

FULL PRESCRIBING INFORMATION

NAME OF THE MEDICINAL PRODUCT

ELAHERE®

QUALITATIVE AND QUANTITATIVE COMPOSITION

Mirvetuximab Soravtansine 5mg/ml

PHARMACEUTICAL FORM

Concentrate for solution for infusion

WARNING: OCULAR TOXICITY

- ELAHERE can cause severe ocular toxicities, including visual impairment, keratopathy, dry eye, photophobia, eye pain, and uveitis [see Warnings and Precautions (5.1) and Adverse Reactions (6.1)].
- Conduct an ophthalmic exam including visual acuity and slit lamp exam prior to initiation of ELAHERE, every other cycle for the first 8 cycles, and as clinically indicated [see Dosage and Administration (2.3)].
- Administer prophylactic artificial tears and ophthalmic topical steroids [see Dosage and Administration (2.3) and Warnings and Precautions (5.1)].
- Withhold ELAHERE for ocular toxicities until improvement and resume at the same or reduced dose [see Dosage and Administration (2.4) and Warnings and Precautions (5.1)].
- Discontinue ELAHERE for Grade 4 ocular toxicities [see Dosage and Administration (2.4) and Warnings and Precautions (5.1)].

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for the treatment of platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer with ELAHERE based on the presence of FR α tumor expression.

2.2 Recommended Dosage

The recommended dosage 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 [see Dosage and Administration (2.5)]. Dosing based on AIBW reduces exposure variability for patients who are either under or overweight.

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

$$\text{AIBW} = \text{Ideal Body Weight (IBW [kg])} + 0.4 * (\text{Actual weight [kg]} - \text{IBW})$$

$$\text{Female IBW [kg]} = 0.9 * \text{height[cm]} - 92$$

2.3 Premedication and Required Eye Care

Premedication

Administer the premedications 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: Premedication Prior to Each ELAHERE Infusion

Premedication	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	acetaminophen 325 mg to 650 mg	
Antiemetic	oral or intravenous	5-HT ₃ serotonin receptor antagonist or appropriate alternatives	Before each dose and thereafter as needed

Consider additional premedications including corticosteroids the day prior to ELAHERE administration for patients who experienced IRRs.

Ophthalmic Exams and Premedication

Ophthalmic Exam: Conduct an ophthalmic exam including visual acuity and slit lamp exam prior to initiation of ELAHERE, every other cycle for the first 8 cycles, and as clinically indicated.

Ophthalmic Topical Steroids: The use of ophthalmic topical steroids is recommended. The initial prescription and renewals of any corticosteroid medication should be made only after examination with a slit lamp. Administer one drop of ophthalmic topical steroids in each eye 6 times daily starting the day prior to each infusion until day 4; then administer one drop in each eye 4 times daily for days 5-8 of each cycle of ELAHERE [see Warnings and Precautions (5.1)].

Lubricating Eye Drops: The use of lubricating eye drops at least four times daily and as needed is recommended during treatment with ELAHERE. Instruct patients to use lubricating eye drops and advise to wait at least 10 minutes after ophthalmic topical steroid administration before instilling lubricating eye drops [see Warnings and Precautions (5.1)].

2.4 Dosage Modifications

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

Table 2: Dosage Reduction Schedule

	ELAHERE Dose Levels
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: Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity of Adverse Reaction*	Dosage Modification
Keratitis/Keratopathy [see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]	Nonconfluent superficial keratitis	Monitor.
	Confluent superficial keratitis, a cornea epithelial defect, or 3-line or more loss in best corrected visual acuity	Withhold until improved or resolved, then maintain at same dose level or consider dose reduction.
	Corneal ulcer or stromal opacity or best corrected distance visual acuity 20/200 or worse	Withhold until improved or resolved, then reduce by one dose level.
	Corneal perforation	Permanently discontinue.
Uveitis [see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]	Grade 1/ Rare cell in anterior chamber	Monitor.
	Grade 2/ 1-2+ Cell or Flare in anterior chamber	Withhold until Grade 1 or less, then maintain dose at same dose level.
	Grade 3/ 3+ Cell or Flare in anterior chamber	Withhold until Grade 1 or less, then reduce dose by one dose level.
	Grade 4/ Hypopyon	Permanently discontinue.
Pneumonitis [see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]	Grade 1	Monitor.
	Grade 2	Withhold until Grade 1 or less, then maintain at same dose level or consider dose reduction.
	Grade 3 or 4	Permanently discontinue.
Peripheral Neuropathy [see Warnings and Precautions (5.3) and Adverse Reactions (6.1)]	Grade 2	Withhold until Grade 1 or less, then reduce by one dose level.
	Grade 3 or 4	Permanently discontinue.
Infusion-Related Reactions/Hypersensitivity [see Adverse Reactions (6.1)]	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 [see Dosage and Administration (2.5)]. - Administer additional premedication for future cycles [see Dosage and Administration (2.3)].

Adverse Reaction	Severity of Adverse Reaction*	Dosage Modification
	Grade 3 or 4	- Immediately stop infusion and administer supportive treatment. - Advise patient to seek emergency treatment and immediately notify their healthcare provider if the infusion-related symptoms recur. - Permanently discontinue.
Hematological [see Adverse Reactions (6.1)]	Grade 3 or 4	Withhold until Grade 1 or less, then resume at one lower dose level.
Other Adverse Reactions [see Adverse Reactions (6.1)]	Grade 3	Withhold 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.

2.5 Instructions for Preparation and Administration

Preparation

- ELAHERE is a hazardous drug. Follow applicable special handling and disposal procedures.
- 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 Recommended Dosage (2.2) and Dose Modifications (2.4)]. 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 drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. ELAHERE is a clear to slightly opalescent, colorless solution.
- 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. Discard any unused drug remaining in the vial.

Dilution

- ELAHERE must be diluted prior to administration with 5% Dextrose Injection to a final concentration of 1 mg/mL to 2 mg/mL.
- ELAHERE is incompatible with 0.9% Sodium Chloride Injection. ELAHERE must not be mixed with any other drugs or intravenous fluids.
- Determine the volume of 5% Dextrose Injection required to achieve the final diluted drug concentration. Either remove excess 5% Dextrose Injection from a prefilled intravenous bag or add the calculated volume of 5% Dextrose Injection 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 solution either at room temperature (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 solutions within 8 hours (including infusion time).
- Do not freeze prepared infusion solution.

Administration

- Inspect the ELAHERE intravenous infusion bag visually for particulate matter and discoloration prior to administration.
- Administer pre-medications prior to ELAHERE administration [see *Premedication and Prophylactic Regimen* (2.3)].
- 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.
- 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% Dextrose Injection to ensure delivery of the full dose. Do not use any other intravenous fluids for flushing.

3 DOSAGE FORMS AND STRENGTHS

Injection: 100 mg/20 mL (5 mg/mL) clear to slightly opalescent, colorless solution in a single-dose vial.

4 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 11

5 WARNINGS AND PRECAUTIONS

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

5.1 Ocular Disorders

ELAHERE can cause severe ocular adverse reactions, including visual impairment, keratopathy (corneal disorders), dry eye, photophobia, eye pain, and uveitis.

Ocular adverse reactions occurred in 59% of patients with ovarian cancer treated with ELAHERE. Eleven percent (11%) of patients experienced Grade 3 ocular adverse reactions, including blurred vision, keratopathy (corneal disorders), dry eye, cataract, photophobia, and eye pain; two patients (0.3%) experienced Grade 4 events (keratopathy and cataract). The most common ($\geq 5\%$) ocular adverse reactions were blurred vision (48%), keratopathy (36%), dry eye (27%), cataract (16%), photophobia (14%), and eye pain (10%). [see *Adverse Reactions* (6.1)].

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; 38% had partial improvement (defined as a

decrease in severity by one or more grades from the worst grade) at last follow up. Ocular adverse reactions led to permanent discontinuation of ELAHERE in 1% of patients.

Premedication and use of lubricating and ophthalmic topical steroid eye drops during treatment with ELAHERE are recommended [see *Dosage and Administration* (2.3)]. Advise patients to avoid use of contact lenses during treatment with ELAHERE unless directed by a healthcare provider.

Refer patients to an eye care professional for an ophthalmic exam including visual acuity and slit lamp exam prior to treatment initiation, every other cycle for the first 8 cycles, and as clinically indicated. Promptly refer patients to an eye care professional for any new or worsening ocular signs and symptoms.

Monitor for ocular toxicity and withhold, reduce, or permanently discontinue ELAHERE based on severity and persistence of ocular adverse reactions. [see *Dosage and Administration* (2.4)].

5.2 Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with ELAHERE.

Pneumonitis occurred in 10% of patients treated with ELAHERE, including 1% with Grade 3 events and 1 patient (0.1%) with a Grade 4 event. One patient (0.1%) died due to respiratory failure in the setting of pneumonitis and lung metastases. One patient (0.1%) died due to respiratory failure of unknown etiology.

Pneumonitis led to permanent discontinuation of ELAHERE in 3% of patients.

Monitor patients for pulmonary signs and symptoms of pneumonitis, which may include hypoxia, cough, dyspnea, 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 $\leq$ Grade 1 and consider dose reduction. Permanently discontinue ELAHERE in all patients with Grade 3 or 4 pneumonitis [see *Dosage and Administration* (2.4)]. Patients who are asymptomatic may continue dosing of ELAHERE with close monitoring.

5.3 Peripheral Neuropathy

Peripheral neuropathy occurred in 36% of patients with ovarian cancer treated with ELAHERE across clinical trials; 3% of patients experienced Grade 3 peripheral neuropathy. Peripheral neuropathy adverse reactions included peripheral neuropathy (20%), peripheral sensory neuropathy (9%), paraesthesia (6%), neurotoxicity (3%), hypoesthesia (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 led to discontinuation of ELAHERE in 0.7% of patients.

Monitor patients for signs and symptoms of neuropathy, such as paresthesia, 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 *Dosage and Administration* (2.4)].

5.4 Embryo-Fetal Toxicity

Based on its mechanism of action, ELAHERE can cause embryo-fetal harm when administered to a pregnant woman because it contains a genotoxic compound (DM4) and affects actively dividing cells.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ELAHERE and for 7 months after the last dose [see *Use in Specific Populations* (8.1, 8.3)].

5.5 Driving and using machines with Elahere.

Elahere may affect your ability to drive and use machines. If you experience blurred vision or nerve damage causing pain, numbness or weakness in your hands, arms or feet, do not drive, use tools, or operate machines until your symptoms are completely better.

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the labeling:

- Ocular Disorders [see *Warnings and Precautions* (5.1)].
- Pneumonitis [see *Warnings and Precautions* (5.2)].
- Peripheral Neuropathy [see *Warnings and Precautions* (5.3)].

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The pooled safety population described in Warnings and Precautions reflect 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 Study 0416, Study 0417, Study 0403 (NCT02631876), and Study 0401 (NCT01609556). The median duration of treatment was 4.4 months (range: 1.0 to 30.0). In the pooled safety population, the most common ($\geq 20\%$) adverse reactions, including laboratory abnormalities, were increased aspartate aminotransferase, fatigue, increased alanine aminotransferase, blurred vision, nausea, increased alkaline phosphatase, diarrhea, abdominal pain, keratopathy, peripheral neuropathy, musculoskeletal pain, decreased lymphocytes, decreased platelets, decreased magnesium, decreased hemoglobin, dry eye, constipation, decreased leukocytes, vomiting, decreased albumin, decreased appetite, and decreased neutrophils.

Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Study 0416

The safety of ELAHERE was evaluated in Study 0416, a multicenter, open-label, active-controlled, randomized, two-arm, study in patients (n=453) with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer [see *Clinical Studies* (12)]. 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 24% of patients treated with ELAHERE. The most common ($\geq 2\%$) serious adverse reactions were intestinal obstruction (5%), abdominal pain (3%), and pleural effusion (3%). Fatal adverse reactions occurred in 3% of patients, including intestinal obstruction, dyspnea in the setting of subileus, neutropenic sepsis, cardiopulmonary failure, respiratory failure, ischemic stroke, and pulmonary embolus.

Permanent discontinuation of ELAHERE due to adverse reactions occurred in 9% of patients. The most common ($\geq 1\%$) 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 54% of patients treated with ELAHERE. Adverse reactions which required dosage delays in $\geq 3\%$ of patients included blurred vision (22%), keratopathy (19%), dry eye (7%), neutropenia (6%), pneumonitis (6%), photophobia (5%), cataract (4%), and peripheral neuropathy (4%).

Dose reductions of ELAHERE due to an adverse reaction occurred in 34% of patients. Adverse reactions which required dose reductions in $\geq 3\%$ of patients included blurred vision (14%), keratopathy (10%), peripheral neuropathy (6%), and dry eye (5%).

Tables 4 and 5 summarize adverse reactions and laboratory abnormalities, respectively, occurring in $\geq 10\%$ of patients who received ELAHERE in Study 0416.

Table 4: Adverse Reactions Occurring in $\geq 10\%$ of Patients with Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer Who Received ELAHERE in Study 0416

Adverse Reaction	ELAHERE (n=218)		Chemotherapy [‡] (n=207)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal disorders				
Abdominal pain*	34	3	23	2
Diarrhea	29	1	17	0.5
Constipation	27	0	19	1
Nausea	27	2	29	2
Vomiting	18	3	18	1
Eye disorders				
Blurred vision [‡]	45	9	3	0
Keratopathy [†]	37	11	0	0
Dry eye [‡]	29	3	5	0
Photophobia	18	0.5	0.5	0
Cataract [^]	16	3	0.5	0
General disorders and administration site conditions				
Fatigue [‡]	47	3	41	7
Nervous system disorders				
Peripheral neuropathy [¶]	37	4	23	4
Headache	14	0	10	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	31	1	21	2
Metabolism and nutrition disorders				
Decreased appetite	18	1	14	1
Respiratory, thoracic, and mediastinal disorders				
Pneumonitis [±]	10	0.5	0.5	0

[‡] Chemotherapy: paclitaxel, pegylated liposomal doxorubicin (PLD), topotecan.

※ Blurred vision includes vision blurred, vitreous floaters, visual acuity reduced, diplopia, accommodation disorder, and visual impairment.

† Keratopathy includes corneal disorder, corneal epithelial microcysts, keratitis, keratopathy, corneal deposits, punctate keratitis, and corneal opacity.

‡ Dry eye includes dry eye and lacrimation increased.

^ Cataract includes cataract and cataract nuclear.

‡ Fatigue includes fatigue and asthenia.

* Abdominal pain includes abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal discomfort.

¶ Peripheral neuropathy includes neuropathy peripheral, peripheral sensory neuropathy, peripheral motor neuropathy, paresthesia, hypoesthesia, polyneuropathy, neurotoxicity, and peripheral sensorimotor neuropathy.

♦ Musculoskeletal pain includes back pain, myalgia, neck pain, arthralgia, musculoskeletal pain, non-cardiac chest pain, bone pain, pain in extremity, musculoskeletal stiffness, musculoskeletal chest pain, and musculoskeletal discomfort.

‡ Pneumonitis includes pneumonitis, interstitial lung disease, respiratory failure, and organizing pneumonia.

Clinically relevant adverse reactions occurring in <10% of patients who received ELAHERE in Study 0416 included infusion related reactions/hypersensitivity (8%).

Table 5: Select Laboratory Abnormalities ≥10% for All Grades, in Patients Who Received ELAHERE in Study 0416

Laboratory Abnormality	ELAHERE (n=218)		Chemotherapy (n=207)	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Liver Function Tests				
Increased aspartate aminotransferase	57	0	14	0
Increased alanine aminotransferase	38	1	15	1
Increased alkaline phosphatase	30	1	13	1
Chemistry				
Decreased albumin	21	1	27	2
Decreased magnesium	21	1	29	2
Decreased sodium	16	0	18	0
Decreased potassium	15	1	11	1
Increased calcium	12	0	5	0
Decreased bicarbonate	11	0	11	0
Increased creatinine	10	0	11	0
Hematology*				
Decreased lymphocytes	27	3	42	11
Decreased leukocytes	23	1	53	10
Decreased neutrophils	22	1	45	17
Decreased hemoglobin	18	1	63	8
Decreased platelets	17	1	20	5

* The denominator used to calculate the rate varied from 63 to 214 (ELAHERE); 63 to 194 (IC Chemo) based on the number of patients with a baseline value and at least one post-treatment value.

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 *Clinical Studies (12)*]. 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 31% of patients treated with ELAHERE. The most common ($\geq 2\%$) serious adverse reactions were intestinal obstruction (8%), ascites (4%), infection (3%), and pleural effusion (3%). Fatal adverse reactions occurred in 2% of patients, including small intestinal obstruction (1%) and pneumonitis (1%).

Permanent discontinuation of ELAHERE due to adverse reactions occurred in 11% of patients. The most common ($\geq 2\%$) adverse reactions leading to permanent discontinuation were intestinal obstruction (2%) and thrombocytopenia (2%). One patient (0.9%) permanently discontinued ELAHERE due to visual impairment (unilateral decrease to BCVA $\leq 20/200$ that resolved to baseline after discontinuation).

Dosage delays of ELAHERE due to an adverse reaction occurred in 39% of patients treated with ELAHERE. Adverse reactions which required dosage delays in $\geq 3\%$ of patients included blurred vision (15%), keratopathy (11%), neutropenia (6%), dry eye (5%), cataracts (3%), and increased gamma-glutamyltransferase (3%).

Dose reductions of ELAHERE due to an adverse reaction occurred in 20% of patients. Adverse reactions which required dose reductions in $\geq 3\%$ of patients included blurred vision (9%) and keratopathy (7%).

Table 6 summarizes the adverse reactions ($\geq 10\%$) in patients treated with ELAHERE in Study 0417.

Table 6: Adverse Reactions ($\geq 10\%$) in Patients with Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer Who Received ELAHERE in Study 0417

Adverse Reaction	All Grades N=106 (%)	Grade 3-4 N=106 (%)
Eye disorders		
Blurred Vision*	50	7
Keratopathy [†]	37	9
Dry eye [‡]	27	2
Cataract	18	3
Photophobia	17	0
Eye pain [§]	10	0
General disorders		
Fatigue	49	3
Gastrointestinal disorders		
Nausea	40	0
Abdominal pain*	36	7
Diarrhea	31	3
Constipation	30	1
Vomiting	19	0
Abdominal distension	11	0
Nervous system disorders		

Adverse Reaction	All Grades N=106 (%)	Grade 3-4 N=106 (%)
Peripheral neuropathy [¶]	33	2
Metabolism and nutrition disorders		
Decreased appetite	18	1
Musculoskeletal and connective tissue disorders		
Arthralgia	17	0
Myalgia	10	0
Respiratory, thoracic, and mediastinal disorders		
Dyspnea [^]	12	0

※ Blurred vision includes vision blurred, vitreous floaters, visual acuity reduced, diplopia, presbyopia, accommodation disorder, visual impairment, and refraction disorder.

† Keratopathy includes corneal disorder, corneal epithelial microcysts, corneal epithelial defect, keratitis, keratopathy, corneal deposits, and punctate keratitis.

‡ Dry eye includes dry eye and lacrimation increased.

§ Eye pain includes eye pain and ocular discomfort.

‡ Fatigue includes fatigue and asthenia.

* Abdominal pain includes abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal discomfort.

¶ Peripheral neuropathy includes neuropathy peripheral, peripheral sensory neuropathy, peripheral motor neuropathy, paresthesia, hypoesthesia, polyneuropathy, and neurotoxicity.

^ Dyspnea includes dyspnea and exertional dyspnea.

Clinically relevant adverse reactions occurring in <10% of patients who received ELAHERE in Study 0417 included infusion related reactions/hypersensitivity (9%), pneumonitis (8%), and uveitis (1%).

Table 7 summarizes the laboratory abnormalities in Study 0417.

Table 7: Select Laboratory Abnormalities ≥10% for All Grades, or ≥2% for Grades 3-4 in Patients Who Received ELAHERE

Laboratory Abnormality	ELAHERE*	
	All Grades (%)	Grade 3-4 (%)
Liver Function Tests		
Increased aspartate aminotransferase	50	2
Increased alanine aminotransferase	39	2
Increased alkaline phosphatase	30	1
Hematology*		
Decreased lymphocytes	35	7
Decreased leukocytes	26	1
Decreased neutrophils	26	3
Decreased hemoglobin	25	3
Decreased platelets	18	2
Chemistry		

Laboratory Abnormality	ELAHERE*	
	All Grades (%)	Grade 3-4 (%)
Decreased albumin	31	1
Decreased magnesium	27	2
Increased creatinine	16	0
Decreased potassium	15	4

* The denominator used to calculate the rate varied from 98 to 101 based on the number of patients with a baseline value and at least one post-treatment value.

Immunogenicity: Anti-Drug Antibody-Associated Adverse Reactions

In studies 0416, 0417, 0401, and 0403 in patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer who received ELAHERE at 6 mg/kg AIBW administered intravenously once every 3 weeks, 9% (57/626) developed anti-drug antibodies. Infusion reactions (including bronchospasm, erythema, eyelid erythema, flushing, hypersensitivity, periorbital edema, rash, allergic rhinitis, face edema) occurred in 26% (15/57) of patients with anti-drug antibodies and in 7% (41/569) who did not develop anti-drug antibodies [see *Clinical Pharmacology* (10.6)].

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form <https://sideeffects.health.gov.il/>

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on ELAHERE

Strong CYP3A4 Inhibitors

DM4 is a CYP3A4 substrate. Concomitant use of ELAHERE with strong CYP3A4 inhibitors may increase unconjugated DM4 exposure [see *Clinical Pharmacology* (10.3)], which may increase the risk of ELAHERE adverse reactions [see *Adverse Reactions* (6)]. Closely monitor patients for adverse reactions with ELAHERE when used concomitantly with strong CYP3A4 inhibitors [see *Warnings and Precautions* (5)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, ELAHERE can cause embryo-fetal harm when administered to a pregnant woman because it contains a genotoxic compound (DM4) and affects actively dividing cells [see *Clinical Pharmacology* (10.1), *Nonclinical Toxicology* (11.1)]. Human immunoglobulin G (IgG) is known to cross the placental barrier; therefore, ELAHERE has the potential to be transmitted from the mother to the developing fetus. There are no available human data on ELAHERE use in pregnant women to inform a drug-associated risk. No reproductive or developmental animal toxicity studies were conducted with mirvetuximab soravtansine. Advise patients of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data: No reproductive or developmental animal toxicity studies have been conducted with mirvetuximab soravtansine. The cytotoxic component of ELAHERE, DM4, disrupts microtubule function, is genotoxic, and can be toxic to actively dividing cells, suggesting it has the potential to cause embryotoxicity and teratogenicity.

8.2 Lactation

Risk Summary

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.

8.3 Females and Males of Reproductive Potential

ELAHERE can cause embryo-fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*].

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating ELAHERE.

Contraception

Females: Advise females of reproductive potential to use effective contraception during treatment with ELAHERE and for 7 months after the last dose.

8.4 Pediatric Use

Safety and effectiveness of ELAHERE have not been established in pediatric patients.

8.5 Geriatric Use

Of the 682 patients with epithelial ovarian cancer who were treated with ELAHERE across studies, 44% of patients were ≥ 65 years old. Grade ≥ 3 adverse reactions occurred in 51% of patients ≥ 65 years and in 45% < 65 years. No clinically meaningful differences in efficacy or safety were observed between patients ≥ 65 years of age compared to younger patients.

Age does not have a clinically meaningful effect on the pharmacokinetics of ELAHERE [*see Clinical Pharmacology (10.3)*].

8.6 Renal Impairment

No dosage adjustment of ELAHERE is recommended for patients with mild to moderate renal impairment (CL_{cr} 30 to 89 mL/min). The effect of severe renal impairment (CL_{cr} 15 to < 30 mL/min) or end-stage renal disease on ELAHERE is unknown [*see Clinical Pharmacology (10.3)*].

8.7 Hepatic Impairment

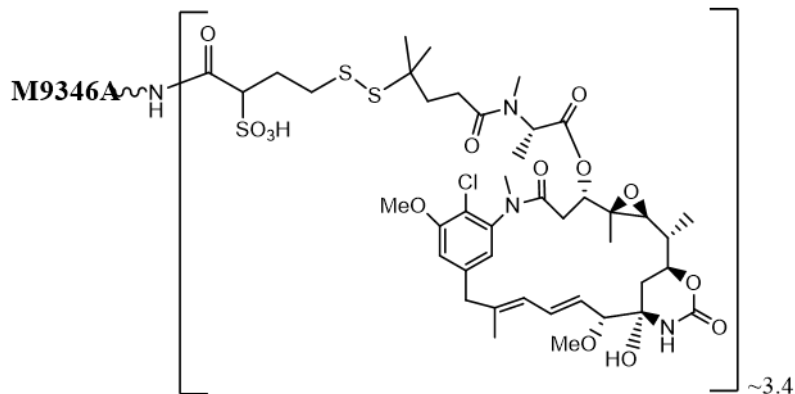
Avoid use of ELAHERE in patients with moderate or severe hepatic impairment (total bilirubin > 1.5 ULN).

No dosage adjustment of ELAHERE is recommended for patients with mild hepatic impairment (total bilirubin $\leq$ ULN and AST $>$ ULN or total bilirubin > 1 to 1.5 times ULN and any AST) [*see Clinical Pharmacology (10.3)*].

9 DESCRIPTION

Mirvetuximab soravtansine is a folate receptor alpha (FR α)-directed antibody-drug conjugate (ADC) consisting of three components: 1) an anti-FR α monoclonal antibody of IgG1 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-yl)disulfanyl)butane-2-sulfonic acid) that covalently attaches DM4 to the mirvetuximab antibody. Mirvetuximab soravtansine has an approximate molecular weight of 150 kDa. An average of 3.4 molecules of DM4 are attached to each antibody molecule. 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.

Mirvetuximab soravtansine has the following structure:



ELAHERE (mirvetuximab soravtansine) injection is supplied as a sterile, preservative-free, clear to slightly opalescent, colorless solution containing 100 mg/20 mL of mirvetuximab soravtansine in single-dose vials. Each mL of solution contains 5 mg of mirvetuximab soravtansine, and sucrose (90 mg), sodium acetate (0.53 mg), glacial acetic acid (0.22 mg), polysorbate 20 (0.1 mg), and Water for Injection. The pH is approximately 5.0.

The ELAHERE vial stoppers are not made with natural rubber latex.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Mirvetuximab soravtansine is an antibody-drug conjugate (ADC). The antibody is a chimeric IgG1 directed against folate receptor alpha (FR α). The small molecule, DM4, is a microtubule inhibitor attached to the antibody via a cleavable linker. Upon binding to FR α , 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.

10.2 Pharmacodynamics

Exposure-Response Relationships

Higher exposure to mirvetuximab soravtansine was associated with higher overall response rates and longer median PFS and 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, ELAHERE did not cause large mean increases (>10 msec) in the QTc interval.

10.3 Pharmacokinetics

The pharmacokinetics were characterized in patients who received mirvetuximab soravtansine 0.16 mg/kg to 8.7 mg/kg adjusted ideal body weight (AIBW) (0.03 times to 1.4 times the approved recommended dose of 6 mg/kg AIBW), unless otherwise noted.

Table 8 summarizes the exposure parameters of mirvetuximab soravtansine, unconjugated DM4, and its metabolite S-methyl-DM4 following 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 8: 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	4.1 (±2.3) ng/mL	7.0 (±6.8) ng/mL
AUC _{tau}	20.6 (±6.8) 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 (±2.9) L.

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

Elimination

For mirvetuximab soravtansine, total plasma clearance (mean [CV%]) of was 19 mL/hour (52%) and the mean terminal phase half-life after the first dose was 4.8 days leading to a steady state at approximately 24 days.

For the unconjugated DM4, the total plasma clearance (mean [CV%]) was 14 L/hour (31%) and the mean terminal phase half-life was 2.8 days.

For S-methyl-DM4, the total plasma clearance (mean [CV%]) was 4.3 L/hour (64%) and the mean terminal phase half-life was 5 days.

Metabolism

The monoclonal antibody portion of mirvetuximab soravtansine is expected to be metabolized 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.

Excretion

S-methyl DM4 and DM4-sulfo-SPDB-lysine were detected in urine within 24 hours of infusion as the main metabolites.

Specific 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 $\leq$ 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 to 89 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

Clinical Studies and Model Informed Approaches

No clinical studies to evaluate the drug-drug interaction potential of mirvetuximab soravtansine were conducted.

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.

In Vitro Studies

Cytochrome P450 (CYP) Enzymes: Unconjugated DM4 is a time-dependent inhibitor of CYP3A4. Unconjugated DM4 and S-methyl DM4 are not 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.

10.6 Immunogenicity

The observed incidence of anti-drug antibodies (ADA), including neutralizing antibody, is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADAs in the studies described below with the incidence of ADAs to mirvetuximab soravtansine in other studies.

With a median treatment duration of 4.4 months in Studies 0416, 0417, 0401, and 0403, in patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer who received mirvetuximab soravtansine at 6 mg/kg AIBW intravenously every 3 weeks, 9% (57/626) of patients developed anti-mirvetuximab soravtansine antibodies. Neutralizing antibodies were detected in 47% (27/57) of patients who were ADA-positive.

No clinically meaningful difference was observed in the trough concentrations of mirvetuximab soravtansine between ADA-positive and ADA-negative patients. Anti-mirvetuximab soravtansine antibody formation was associated with a higher incidence of infusion-related reactions [see *Adverse Reactions (6.1)*]. The effect of anti-drug antibodies on effectiveness has not been fully characterized. Based on limited data, the presence of anti-mirvetuximab soravtansine antibodies may be associated with decreased efficacy in ADA-positive patients when compared to ADA-negative patients.

11 NONCLINICAL TOXICOLOGY

11.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

DM4 and the metabolite, S-methyl DM4, were clastogenic in the in vivo rat bone marrow micronucleus study. DM4 and S-methyl DM4 were not mutagenic in the bacterial reverse mutation (Ames) assay.

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

12 CLINICAL STUDIES

Study 0416

The efficacy of ELAHERE was evaluated in Study 0416 (MIRASOL, NCT04209855), a multicenter, open-label, active-controlled, randomized, two-arm, trial in patients (n=453) with FRα positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer. Patients were permitted to receive up to three prior lines of systemic therapy. The trial enrolled patients whose tumors were positive for FRα expression as determined by the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay. Patients were excluded if they had corneal disorders, ocular conditions requiring ongoing treatment, Grade >1 peripheral neuropathy, or noninfectious interstitial lung disease.

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. Tumor response assessments occurred every 6 weeks for the first 36 weeks and every 12 weeks thereafter. Randomization 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 randomization.

The major efficacy outcome measures were investigator-assessed progression-free survival (PFS), confirmed overall response rate (ORR), and overall survival (OS). PFS and ORR were evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.

The median age was 63 years (range: 29 to 88); 66% were White, 12% were Asian, 3% were Black or African American, and 18% did not have race reported. Six percent of patients were Hispanic or Latino. Nearly all patients had an ECOG PS of 0 (55%) or 1 (44%). Fourteen percent of patients had received 1 prior line of systemic therapy, 39% of patients had received 2 prior lines of systemic therapy, and 47% of patients had received 3 prior lines of systemic therapy. Thirty-seven percent of patients received prior systemic therapy for platinum-resistant disease. Sixty-two percent of patients received prior bevacizumab and 55% had received a prior PARP inhibitor.

ELAHERE 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 summarized in Table 9 and [Figures 1 and 2](#).

Table 9: Efficacy Results in Study 0416

	ELAHERE n=227	Chemotherapy* n=226
Progression-free survival (PFS)		
Number (%) of patients with 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 ^a	<0.0001	
Overall Survival (OS)		
Number (%) of patients with 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 ^a	0.0046	
Confirmed overall response rate (ORR)		
Number of patients with measurable disease at baseline	225	224

	ELAHERE n=227	Chemotherapy* n=226
ORR (95% CI)	42% (36, 49)	16% (12, 22)
Complete response	5%	0%
Partial response	37%	16%
p-value ^b	<0.0001	

* Chemotherapy: paclitaxel, PLD, or topotecan.
^a Two-sided p-value based on stratified log-rank test.
^b Two-sided p-value based upon Cochran-Mantel-Haenszel (CMH) test.

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

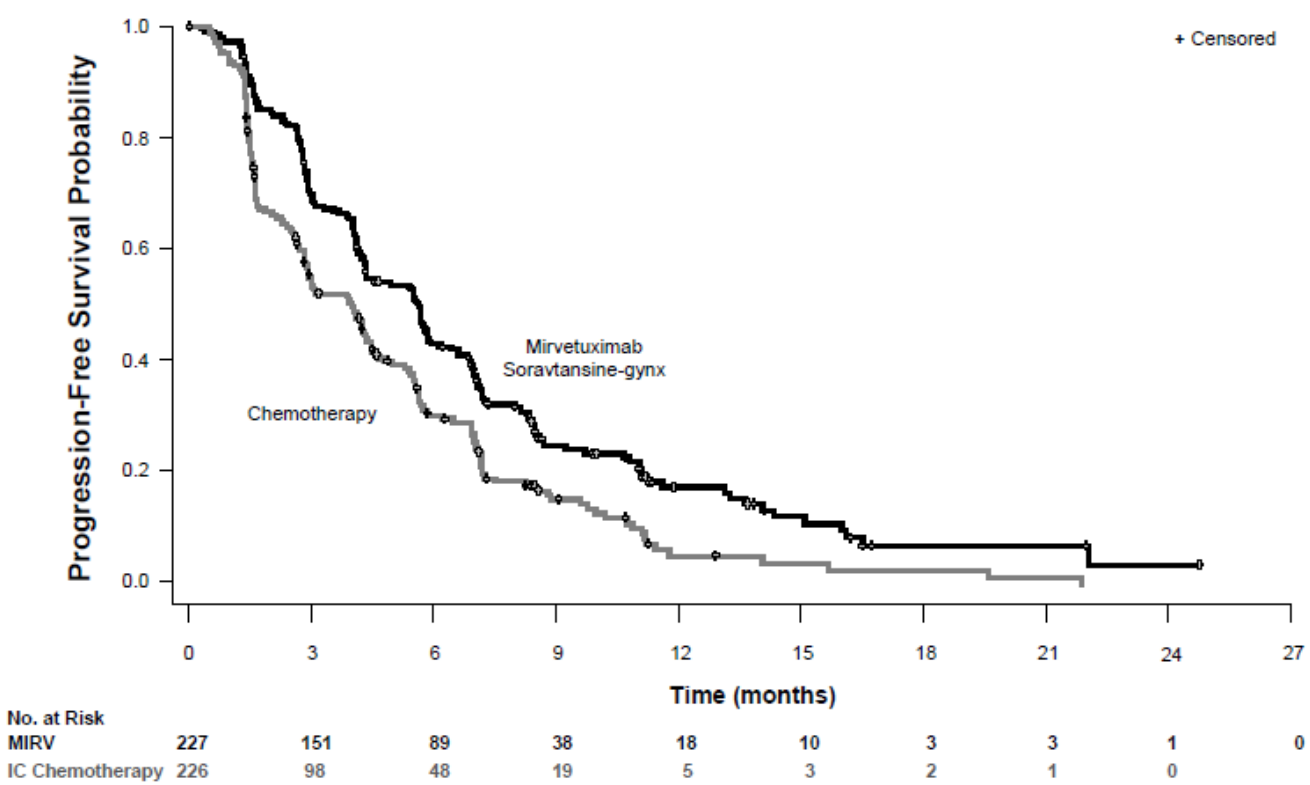
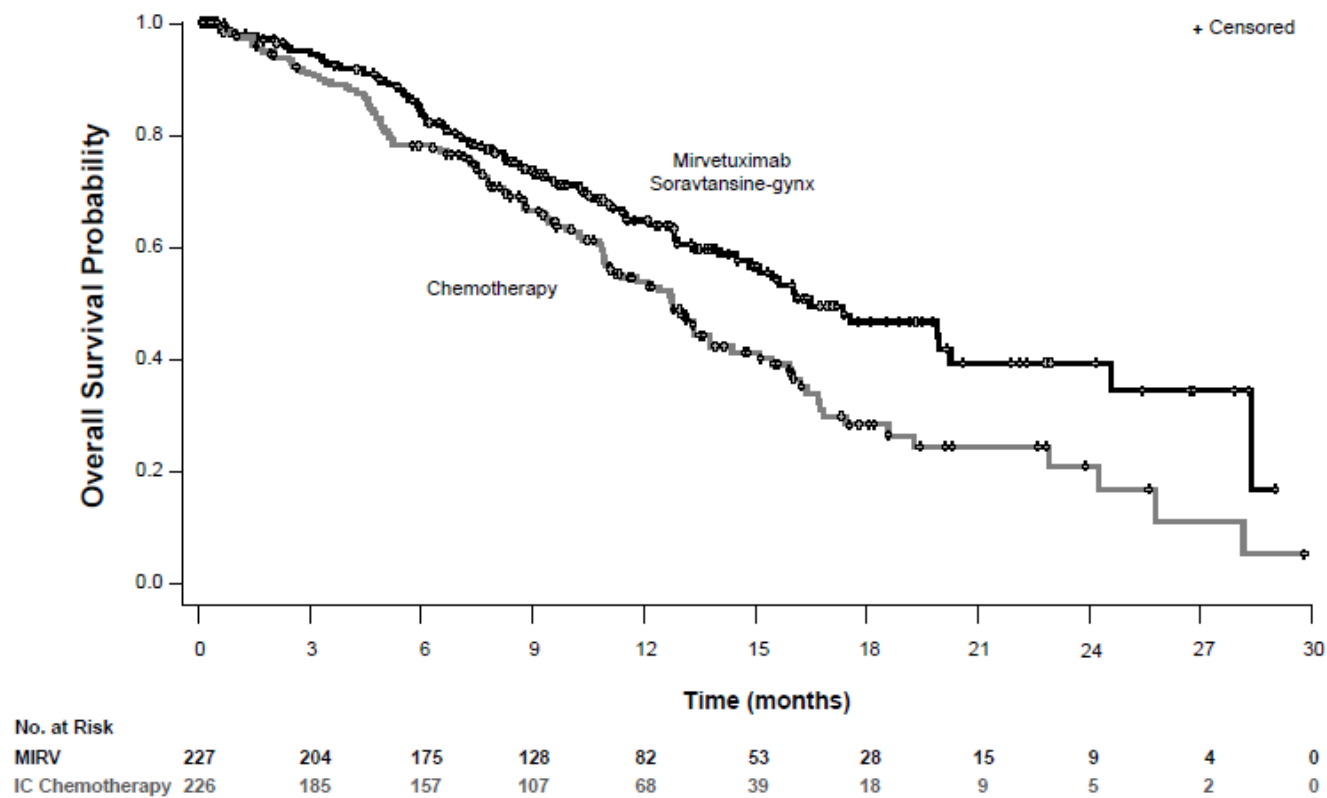


Figure 2: Kaplan-Meier Curve for Overall Survival in Study 0416



Study 0417

The efficacy of ELAHERE was evaluated in Study 0417 (SORAYA, NCT04296890), a single-arm trial of patients with FR α positive, platinum-resistant 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 tumors were positive for FR α expression as determined by the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay. Patients were excluded if they had corneal disorders, ocular conditions requiring ongoing treatment, Grade >1 peripheral neuropathy, or noninfectious interstitial lung disease.

Patients received ELAHERE 6 mg/kg (based on adjusted ideal body weight) as an intravenous infusion every 3 weeks until disease progression or unacceptable toxicity. Tumor response assessments occurred every 6 weeks for the first 36 weeks and every 12 weeks thereafter.

The major efficacy outcome measures were investigator-assessed overall response rate (ORR) and duration of response (DOR) evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.

The efficacy evaluable population included 104 patients with platinum-resistant disease, who had measurable disease, and received at least one dose of ELAHERE. In these 104 patients, the median age was 62 years (range: 35 to 85); 96% were White, 2% were Asian, and 2% did not have race reported. Two percent of patients were Hispanic or Latino. All patients had an ECOG PS of 0 (57%) or 1 (43%). Ten percent of patients had received 1 prior line of systemic therapy, 39% of patients had received 2 prior lines of systemic therapy, and 50% of patients had received 3 prior lines of systemic therapy. All patients had received prior bevacizumab and 47% had received a prior PARP inhibitor.

Efficacy results for Study 0417 are summarized in Table 10.

Table 10: Efficacy Results in Study 0417

	ELAHERE (N=104)
Confirmed Overall Response Rate ^a (95% CI)	32% (23, 42)
Complete response rate	5%
Partial response rate	27%
Duration of Response	N=33
Median duration of response, months (95% CI)	6.9 (5.6, 9.7)

^a Investigator assessment.

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

13 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Each ELAHERE (mirvetuximab soravtansine) injection carton contains:

- One single-dose vial containing 100 mg of mirvetuximab soravtansine in 20 mL (5 mg/mL) of clear to slightly opalescent, colorless sterile solution.

Storage and Handling

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.

ELAHERE is a hazardous drug. Follow applicable special handling and disposal procedures¹.

The expiry date of the product is indicated on the packaging materials

14 MANUFACTURER

ABBVIE Inc.,
1 North Waukegan Road, North Chicago, IL 60064, USA

15 REGISTRATION HOLDER

Neopharm (Israel) 1996 Ltd.
6 Hashiloach Street, POB 7063, Petah Tikva, 4917001

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