheral neuropathy during treatment with Elahere (see Section 4.4 Special Warnings and Precautions for Use and Section 4.8 Undesirable Effects).

4.8 Undesirable effects

Clinical Trials Experience

Study 0416 (MIRASOL)

The safety of Elahere was evaluated in Study 0416, a multicenter, open-label, active-controlled, randomised, two-arm study (Elahere versus chemotherapy), in patients (n=453) with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer (see Section 5.1 Pharmacodynamic properties – Clinical Studies). Patients received Elahere 6 mg/kg AIBW once every 3 weeks until disease progression or unacceptable toxicity. The median duration of treatment was 5 months (range: 0.69 to 27.4).

Serious adverse reactions occurred in 11% of patients treated with Elahere. The most common (≥ 2%) serious adverse reaction was abdominal pain (3%).

Permanent discontinuation of Elahere due to adverse reactions occurred in 6% of patients. The most common (≥ 1%) adverse reactions leading to permanent discontinuation were pneumonitis (2%), blurred vision (1%), and peripheral neuropathy (1%).

Dosage delays of Elahere due to an adverse reaction occurred in 41% of patients treated with Elahere. Adverse reactions which required dosage delays in ≥ 3% of patients included blurred vision (19%), keratopathy (17%), dry eye (6%), neutropenia (5%), pneumonitis (5%), photophobia (4%), and cataract (4%).

Dose reductions of Elahere due to an adverse reaction occurred in 33% of patients. Adverse reactions which required dose reductions in ≥ 3% of patients included blurred vision (14%), keratopathy (10%), peripheral neuropathy (6%), dry eye (5%), and fatigue (3%).

Table 4 summarises adverse reactions occurring in patients who received Elahere in Study 0416. Adverse reactions are listed by MedDRA body system organ class, rate, and frequency. 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).

Table 4. Adverse Reactions Occurring in Patients with Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer Who Received Elahere in Study 0416

Adverse Reaction by System Organ Class	**Elahere (N=218)**		**Chemotherapy (N=207)**	
	All grades % (frequency)	**Grade 3 or 4 %**	**All grades %**	**Grade 3 or 4 %**
Gastrointestinal disorders				
Abdominal pain[a]	34 (very common)	3	23	2
Diarrhoea	29 (very common)	1	17	<1
Constipation	27 (very common)	0	19	<1
Nausea	27 (very common)	2	29	2
Vomiting	18 (very common)	3	18	1
Eye disorders				
Blurred vision event[b]	45 (very common)	9	3	0
Keratopathy[c]	37 (very common)	11	0	0
Dry eye[d]	29 (very common)	3	5	0
Photophobia	18 (very common)	<1	<1	0

Adverse Reaction by System Organ Class	Elahere (N=218)		Chemotherapy (N=207)	
	All grades % (frequency)	Grade 3 or 4 %	All grades %	Grade 3 or 4 %
Cataract[e]	16 (very common)	3	<1	0
Ocular discomfort[f]	12 (very common)	0	<1	0
General disorders and administration site conditions				
Fatigue[g]	47 (very common)	3	41	7
Nervous system disorders				
Peripheral neuropathy[h]	37 (very common)	4	23	4
Headache	14 (very common)	0	10	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[i]	32 (very common)	<1	22	2
Blood and lymphatic system disorders				
Neutropenia	11 (very common)	<1	29	17
Anaemia	10 (common)	<1	34	10
Thrombocytopenia	7 (common)	<1	16	6
Investigations				
Aspartate aminotransferase increased	11 (very common)	<1	4	0
Alanine aminotransferase increased	9 (common)	<1	4	0
Weight decreased	9 (common)	0	3	0
Blood alkaline phosphatase increased	4 (common)	0	2	0
Gamma-glutamyltransferase increased	3 (common)	0	<1	0
Metabolism and nutrition disorders				
Decreased appetite	18 (very common)	1	14	<1
Dehydration	4 (common)	<1	<1	0
Respiratory, thoracic and mediastinal disorders				
Pneumonitis[j]	10 (common)	<1	<1	0
Injury, poisoning and procedural complications				
Infusion related reaction/Hypersensitivity[k]	8 (common)	0	13	<1
Hepatobiliary disorders				
Hyperbilirubinemia	<1 (uncommon)	0	0	0

[a] Abdominal pain includes PTs abdominal pain, abdominal pain upper, abdominal discomfort, and abdominal pain lower
[b] Blurred vision event includes PTs vision blurred, visual acuity reduced, visual impairment, vitreous floaters, accommodation disorder, and diplopia
[c] Keratopathy includes PTs keratopathy, keratitis, corneal epithelial microcysts, punctate keratitis, corneal deposits, corneal disorder, and corneal opacity
[d] Dry eye includes PTs dry eye, and lacrimation increased
[e] Cataract includes PTs cataract, and cataract nuclear
[f] Ocular discomfort includes PTs ocular discomfort, eye pain, eye irritation, and eye pruritus
[g] Fatigue includes PTs fatigue, and asthenia
[h] Peripheral neuropathy includes PTs neuropathy peripheral, peripheral sensory neuropathy, paraesthesia, neurotoxicity, hypoesthesia, peripheral sensorimotor neuropathy, polyneuropathy, and peripheral motor neuropathy
[i] Musculoskeletal pain includes PTs arthralgia, back pain, myalgia, pain in extremity, muscle spasms, non-cardiac chest pain, musculoskeletal stiffness, neck pain, bone pain, musculoskeletal pain, musculoskeletal chest pain, and musculoskeletal discomfort
[j] Pneumonitis includes PTs pneumonitis, interstitial lung disease, respiratory failure, and organizing pneumonia
[k] Infusion related reaction/hypersensitivity includes SMQ Hypersensitivity narrow and PTs erythema, and flushing occurring within 3 days of dosing

Study 0417 (SORAYA)

The safety of Elahere was evaluated in Study 0417, a single-arm, open-label study in patients (n=106) with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer (see Section 5.1 Pharmacodynamic Properties – Clinical Studies). Patients received Elahere 6 mg/kg AIBW once every 3 weeks until disease progression or unacceptable toxicity. The median duration of treatment was 4.2 months (range: 0.7 to 13.3).

Serious adverse reactions occurred in 9% of patients treated with Elahere. The most common (≥ 2%) serious adverse reaction was pneumonitis (3%).

Permanent discontinuation of Elahere due to adverse reactions occurred in 10% of patients. The most common (≥ 2%) adverse reactions leading to permanent discontinuation were thrombocytopenia (4%), and pneumonitis (2%). One patient (0.9%) permanently discontinued Elahere due to visual impairment (unilateral decrease to BCVA ≤ 6/60 that resolved to baseline after discontinuation).

Dosage delays of Elahere due to an adverse reaction occurred in 33% of patients treated with Elahere. Adverse reactions which required dosage delays in ≥ 3% of patients included blurred vision (15%), keratopathy (14%), neutropenia (7%), dry eye (4%), cataract (4%), pneumonitis (4%), thrombocytopenia (3%) and gamma-glutamyl transferase increased (3%).

Dose reductions of Elahere due to an adverse reaction occurred in 20% of patients. Adverse reactions which required dose reductions in ≥ 3% of patients included blurred vision (12%) and keratopathy (8%).

Table 5 summarises the adverse reactions in patients treated with Elahere in Study 0417. Adverse reactions are listed by MedDRA body system organ class, rate, and frequency. 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).

Table 5. Adverse Reactions Occurring in Patients with Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer Who Received Elahere in Study 0417

Adverse Reaction by System Organ Class	**Elahere (N=106)**	
	All grades % (frequency)	**Grade 3 or 4 %**
Gastrointestinal disorders		
Nausea	39 (very common)	0
Abdominal pain[a]	36 (very common)	7
Diarrhoea	31 (very common)	3
Constipation	30 (very common)	< 1
Vomiting	19 (very common)	0
Eye disorders		
Blurred vision event[b]	49 (very common)	8
Keratopathy[c]	39 (very common)	9
Dry eye[d]	28 (very common)	2
Cataract	20 (very common)	5
Photophobia	16 (very common)	0
Ocular discomfort[e]	13 (very common)	0
General disorders and administration site conditions		
Fatigue[f]	49 (very common)	3
Nervous system disorders		
Peripheral neuropathy[g]	35 (very common)	3
Headache	9 (common)	0

Adverse Reaction by System Organ Class	Elahere (N=106)	
	All grades % (frequency)	Grade 3 or 4 %
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[h]	38 (very common)	< 1
Blood and lymphatic system disorders		
Neutropenia	15 (very common)	2
Anaemia	13 (very common)	2
Thrombocytopenia	9 (common)	2
Investigations		
Aspartate aminotransferase increased	15 (very common)	2
Gamma-glutamyltransferase increased	12 (very common)	5
Alanine aminotransferase increased	11 (very common)	< 1
Blood alkaline phosphatase increased	11 (very common)	2
Weight decreased	7 (common)	0
Metabolism and nutrition disorders		
Decreased appetite	19 (very common)	< 1
Dehydration	<1 (uncommon)	0
Respiratory, thoracic and mediastinal disorders		
Pneumonitis[i]	10 (very common)	2
Injury, poisoning and procedural complications		
Infusion related reaction/hypersensitivity[j]	9 (common)	< 1
Hepatobiliary disorders		
Hyperbilirubinaemia	3 (common)	0

[a] Abdominal pain includes PTs abdominal pain, abdominal pain upper, abdominal discomfort, and abdominal pain lower.
[b] Blurred vision event includes PTs vision blurred, visual acuity reduced, visual impairment, vitreous floaters, accommodation disorder, diplopia, presbyopia, and refraction disorder.
[c] Keratopathy includes PTs keratopathy, keratitis, corneal epithelial microcysts, punctate keratitis, corneal deposits, and corneal epithelium defect.
[d] Dry eye includes PTs dry eye, and lacrimation increased.
[e] Ocular discomfort includes PTs ocular discomfort, eye pain, eye irritation, eye pruritus, and foreign body sensation in eyes
[f] Fatigue includes PTs fatigue and asthenia.
[g] Peripheral neuropathy includes PTs neuropathy peripheral, peripheral sensory neuropathy, paraesthesia, neurotoxicity, hypoesthesia, polyneuropathy, and peripheral motor neuropathy.
[h] Musculoskeletal pain includes PTs arthralgia, back pain, myalgia, pain in extremity, muscle spasms, non-cardiac chest pain, musculoskeletal discomfort, musculoskeletal stiffness, musculoskeletal pain, and musculoskeletal chest pain.
[i] Pneumonitis includes PTs pneumonitis, interstitial lung disease, and respiratory failure.

[j] Infusion related reaction/hypersensitivity includes SMQ Hypersensitivity narrow and PTs erythema, erythema of eyelid, and flushing occurring within 3 days of dosing.

Important Adverse Reactions

The pooled safety population reflects exposure to Elahere in 682 patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer at 6 mg/kg AIBW administered intravenously once every 3 weeks until disease progression or unacceptable toxicity in four clinical studies.

Ocular Disorders

Ocular adverse reactions occurred in 59% of patients in the pooled safety population. 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 (5%) and keratopathy and cataract (both 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).

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 Elahere in 1% of patients.

Pneumonitis

Pneumonitis occurred in 10% of patients in the pooled safety population, 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 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 Elahere dose delays in 3%, dose reductions in 1%, and permanent discontinuation in 3% of patients.

Peripheral Neuropathy

Peripheral neuropathy occurred in 36% of patients in the pooled safety population; 3% of patients experienced Grade 3 peripheral neuropathy. Peripheral neuropathy adverse reactions included peripheral neuropathy (20%), peripheral sensory neuropathy (9%), paraesthesia (6%), neurotoxicity (3%), hypoaesthesia (1%), peripheral motor neuropathy (0.9%), polyneuropathy (0.3%), and peripheral sensorimotor neuropathy (0.1%).

The median time to onset of peripheral neuropathy was 5.9 weeks (range 0.1 to 126.7). Of the patients who experienced peripheral neuropathy, 23% had complete resolution and 12% had partial improvement (defined as a decrease in severity by one or more grades from the worst grade) at last follow up. Peripheral neuropathy resulted in Elahere dose delays in 2%, dose reductions in 4%, and led to permanent discontinuation in 0.7% of patients.

Immunogenicity

In four clinical studies including 626 patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer treated with mirvetuximab soravtansine 6 mg/kg AIBW administered once every 3 weeks, anti-drug antibodies (ADA) were detected in 9% of patients. Due to the small numbers of patients in the groups analysed, the impact of ADA on efficacy could not be determined.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

There is no known treatment/antidote available for overdose of mirvetuximab soravtansine. In the event of overdose, monitor the patient for any signs or symptoms of adverse reactions and administer appropriate supportive treatment.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

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 a chimeric IgG1 directed against FRα. The small molecule, DM4, is a microtubule inhibitor attached to the antibody via a cleavable linker. Upon binding to FRα, mirvetuximab soravtansine is internalized 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.

Pharmacodynamics

Exposure-Response Relationships

Higher exposure to mirvetuximab soravtansine was associated with higher overall response rates and longer median progression-free survival (PFS) and overall survival (OS); higher exposure to mirvetuximab soravtansine was also associated with higher incidence of ocular adverse reactions as well as marginally increased peripheral neuropathy.

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 Studies

Study 0416 (MIRASOL)

The efficacy and safety of Elahere were studied in Study 0416 (MIRASOL), a multicenter, open-label, active-controlled, randomized, two-arm phase 3 study that enrolled platinum-resistant advanced high-grade serous epithelial ovarian, primary peritoneal or fallopian tube cancers patients whose tumours were FRα positive as determined by the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay (≥ 75% of tumour staining at ≥ 2+ intensity) evaluated at a central laboratory. Patients were excluded if they had active or chronic corneal disorders, ocular conditions requiring ongoing treatment, Grade > 1 peripheral neuropathy, or non-infectious ILD.

Patients were randomized (1:1) to receive Elahere 6 mg/kg (based on adjusted ideal body weight) as an intravenous infusion every 3 weeks or investigator's choice of chemotherapy (paclitaxel, pegylated liposomal doxorubicin [PLD], or topotecan) until disease progression or unacceptable toxicity. Tumour response assessments occurred every 6 weeks for the first 36 weeks and every 12 weeks thereafter. Randomisation was stratified by the following factors: number of prior lines of therapy (1 vs. 2 vs. 3) and chemotherapy (paclitaxel vs. PLD vs. topotecan) chosen prior to randomisation.

The major efficacy outcome measures were investigator-assessed PFS, confirmed objective response rate (ORR), and OS. PFS and ORR were evaluated according to Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1. Additional efficacy measures included: patient-reported outcome (PRO) assessment of European Organisation for Research and Treatment of Cancer (EORTC) QLQ-OV28; duration of response (DOR); and time to second disease progression (PFS2).

Table 6. Demographics and Baseline Characteristics in Study 0416

	Elahere N=227	**IC chemotherapies N=226**
Age, median (range)	64 (32, 88)	62 (29, 87)
Race, n (%)		
Caucasian	156 (69)	145 (64)
Black or African American	8 (4)	5 (2)
Asian	28 (12)	25 (11)
Not reported	32 (14)	49 (22)
Primary diagnosis, n (%)		
Epithelial ovarian	182 (80)	182 (81)
Fallopian tube	27 (12)	23 (10)
Primary peritoneal	16 (7)	20 (9)
BRCA status, n (%)		
Positive	29 (13)	36 (16)
Negative/Unknown	198 (87)	190 (84)
ECOG performance, n (%)		
0	130 (57)	120 (53)
1	97 (43)	101 (45)
Number of prior systemic therapies, n (%)		
1	29 (13)	34 (15)
2	90 (40)	88 (39)
3	108 (48)	104 (46)
Prior therapy with, n (%)		
Bevacizumab	138 (61)	143 (63)
PARP inhibitor	124 (55)	127 (56)
Platinum-Free Interval[a], n (%)		
≤ 3 months	88 (39)	99 (44)
> 3 to ≤ 6 months	138 (61)	124 (55)

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

The primary analysis demonstrated a statistically significant improvement in PFS, ORR, and OS for patients randomized to Elahere as compared with chemotherapy. Efficacy results for Study 0416 are shown in Table 7. The Kaplan Meier curves for investigator-assessed PFS (median follow-up of 11.2 months) and for OS (median follow-up of 13.1 months) are presented in Figure 1 and Figure 2, respectively.

Table 7. Efficacy Results in Study 0416

	Elahere N=227	**IC chemotherapies[a] N=226**
Progression-free survival (PFS)[b]		
Number of events (%)	176 (78)	166 (73)
Median, months (95% CI)	5.6 (4.3, 5.9)	4.0 (2.9, 4.5)
Hazard ratio (95% CI)	0.65 (0.52, 0.81)	
p-value[c]	< 0.0001	
Objective response rate (ORR)[d]		
n (%) (95% CI)	96 (42) (35.8, 49.0)	36 (16) (11.4, 21.4)
Odds Ratio (95% CI)	3.81 (2.440, 5.940)	
p-value[e]	< 0.0001	
Complete response, n (%)	12 (5)	0
Partial response, n (%)	84 (37)	36 (16)
Overall survival (OS)[f]		
Number of events (%)	90 (40)	114 (50)
Median, months (95% CI)	16.5 (14.5, 24.6)	12.7 (10.9, 14.4)
Hazard ratio (95% CI)	0.67 (0.50, 0.88)	
p-value[c]	0.0046	
Duration of response[g]		
N’	96	36
Number of events (%)	64 (67)	29 (81)
Median, months (95% CI)	6.8(5.6, 8.3)	4.5 (4.2, 5.8)
Progression-Free Survival-2 (PFS2)[h]		
Number of events (%)	129 (57)	150 (66)
Median, months (95% CI)	11.0 (9.4, 12.4)	8.0 (6.7, 9.4)
Hazard ratio (95% CI)	0.63 (0.50, 0.80)	
p-value[c]	0.0001	

[a] Chemotherapy: paclitaxel, PLD, or topotecan.

[b] PFS is defined as the time from the date of randomisation until the date of progressive disease per investigator assessment or death from any cause, whichever occurred first.
[c] Two-sided p-value based on stratified log-rank test adjusted for number of prior lines of therapy (1 vs. 2 vs. 3) and chemotherapy (paclitaxel vs. PLD vs. topotecan) chosen prior to randomisation.
[d] Objective response rate is defined as proportion of patients with complete or partial response per investigator assessment.
[e] Two-sided p-value based upon Cochran-Mantel-Haenszel (CMH) test adjusted for number of prior lines of therapy (1 vs. 2 vs. 3) and chemotherapy (paclitaxel vs. PLD vs. topotecan) chosen prior to randomization.
[f] OS is defined as the time from the date of randomisation until the date of death from any cause.
[g] DOR is defined as the time from the date of first response (CR or PR) to the date of progressive disease per investigator assessment or death from any cause, whichever occurred first. DOR is evaluated in the subjects who achieved CR or PR (N').
[h] PFS2 is defined as the time from date of randomization until second disease progression per investigator assessment or death from any cause, whichever occurred first.

Figure 1. Kaplan-Meier Curve for Progression-free Survival in Study 0416

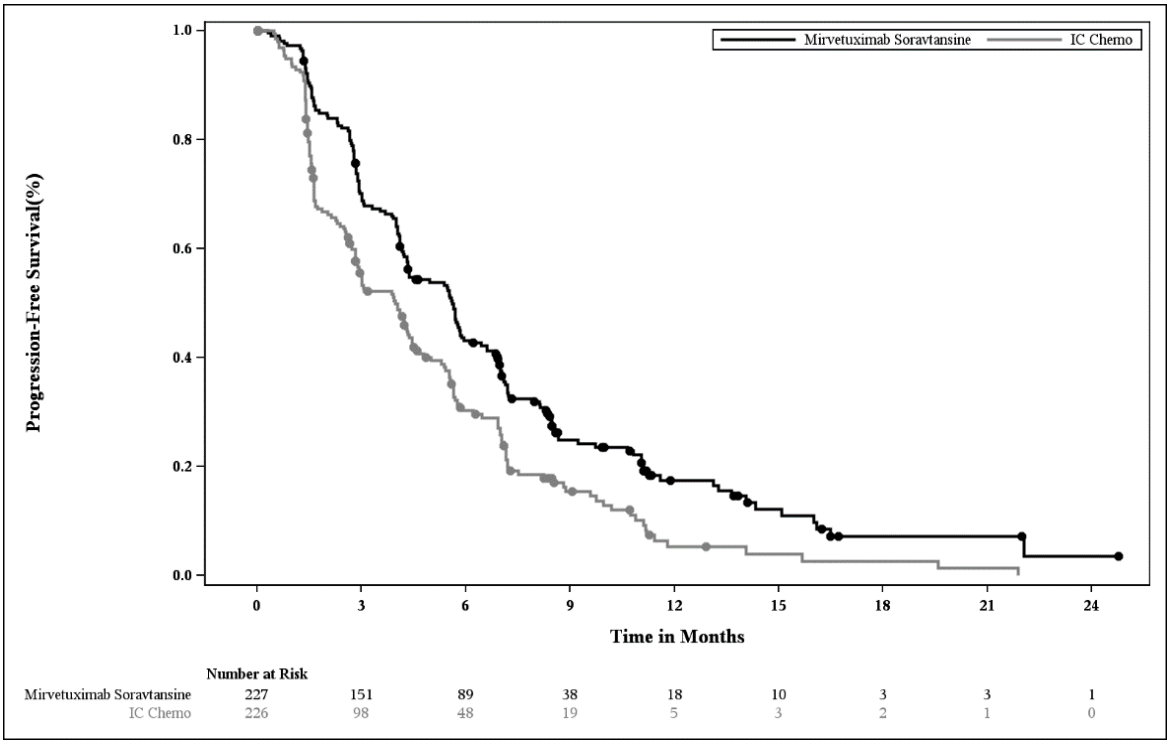
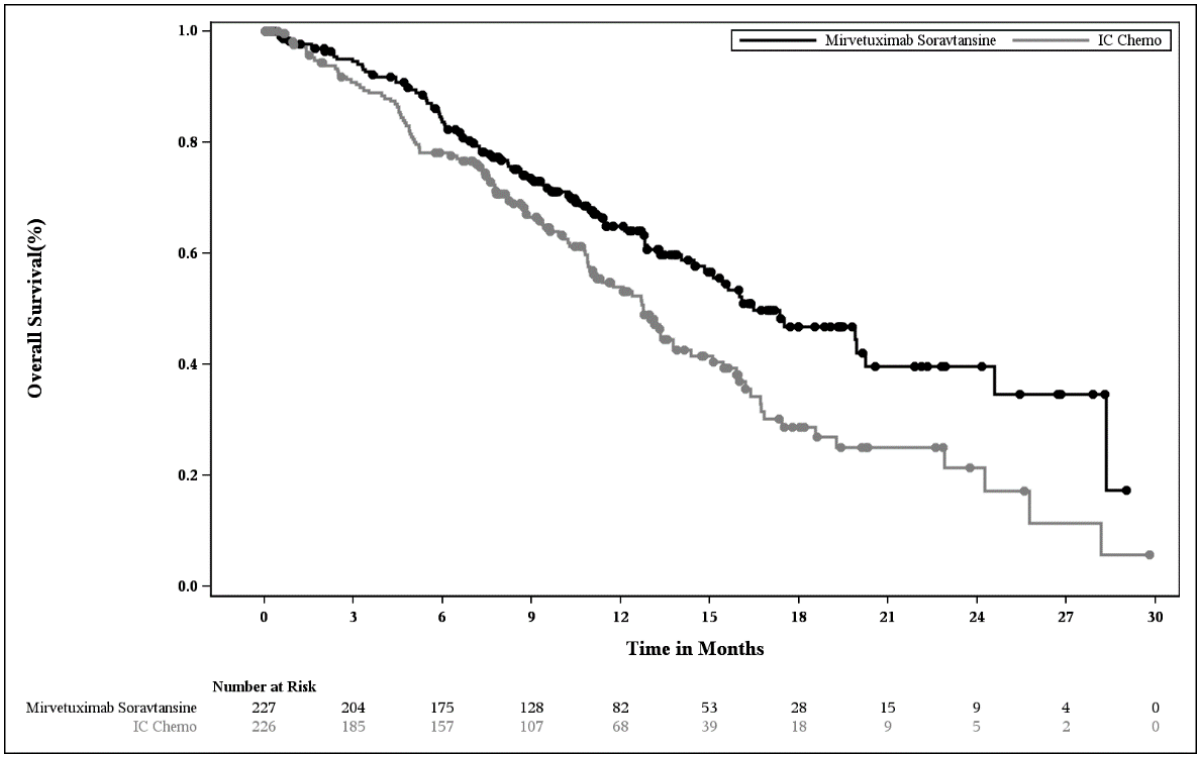


Figure 2. Kaplan-Meier Curve for Overall Survival in Study 0416



Patient-Report Outcomes (PRO)

PRO questionnaires were collected using the EORTC QLQ-OV28, EORTC QLQ-C30, EQ-5D-5L and PGIS. In the pre-specified secondary endpoint EORTC QLQ-OV28 primary responder analysis (abdominal/GI subscale), 21% of patients treated with mirvetuximab soravtansine had a 15-point reduction of the symptoms from baseline at Week 8/9 compared to 15% of patients treated with chemotherapy (p-value = 0.2611).

Pre-specified exploratory analyses of least square mean change from baseline to week 24 in abdominal/GI subscale score was -2.7 for mirvetuximab soravtansine and +3.3 for IC chemo (nominal p-value = 0.0056).

Pre-specified exploratory analyses of least square mean change from baseline to week 24 in EORTC QLQ-C30 global health status/QoL, was -0.5 for mirvetuximab soravtansine and -7.7 for IC chemo (nominal p-value = 0.0005). Pre-specified exploratory analyses of least square mean change from baseline to week 24 in EORTC QLQ-C30 fatigue symptom burden, was +1.5 for mirvetuximab soravtansine and +12.2 for IC chemo (nominal p-value < 0.0001).

These results should be interpreted in the context of the open-label study design.

Study 0417 (SORAYA)

The efficacy of Elahere was evaluated in Study 0417 (SORAYA), a single-arm trial of patients with FRα-positive, platinum-resistant high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer (n=106). Patients were permitted to receive up to three prior lines of systemic therapy. All patients were required to have received prior bevacizumab. The trial enrolled patients whose tumours were positive for FRα expression as determined by the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay (≥ 75% of tumour staining at ≥ 2+ intensity) evaluated at a central laboratory. Patients were excluded if they had active or chronic corneal disorders, ocular conditions requiring ongoing treatment, Grade > 1 peripheral neuropathy, or non-infectious ILD.

Patients received Elahere 6 mg/kg AIBW as an intravenous infusion every 3 weeks until disease progression or unacceptable toxicity. Tumour response assessments occurred every 6 weeks for the first 36 weeks and every 12 weeks thereafter.

The major efficacy outcome measures were investigator-assessed ORR and duration of response evaluated according to RECIST, version 1.1. In 106 patients who received at least one dose of Elahere, the median age was 62 years (range: 35 to 85); 96% were Caucasian, 2% were Asian, and 2% did not have race reported. All patients had an ECOG PS of 0 (57%) or 1 (43%). Nine percent of patients had received 1 prior line of systemic therapy, 39% of patients had received 2 prior lines of systemic therapy, and 51% of patients had received 3 prior lines of systemic therapy. All patients had received prior bevacizumab and 48% had received a prior PARP inhibitor.

Efficacy results for Study 0417 are shown in Table 8.

Table 8. Efficacy Results in Study 0417

	Elahere (N=105[a])
Confirmed Objective Response Rate[b]	
n (%) (95% CI)	34 (32) (24, 42)
Complete response rate n (%)	5 (5)
Partial response rate n (%)	29 (28)
Duration of Response	N=34
Median, months (95% CI)	6.9 (5.6, 9.7)

[a] Based on Efficacy Evaluable population.
[b] Investigator assessment.

Response assessment results using independent radiology review were consistent with investigator assessment.

5.2 Pharmacokinetic properties

Pharmacokinetics

The IV pharmacokinetics were characterised after patients were administered mirvetuximab soravtansine 0.16 mg/kg to 8.7 mg/kg AIBW dosages (i.e., 0.027 times to 1.4 times the approved recommended dosage 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 IV administration after the first cycle (3-weeks). 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 and the peak S-methyl-DM4 concentrations were observed approximately 3 days after administration. Steady state concentrations of mirvetuximab soravtansine, DM4, and S-methyl-DM4 were reached after one 3-week cycle. Accumulation of the mirvetuximab soravtansine, DM4, and S-methyl-DM4 was minimal following multiple cycles.

Table 9. Exposure parameters of mirvetuximab soravtansine, unconjugated DM4, and S-methyl DM4 after first cycle at a dosage of 6 mg/kg

	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

C_{max} = maximum concentration, AUC_{tau} = area under the concentration vs. time curve over the dosing interval (21 days).

Distribution

The mean (±SD) steady state volume of distribution of mirvetuximab soravtansine was 2.6 (±2.98) L.

Human plasma protein binding of DM4 and S-methyl DM4 was >99%, *in vitro*.

Metabolism

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 metabolized by CYP3A4 and eliminated via biliary excretion in the faeces.

Drug Interactions

In in vitro studies, 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. Unconjugated DM4 and S-methyl DM4 are substrates of P-glycoprotein (P-gp) but are not inhibitors of P-gp.

In four clinical studies, there were no differences in exposure between patients who received concomitant weak or moderate CYP3A4 inhibitors or P-glycoprotein P-gp inhibitors and those who did not.

Pharmacokinetics in Special Populations

Paediatric

The pharmacokinetics of Elahere in paediatric patients has not been established.

Geriatric

Pharmacokinetics of Elahere was not different in patients ≥ 65 years of age compared to younger patients.

Renal Impairment

No clinically significant differences in the pharmacokinetics of mirvetuximab soravtansine were observed based on mild to moderate renal impairment (CrCl ≥ 30 and < 90 mL/min). The pharmacokinetics of mirvetuximab soravtansine in patients with severe renal impairment (CrCl 15 to 30 mL/min) or end-stage renal disease is unknown.

Hepatic Impairment

No clinically significant differences in the pharmacokinetics of mirvetuximab soravtansine were observed based on mild hepatic impairment (total bilirubin ≤ ULN and any AST > ULN or total bilirubin > 1 to 1.5 times ULN and any AST). The pharmacokinetics of mirvetuximab soravtansine in patients with moderate to severe hepatic impairment (total bilirubin >1.5 ULN with any AST) is unknown.

Body Weight

No clinically significant differences in the pharmacokinetics of mirvetuximab soravtansine were observed based on body weight (36 to 136 kg).

Gender or Race

Mirvetuximab soravtansine is indicated for female patients with ovarian cancer, and thus sex was not assessed. No clinically significant differences in the pharmacokinetics of mirvetuximab soravtansine were observed based on race (Caucasian, Black, or Asian).

5.3 Preclinical safety data

Animal Pharmacology and/or Toxicology

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, and attenuation and degeneration/necrosis of the corneal epithelium. In rabbits, these findings were dose and schedule dependent with fewer overall findings and recovery of those findings observed in the 3-week dosing schedule (the clinical dosing schedule).

Mutagenicity

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.

Carcinogenicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glacial acetic acid
Polysorbate 20
Sodium acetate
Sucrose
Water for injections

6.2 Incompatibilities

Elahere is incompatible with sodium chloride 9 mg/mL (0.9% w/v) solution for infusion. This medicinal product must not be mixed with other medicinal products or intravenous fluids except those mentioned in Section 4.2 Dose and method of administration.

6.3 Shelf life

60 months.

Storage of diluted solution

If the diluted infusion solution is not used immediately, store the solution either at ambient temperature (18°C to 25°C) for no more than 8 hours (including infusion time), or under refrigeration at 2°C to 8°C for no more than 24 hours.

If refrigerated, allow the infusion bag to reach room temperature prior to administration.

After refrigeration, administer diluted infusion solution within 8 hours (including infusion time).

Do not freeze prepared infusion solution.

6.4 Special precautions for storage

Store Elahere vials upright in a refrigerator at 2°C to 8°C until the time of preparation in the original carton to protect from light. Do not freeze or shake.

For storage conditions after dilution of Elahere vial, refer to Section 6.3 Shelf Life.

6.5 Nature and contents of container

20 mL Type 1 glass vial with butyl rubber serum stopper and aluminium seal with a polypropylene flip-off plastic cap. The vial stopper is not made with natural rubber latex. Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

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 incompatible with 0.9% (w/v) sodium chloride.
- Elahere must not be mixed with any other drugs or intravenous fluids.
- Determine the volume of 5% glucose required to achieve the final diluted drug concentration. Either remove excess 5% glucose from a prefilled 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 drug 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 Shelf life. 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).

Disposal

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

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

AbbVie Limited
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Wellington, 6011
NEW ZEALAND
PH: 0800 900 030

9. DATE OF FIRST APPROVAL

2 October 2025