10 October 2024
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Elahere (mirvetuximab soravtansine)
Treatment of ovarian cancer
EU/3/15/1458

Sponsor: Abbvie Deutschland GmbH & Co. KG

Note

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

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1. Product and administrative information

Product	
Designated active substance	Humanised anti-folate receptor 1 monoclonal antibody conjugated to maytansinoid DM4
Other name	--
International Non-Proprietary Name	Mirvetuximab soravtansine
Tradename	Elahere
Orphan condition	Treatment of ovarian cancer
Sponsor's details:	Abbvie Deutschland GmbH & Co. KG Knollstrasse 67061 Ludwigshafen Am Rhein Germany
Orphan medicinal product designation procedural history	
Sponsor/applicant	ImmunoGen Europe Limited
COMP opinion	12 February 2015
EC decision	19 March 2015
EC registration number	EU/3/15/1458
Post-designation procedural history	
Transfer of sponsorship	Transfer from ImmunoGen Europe Limited to ImmunoGen BioPharma (Ireland) Limited – EC decision of 8 May 2019
Transfer of sponsorship	Transfer from ImmunoGen BioPharma (Ireland) Limited to Abbvie Deutschland GmbH & Co. KG – EC decision of 6 May 2024
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Johanna Lähteenvuo / Alexandre Moreau
Applicant	Abbvie Deutschland GmbH & Co. KG
Application submission	29 September 2023
Procedure start	26 October 2023
Procedure number	EMA/H/C/005036
Invented name	Elahere
Therapeutic indication	Elahere as monotherapy is indicated for the treatment of adult patients with folate receptor-alpha (FRα) positive, platinum-resistant high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received one to three prior systemic treatment regimens. Further information on Elahere can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/elahere
CHMP opinion	19 September 2024
COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	Brigitte Schwarzer-Daum / Jana Mazelova
Sponsor's report submission	13 May 2024

COMP discussion and adoption of list of questions	10-12 September 2024
Oral explanation cancellation	8 October 2024
COMP opinion	10 October 2024

2. Grounds for the COMP opinion

2.1. Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2015 was based on the following grounds:

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing humanized anti-folate receptor 1 monoclonal antibody conjugated to maytansinoid DM4 was considered justified based on studies performed on valid preclinical models and preliminary clinical data showing antitumour activity;
- the condition is chronically debilitating in particular due to pain, weight loss, ascites and vaginal bleeding, and life-threatening with approximately half of the patients surviving less than five years;
- the condition was estimated to be affecting not more than 3 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing humanised anti-folate receptor 1 monoclonal antibody conjugated to maytansinoid DM4 may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate improved effects in reduction of tumour burden when used in combination with existing treatments as well as preliminary clinical data in patients who have relapsed or are refractory to authorised treatments. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing humanised anti-folate receptor 1 monoclonal antibody conjugated to maytansinoid DM4 as an orphan medicinal product for the orphan indication: treatment of ovarian cancer.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Ovarian cancer is a varied group of neoplasms characterised as a malignant transformation of tissue on the surface of the ovaries. The majority of cases of ovarian cancer are of epithelial origin (approximately 90%) with the remainder coming from germ cells or sex cord stromal cells.

The exact cause of ovarian cancer remains unknown but many associated risk factors have been identified. A woman's reproductive history appears to contribute significantly to her lifetime risk of ovarian cancer. Family history also plays a very important role in the development of ovarian cancer.

The clinical presentation of epithelial ovarian carcinoma, fallopian tubal carcinoma, and peritoneal carcinoma may be either acute or subacute. Women who present in an acute fashion are typically those with advanced disease who present with a condition that requires urgent care and evaluation (e.g. pleural effusion, bowel obstruction). Most patients with early-stage disease are asymptomatic, and in general the symptoms of ovarian cancer are nonspecific and often mimic the presence of upper abdominal disease, making diagnosis of early ovarian cancer difficult. Typically, only patients with more advanced disease present with definitive symptoms such as abdominal distension, effusions (pleural or peritoneal) and the development of respiratory symptoms. Thus, ovarian cancer is rarely diagnosed in its early stages (stages I/II), often going undetected until it has spread beyond the ovary (stages III/IV).

The proposed condition has been designated previously and it is accepted.

The approved therapeutic indication ‘’ELAHERE as monotherapy is indicated for the treatment of adult patients with folate receptor-alpha (FRα) positive, platinum-resistant high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received one to three prior systemic treatment regimens (see section 4.2)” falls within the scope of the designated orphan condition “Treatment of ovarian cancer”.

Intention to diagnose, prevent or treat

The medical plausibility is confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

Ovarian cancer remains a chronically debilitating and life-threatening disease.

The sponsor discussed the life-threatening nature of the disease with more than 70% of patients with advanced ovarian cancer relapsing within 5 years and eventually die because their cancer becomes resistant to available platinum and taxane (Heintz et al., 2006; Markman et al., 2004).

The COMP considered that these references are quite old however about a third of patients do not respond to primary platinum-based chemotherapy treatment, and over time, eventually, 80% of other

patients develop chemoresistance, which makes the recurrence of disease incurable (Lukanović et al., 2022). In Europe, ovarian cancer led to >26,000 deaths, or 4.63 in 100,000, in 2017 (Dalmartello et al, 2022). In the Nordic countries, ovarian cancer shows >80% 1-year and 50% 5-year survival (NORDCAN, 2019).

The sponsor also discussed the chronically debilitating nature of the disease with platinum resistant ovarian patients developing progressive disease and becoming increasingly symptomatic with abdominal pain due to malignant ascites, increasing tumour mass leading to bowel obstruction, inability to tolerate medication or take food, and declining performance status precluding further anticancer therapy.

The sponsor did not identify any significant changes in the seriousness of ovarian cancer since the orphan designation was granted in 2015. The COMP has previously accepted that the clinical course of ovarian cancer can be chronically debilitating due to pain, weight loss, ascites and vaginal bleeding, and life-threatening with reduced life expectancy. The severe nature of ovarian cancer earlier acknowledged by the COMP remains acceptable for this procedure.

Number of people affected or at risk

At the time of Orphan designation in 2015, the prevalence was agreed to be not more than 3 in 10,000 by the COMP.

According to the sponsor the prevalence has been changed and they propose a new prevalence estimate of 4.6 in 10,000 persons.

The sponsor claimed that since most of the databases/registries provide incidence and period prevalence data, the prevalence was estimated based on incidence and duration of disease based on the formula: Prevalence (P) = Incidence (I) x Duration (D).

Incidence

The incidence data of ovarian cancer for 2022 used are presented in Table 1.

Table 1. Estimates of ovarian cancer incidence in Europe for 2022

Country	Number of cases	Crude rate per 100,000 (female population)	ASR (Europe) per 100,000 (female population)
Austria	745	16.4	14.9
Belgium	830	14.1	13.4
Bulgaria	676	19.2	16.7
Croatia	476	23.8	20.3
Cyprus	93	20.1	22.0
Czechia	920	17.3	15.6
Denmark	441	14.9	14.0
Estonia	135	19.3	17.0
Finland	457	16.3	14.1
France	5,696	16.3	14.5
Germany	7,547	17.9	14.6
Greece	983	18.4	15.7
Hungary	1,012	20.1	18.0
Ireland	444	17.4	20.1

Country	Number of cases	Crude rate per 100,000 (female population)	ASR (Europe) per 100,000 (female population)
Italy	6,021	19.9	16.3
Latvia	298	29.6	25.7
Lithuania	366	24.4	21.1
Luxembourg	46	14.4	16.1
Malta	44	17.5	17.0
Netherlands	1,461	16.5	15.5
Poland	4,678	24.1	22.5
Portugal	682	12.6	10.4
Romania	1,788	18.2	16.8
Slovakia	502	18.1	17.6
Slovenia	195	18.6	15.9
Spain	3,455	14.3	13.0
Sweden	723	13.9	13.8
EU-27 + IS + NO*	41,219		

Abbreviations: ASR (Europe) = age-standardised rate (standardised for European 2013 standard population); IS = Iceland; NO = Norway.
*No data available for Liechtenstein.
Source: ECIS, 2023

In total, 41,219 new cases of ovarian cancer were extrapolated by ECIS for the European Economic Area (EEA) (27 EU Member States plus Iceland and Norway) for 2022. No data was available for Liechtenstein.

As of 01 January 2022, the total population of 27 EU Member States plus Iceland and Norway was 452,536,809 (Eurostat, 2023). 41,219 newly diagnosed cases in this population correspond to a crude ovarian cancer incidence rate (for both sexes) of 9.1 per 100,000 inhabitants.

For the incidence of fallopian tube and primary peritoneal cancer a nationwide population-based study was conducted using data from the Swedish cancer registry on 46,350 women aged 18 or older with a diagnosis of epithelial ovarian, fallopian tube, peritoneal, or undesignated abdominal/pelvic cancer 1960 to 2014 (Leandersson et al., 2021). 6,948 (15%) cases of undesignated abdominal/pelvic cancer were reported, resulting in 39,402 cases diagnosed with either epithelial ovarian, fallopian tube, or peritoneal cancer. Based on this study a percentage of 4.7% of patients with fallopian tube cancer or peritoneal cancer reported for the period between 1960 and 2014. For the time period between 2010 and 2014, 17% of patients were diagnosed either with fallopian tube cancer or peritoneal cancer.

The Munich cancer registry, covering a region with 4.8 million inhabitants in Southern Germany, reported 5,399 cases of ovarian cancer, 327 cases of fallopian tube cancer and 416 cases of peritoneal cancer for the period between 1998 and 2014 (Rottmann et al., 2017). From the total patients analysed (6,142 patients), 87.9% were diagnosed with ovarian cancer and 12.1% were diagnosed with fallopian tube cancer or peritoneal cancer.

Both publications are considered the most relevant and recent ones by the sponsor, thus, they propose to use the mean of 14.6% as derived from the period between 2010 and 2014 from the Swedish study and from the German study to correct the crude incidence rate of the orphan condition "ovarian cancer". Crude incidence estimate for fallopian tube and primary peritoneal cancer: 9.1/100,000 x 0.146 = 1.3/100,000.

Disease duration

For the disease duration, the sponsor used three databases which provide long-term data on survival rates in yearly increments: up to 10 years for Germany and Ireland, and up to 9 years for The Netherlands. The methodology applied below considers the average lifetime of the patients after diagnosis, and requires only a few assumptions, which are explained in the footnotes of the calculation tables (Table 2, Table 3, and Table 4).

Table 2. Estimated disease duration based on German survival data for the period 2017 – 2018

Years after diagnosis	**Average Disease Duration (D) until death or cure [years]**	**Absolute survival [%]**	**Death rate (delta to previous year) [% all cases] (for > 10 years: cure rate)**	**Contribution to overall average disease duration** = Death rate x D/ 100 [years]
1	0.50	73	27	0.135
2	1.50	61	12	0.180
3	2.50	51	10	0.250
4	3.50	44	7	0.245
5	4.50	39	5	0.225
6	5.50	35	4	0.220
7	6.50	32	3	0.195
8	7.50	30	2	0.150
9	8.50	28	2	0.170
10	9.50	27	1	0.095
10+[1]	10.00	27	27	2.700
Average disease duration [years]				4.565

[1] The estimate for group "10+"considers that the majority of these patients, in particular patients diagnosed and treated at an early stage (NIH, 2023) are permanently cured within the first 10 years after diagnosis. It also considers the median age of 69 years at time of diagnosis of patients (Robert Koch Institut, 2022).
Source: German Centre for Cancer Registry Data, 2022.

Table 3. Estimated disease duration based on Dutch survival data for the period 2011 – 2019

Years after diagnosis	**Average Disease Duration (D) until death or cure [years]**	**Survival (%)**	**Death rate (delta to previous year) [% all cases] (for > 10 years: cure rate)**	**Contribution to overall average disease duration** = Death rate x D/ 100 [years]
1	0.50	74	26.00	0.130
2	1.50	60	14.00	0.210
3	2.50	50	10.00	0.250
4	3.50	43	7.00	0.245
5	4.50	38	5.00	0.225
6	5.50	35	3.00	0.165
7	6.50	33	2.00	0.130

Years after diagnosis	**Average Disease Duration (D) until death or cure [years]**	**Survival (%)**	**Death rate (delta to previous year) [% all cases] (for > 10 years: cure rate)**	**Contribution to overall average disease duration** = Death rate x D/ 100 [years]
8	7.50	31	2.00	0.150
9	8.50	30	1.00	0.085
10	9.50	29[1]	1.00	0.095
10+[2]	10.00	29	29.00	2.900
Average disease duration **[years]**				4.585

[1] Absolute survival is estimated by the applicant.
[2] The estimate for group "10+" considers that the majority of these patients, in particular patients diagnosed and treated at an early stage (NIH, 2023) are permanently cured within the first 10 years after diagnosis. It also considers the median age of 69 years at time of diagnosis of patients (Robert Koch Institut, 2022).
Source: IKNL, 2023

Table 4. Estimated disease duration based on Irish survival data for the period 2010 – 2014

Years after diagnosis	**Average Disease Duration (D) until death or cure [years]**	**Net survival (%)**	**Death rate** (delta to previous year) [% all cases] (for > 10 years: cure rate)	**Contribution to overall average disease duration** = Death rate x D/ 100 [years]
0.25	0.13	84.5	15.50	0.019
0.5	0.25	78.7	5.80	0.015
0.75	0.38	75.0	3.70	0.014
1	0.50	71.3	3.70	0.019
2	1.50	56.3	15.00	0.225
3	2.50	47.3	9.00	0.225
4	3.50	41.6	5.70	0.200
5	4.50	37.5	4.10	0.185
6	5.50	35.5	2.00	0.110
7	6.50	34.2	1.30	0.084
8	7.50	33.5	0.70	0.053
9	8.50	32.9	0.60	0.051
10	9.50	32.4	0.50	0.048
10+[1]	10.00	32.4	32.40	3.240
Average disease duration [years]				**4.438**

[1] The estimate for group "10+" considers that the majority of these patients, in particular patients diagnosed and treated at an early stage (NIH, 2023) are permanently cured within the first 10 years after diagnosis. It also considers the median age of 69 years at time of diagnosis of patients (Robert Koch Institut, 2022).
Source: National Cancer Registry Ireland, 2023.

Based on the above calculations, average disease duration for Germany and The Netherlands is 4.6 years. For Ireland, average disease duration is 4.4 years. Relative survival rates in The Netherlands and Germany were above the European average and thus, are considered representative for a conservative estimation of Europe-wide disease duration. Accordingly, a disease duration for ovarian cancer patients of 4.6 years was assumed.

Prevalence

A summary of the point prevalence calculation is presented in Table 5.

Table 5. Calculation of point prevalence for the orphan condition ovarian cancer

Incidence per 10,000 in the EEA	**Duration (years)**	**Prevalence per 10,000 inhabitants**
1.0	4.6	4.6

Based on these data, a current ovarian cancer point prevalence of 4.6 per 10,000 persons.

The COMP discussed the prevalence and considered the NORDCAN database. According to the 2022 data, the 10-year prevalence for ovarian cancer only is 4.2 in 10,000 persons. The COMP concluded that NORDCAN could be used even if the incidence might be lower in other countries, but as the duration of the disease is longer, this would make the prevalence similar. However, since this prevalence covers only the ovarian and not the other subtypes (fallopian tube and primary peritoneal cancer) and it is representative for Nordic countries only the COMP concluded that the prevalence for all the EU countries is above 4.2 in 10,000 persons and agreed on a figure of 4.6 in 10,000 persons.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

The sponsor presented the medicinal products which are authorised for ovarian cancer in Table 6 below. The sponsor argued that only the medicinal products which are authorised for the treatment of platinum-resistant ovarian cancer should be considered satisfactory methods.

Table 6. Medicinal products centrally authorised in the European Union for the treatment of ovarian cancer[a]

Product name **Active substance**	**Authorised indication**	**Satisfactory method**
Apealea Paclitaxel	The indication for the centralised authorised medicinal product is: In combination with carboplatin for the treatment of adult patients with first relapse of platinum-sensitive epithelial ovarian cancer, primary peritoneal cancer and fallopian tube cancer. However, paclitaxel has been nationally authorized in several European countries for the treatment of ovarian cancer after failure of standard platinum-containing therapy.	Yes; Elahere is indicated for the platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer. In several European countries, paclitaxel is authorised for the treatment of ovarian cancer after failure of standard platinum-containing therapy therefore it is considered as satisfactory method
Avastin Bevacizumab	In combination with carboplatin and paclitaxel is indicated for the front-line treatment of adult patients with advanced (International Federation of Gynaecology and Obstetrics (FIGO) stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer. In combination with carboplatin and gemcitabine or in combination with carboplatin and paclitaxel, is indicated for treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other vascular endothelial growth factor (VEGF) inhibitors or VEGF receptor–targeted agents. In combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin (PLD) is indicated for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents	No; Avastin is authorised for the first line and first recurrence of platinum-sensitive ovarian cancer and for up to the third line of platinum-resistant ovarian cancer. Elahere is indicated for up to the fourth line of platinum-resistant ovariar cancer therefore the indication of Elahere is broader.

Caelyx pegylated liposomal Doxorubicin	Treatment of advanced ovarian cancer in women who have failed a first-line platinum-based chemotherapy regimen	Yes; There is an overlap with Elahere's indication which covers platinum-resistant ovariar cancer after one to three prior systemic treatment regimens
Hycamtin Topotecan	As monotherapy for the treatment of patients with metastatic carcinoma of the ovary after failure of first-line or subsequent therapy.	Yes There is an overlap with Elahere's indication which covers platinum-resistant ovariar cancer after one to three prior systemic treatment regimens
Lynparza Olaparib	As monotherapy for the: maintenance treatment of adult patients with advanced (FIGO stages III and IV) BRCA1/2-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy. maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy. In combination with bevacizumab for the: maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with HRD positive status defined by either a BRCA1/2 mutation and/or genomic instability.	No; Lynparza is for the BRCA1/2-mutated high-grade epithelial ovarian cancer and for the maintenance treatment of ovarian cancer.
Phelinun Melphalan	High-dose of PHELINUN used alone or in combination with other cytotoxic medicinal products and/or total body irradiation is indicated in the treatment of ovarian cancer.	Yes; There is an overlap with Elahere's indication which covers platinum-resistant ovariar cancer after one to three prior systemic treatment regimens

Rubraca Rucaparib	As monotherapy for the maintenance treatment of adult patients with advanced (FIGO Stages III and IV) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy. As monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy	No; Rubraca is for the maintenance treatment of advanced and platinum-sensitive ovarian cancer
Yondelis Trabectedin	In combination with PLD for the treatment of patients with relapsed platinum-sensitive ovarian cancer.	No; Elahere is indicated for the platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer
Zejula Niraparib	As monotherapy for the maintenance treatment of adult patients with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy. As monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.	No; Zejula is for the maintenance treatment of advanced and platinum-sensitive ovarian cancer

Abbreviations: HRD = homologous recombination deficiency; IV = intravenous(ly); MAH = marketing authorisation holder.
[a] As of 25 March 2024. Drug products are listed in alphabetical order according to product name. Generics are not listed.

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 (see section 4.2)".

Based on the table above, the medicinal products which are considered as satisfactory methods are pegylated liposomal doxorubicin, topotecan, paclitaxel and melphalan.

Significant benefit

The sponsor did not request protocol assistance (PA) for the justification of significant benefit.

- *Significant benefit of mirvetuximab soravtansine as compared to* pegylated liposomal doxorubicin, topotecan and paclitaxel

The sponsor claimed significant benefit of mirvetuximab soravtansine verus pegylated liposomal doxorubicin, topotecan and paclitaxel based on improved efficacy and safety. In the pivotal randomised Study 0416, a statistically significant improvement in PFS and ORR, combined with a differentiated and manageable AE profile, resulted in a robust, statistically significant, and clinically meaningful improvement in OS for mirvetuximab soravtansine compared with standard of care chemotherapy.

The argument of improved efficacy was based on the results of the study IMGN853-0416, a multicentre, 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 FOLR1 (FOLR1-2.1). Platinum-resistant disease was defined as EOC that recurred within 6 months of the last dose of platinum.

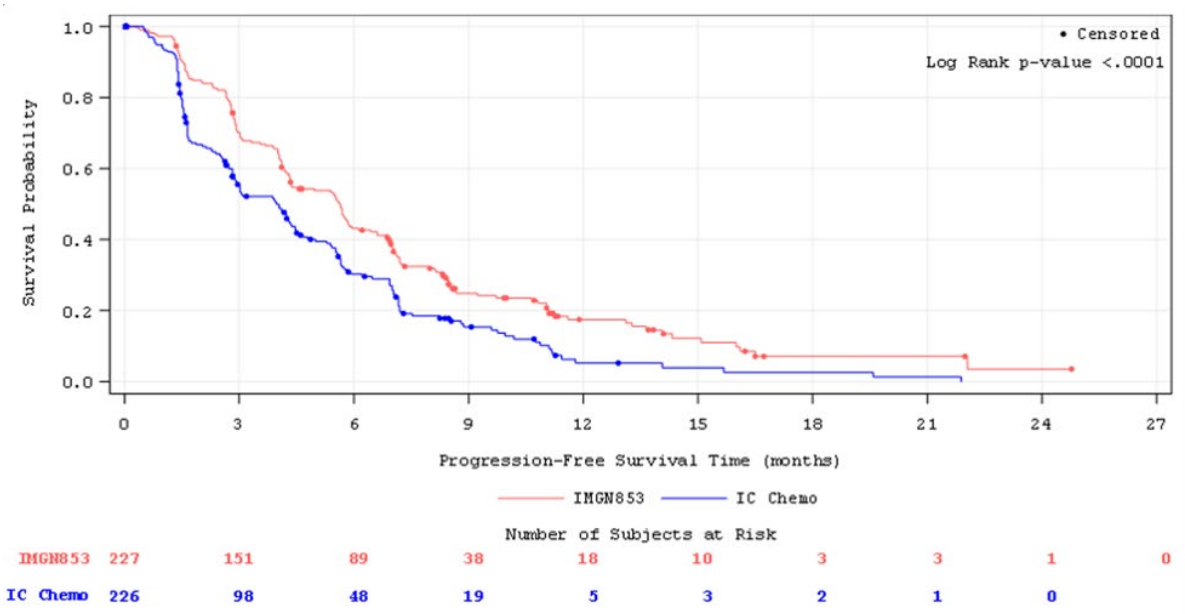
Patients were randomised 1:1 to receive either ELAHERE 6 mg/kg AIBW IV (N=227) at Day 1 of each 3-week cycle or one of the following chemotherapies (N=226) as decided by the investigator prior to randomisation:

- Paclitaxel (Pac) 80 mg/m^2 administered QW;
- Pegylated liposomal doxorubicin (PLD) 40 mg/m^2 administered Q4W;
- Topotecan (Topo) 4 mg/m^2 administered on Days 1, 8, and 15 every 4 weeks or for 5 consecutive days at 1.25 mg/m^2 from Days 1 5 Q3W

The primary efficacy outcome measure was progression free survival (PFS) based on investigator assessment using RECIST 1.1 criteria. Objective response rate (ORR), Overall Survival (OS), and patient-reported outcome (PRO) assessment of European organisation for research and treatment of cancer (EORTC) QLQ-OV28 were key secondary efficacy outcome measures.

Study 0416 met its primary endpoint, with a statistically significant improvement in PFS with mirvetuximab soravtansine compared with IC chemotherapy (median PFS: 5.62 vs 3.98 months; HR 0.65, p-value < 0.0001) (Figure 1). The PFS benefit shown for mirvetuximab soravtansine over investigator's choice (IC) chemotherapy was maintained beyond first progression (PFS2 analysis) with an HR of 0.63 (95% CI: 0.497, 0.803) and a nominal p-value of 0.0001.

Figure 1. Kaplan-Meier plot for investigator-assessed progression-free survival ITT population



Abbreviations: IC Chemo = investigator's choice of chemotherapy; IMGN853 = mirvetuximab soravtansine; ITT = intention-to-treat.
Note: PFS is defined as the time from the date of first dose of mirvetuximab soravtansine until the date of PD or death from any cause, whichever occurred first.

Mirvetuximab soravtansine showed a higher ORR compared with IC chemotherapy (42.3% vs 15.9%; odds ratio 3.81, p-value < 0.0001), including 12 patients with mirvetuximab soravtansine with CRs versus none with IC chemotherapy. In addition, OS was longer with mirvetuximab soravtansine versus IC chemotherapy in Study 0416 (median OS: 16.46 vs 12.75 months; HR 0.67, p-value 0.0046), representing a more than 3.5-month improvement in OS.

With a median follow-up of 9.92 months (95% CI: 8.87, 14.85), the median investigator-assessed duration of response (DOR) was 6.77 months (95% CI: 5.62, 8.31) for patients randomised to mirvetuximab soravtansine versus 4.47 months (95% CI: 4.17, 5.82) for patients randomised to IC chemotherapy (nominal p value 0.0330).

In subgroup analyses, improvements in PFS and OS in patients treated with mirvetuximab soravtansine compared with IC chemotherapy were consistent across patient subgroups irrespective of age, prior bevacizumab exposure, prior PARP inhibitor exposure, number of prior lines, and type of IC chemotherapy.

Finally, nominal p-values less than 0.05 were obtained in most of the PRO analyses, demonstrating a favourable effect of mirvetuximab soravtansine versus IC chemotherapy and a consistent trend demonstrating an improved patient Quality of life (QoL) based on the PRO instruments.

Regarding the argument of improved safety, the sponsor claimed that in the pivotal study 0416, for patients randomised to the mirvetuximab soravtansine group, there were fewer ≥ grade 2 treatment-emergent adverse event (TEAEs) and fewer discontinuations. While myelosuppression is an important safety issue with IC chemotherapy, mirvetuximab soravtansine was associated with less myelosuppression compared with IC chemotherapy, with lower rates of neutropenia (11% vs 29% all grades; < 1% vs 17% ≥ grade 3), thrombocytopenia (7% vs 16% all grades; < 1% vs 6% ≥ grade 3) and anaemia (10% vs 34% all grades; < 1% vs 10% ≥ grade 3). The majority of gastrointestinal adverse event (AE) were of grade 1 or grade 2 severity in both treatment groups. 4% of patients experienced a ≥ grade 3 TEAE considered related to study treatment in both treatment groups.

The sponsor also claimed that the ocular AE profile of mirvetuximab soravtansine has been well characterised through an extensive development programme. Ocular events as observed with other antibody-drug conjugate (ADCs) containing tubulin-directed payloads, were of low grade and reversible. Unlike other ADCs, the keratopathy associated with single-agent mirvetuximab soravtansine has no inflammatory component, no corneal ulcers or perforation have been reported, and ophthalmic examinations confirmed resolution of objective ocular findings. As expected, a greater proportion of patients treated with mirvetuximab soravtansine than IC chemotherapy reported ocular TEAEs, which included vision blurred (41% vs 2%), keratopathy (32% vs 0%), dry eye (28% vs 2%), photophobia (18% vs < 1%), cataract (15% vs < 1%), and visual acuity reduced (12% vs 0%).

COMP discussion

Regarding the argument on improved efficacy, the COMP agreed that the median PFS was improved compared to IC which included pegylated liposomal doxorubicin, topotecan and paclitaxel. A statistically significant PFS difference in the pivotal 0416 study of 1.6 months (5.62 vs. 3.98 months), and an OS benefit of 3.7 months (16.46 vs. 12.75 months) can justify the significant benefit. However, the applicant presented only pooled data from the comparator arm. Since randomisation was stratified by number of prior lines of therapy (1 vs 2 vs 3) and by Investigator's choice of chemotherapy (IC Chemo) (Paclitaxel vs pegylated liposomal doxorubicin vs topotecan) the applicant should present the subgroup analyses of the efficacy results based on the Investigator's choice treatment (pegylated liposomal doxorubicin, topotecan and paclitaxel) and by the prior lines of treatments, separately.

Regarding the argument of improved safety, the COMP concluded that because of the quantitative and qualitative differences on the safety profile, the claim of a better safety profile of mirvetuximab soravtansine in comparison to pegylated liposomal doxorubicin (Caelyx) and topotecan (Hycamptin). cannot be concluded on at present stage.

- *Significant benefit of mirvetuximab soravtansine* versus melphalan

The sponsor claimed significant benefit of mirvetuximab soravtansine versus melphalan based on improved efficacy.

A retrospective observational study included patients with recurrent epithelial ovarian cancer (EOC) treated with melphalan between February 2007 to July 2020. Eligibility criteria included having a histological confirmation of EOC, previous treatment with carboplatin plus paclitaxel regimens, and disease recurrence during treatment with or within 6 months of the end of the platinum-based chemotherapy (Conteduca et al., 2021). A total of 75 platinum-resistant EOC patients were enrolled. Median age was 69 years (range 41-82). Median of previous therapies before melphalan was 4 (range 1-7). Median PFS and OS were 3.6 months (range 2.9-4.7) and 9.5 months (range 8.0-14.1), respectively. Median PFS was 2.6 months (1.9-4.4) for patients with wildtype breast cancer susceptibility gene (BRCA) gene, and 6.2 months (3.7-nr) for BRCA-deficient patients. Median OS was 8.0 months (4.0-12.0) for patients with wildtype BRCA gene, and 25.9 months (3.7-nr) for BRCA-deficient patients. This study must be interpreted with caution given its retrospective nature.

In the prospective randomised controlled study 0416 in patients treated with mirvetuximab soravtansine, median PFS was 5.62 months and median OS was 16.46 months irrespective of BRCA status, demonstrating a favourable outcome as compared to a median PFS of 3.6 months in patients treated with melphalan.

COMP discussion

The COMP argued that is it very challenging to conclude on the data presented since for melphalan the data are based on a retrospective study. The sponsor should elaborate more on the better efficacy of

mirvetuximab soravtansin versus melphalan considering the issues regarding the limited prospective data for melphalan. The sponsor should provide supplementary information regarding the relative efficacy of mirvetuximab soravtansin versus melphalan based on comparison between patients treated with mirvetuximab soravtansin in Study 0416 versus patients treated with melphalan in the retrospective observational study using different methods of comparisons. The baseline characteristics of the patients' populations should be considered.

In the written responses, the sponsor presented their responses to the COMP's list of questions regarding the relative efficacy of mirvetuximab soravtansin (Elahere) versus melphalan (Phelinun) between patients treated with mirvetuximab soravtansin in Study 0416 versus patients treated with melphalan in the retrospective observational study using different methods of comparisons and the subgroup analyses of the efficacy results based on the investigator's choice treatment (pegylated liposomal doxorubicin, topotecan and paclitaxel).

Comments on sponsor's response to the COMP list of issues

1. Regarding the relative efficacy of mirvetuximab soravtansin (Elahere) versus melphalan (Phelinun) the sponsor argued that the Conteduca study that reports efficacy outcomes for patients with platinum-resistant ovarian cancer (PROC) is the most relevant population that can be used to compare the efficacy outcome of the pivotal Study 0416.

   The sponsor argued that while melphalan is approved in Europe for the treatment of ovarian cancer, information regarding the efficacy of melphalan among patients with ovarian cancer is limited and with conflicting results (Davis-Perry 2003, Hasan 2003). Additionally, melphalan is not a recommended therapy per ESMO and NCCN guidelines, and consequently is not used by prescribers. Recognizing the limitation of a retrospective cross-trial comparison, the MAIC methodology takes into account baseline characteristics and offers the most appropriate method for the comparison as requested by the COMP. The retrospective, observational study of melphalan-treated patients as presented in the Conteduca study represents the largest sample with group-level data (Conteduca 2021). The study included 75 patients with a histological confirmation of EOC, previous treatment with carboplatin plus paclitaxel regimens (median number of prior treatments was 4), and disease recurrence during treatment with or within 6 months of the end of the platinum-based chemotherapy. For the entire study population, the reported median PFS and OS were 3.6 months (95% CI: 2.9 to 4.7) and 9.5 months (95% CI: 8.0 to 14.1), respectively. A total of 1 patient reported a CR and 6 patients with PR, resulting in an ORR of 9.3%.

   Given that a Kaplan-Meier curve for the overall population was not presented in the Conteduca study, a matching-adjusted indirect comparisons (MAIC) analysis was chosen to estimate median PFS and median OS by reweighting the subject level data from Study 0416 to match the baseline characteristics in the Conteduca study. Adjusted and unadjusted ORR for subjects from Study 0416 and the corresponding odds ratios compared to the subjects in the Conteduca study are also provided. The matching baseline variables presented are those that were considered most readily matchable given the available data in the Conteduca study and the design and data collection methods used in Study 0416. The matched variables also reflect clinical consensus regarding their potential prognostic value (Colombo 2019, Perez-Fidalgo 2024).

   A summary of baseline characteristics included in the MAIC with unadjusted and adjusted values is presented in Table 7. Of note, the number of prior lines of therapy is grouped into 2 or less versus more than 2 given that subjects from Study 0416 had received 1 to 3 lines of prior therapy. Subjects with unknown pre-treatment hemoglobin, pre-treatment NLR, or pre-treatment PLR were

grouped with subjects with high levels of that variable respectively, thereby enabling matching of subjects with low level of the variable. According to the sponsor, the summary of baseline characteristics from Study 0416 using adjusted values are the same as the values reported in the Conteduca study, indicating a good fit of data for the MAIC model.

Table 8 presents a comparison of the results using the MAIC method for the endpoints of median PFS, median OS, and ORR in matching subjects from Study 0416 and the reported results from the Conteduca study.

Table 7. Comparison of Matched Baseline Characteristics (Conteduca Study Population and Matched MIRV Subjects from Study 0416)

Variable (unit) **Category**	**Melphalan-Treated Patients[a,b]** **(N=75)**	**MIRV Matched Subjects** **(N=227)**	
		Unadjusted	**Adjusted**
Age (years)			
Mean[c]	69	63.3	69
Number of previous therapies (%)			
≤ 2 lines	20	52.4	20
> 2 lines	80	47.6	80
Grade (%)[d]			
G1/2	8	6.6	8
G3	73.3	37.9	73.3
G4 or unknown	18.7	55.5	18.7
BRCA status (%) [e]			
Mutated	14.7	12.8	14.7
Negative/Unknown	85.3	87.2	85.3
Pre-treatment haemoglobin (g/dL) (%)			
> 12.5	30.7	26.9	30.7
≤ 12.5 or unknown	69.3	73.1	69.3
Pre-treatment NLR (%)			
≥ 3	54.7	47.1	54.7
< 3 or unknown	45.3	52.9	45.3
Pre-treatment PLR (%)			
≥ 210	54.7	41	54.7
< 210 or unknown	45.3	59	45.3

Abbreviations: NLR = neutrophil-to-lymphocyte ratio; PRL = platelet-to-lymphocyte ratio
From Conteduca et al.
Percentages reported in Conteduca et al are calculated based on non-missing observations. Percentages listed in this table were recalculated based on the overall population in Conteduca study.
Only median age with corresponding range were reported in Conteduca et al. As mean is needed for the MAIC model, mean age was assumed to equal median age for the modeling.
Subjects with unknown data were grouped with those with Grade 4, as there were no Grade 4 subjects in the Conteduca study, and 2 Grade 4 subjects in Study 0416.
Positive BRCA status and negative/unknown BRCA status were collected in Study 0416. Therefore, the wild-type and not available/unknown categories in the Conteduca study were combined for the matching.

Table 8. Comparison of Endpoints Between Melphalan-Treated Subjects as Reported in the Conteduca Study and Matched MIRV-Treated Subjects from Study 0416

Parameter	Melphalan Treated [a] (N=75)	MIRV Matched Subjects (N=227)	
		Unadjusted	Adjusted
Median PFS in months (95% CI)	3.6 (2.9, 4.7)	5.62 (4.34, 5.95)	5.0 (3.02, 7.00)
Median OS in months (95% CI)	9.5 (8.0, 14.1)	16.46 (14.46, 24.57)	16.1 (11.4, 20.2)
ORR[b] (%) Odds ratio (95% CI)	9.3	42.3 7.12 (3.13, 16.19)	36.9 5.70 (1.99, 14.73)

As reported in Conteduca et al
Total number of patients who reported CR or PR

COMP discussion

The applicant has performed a matched analysis comparing Elahere vs melphalan. The matching considered baseline characteristics such as age, disease grade, BRCA status, number of previous therapies (≤2, >2), pretreatment hemoglobin (>12-5, ≤12.5 or unknown), neutrophil-to-lymphocyte ratio (NRL) (≥3, <3 or unknown), and platelet-to-lymphocyte (PLR) (≥210, <210 or unknown). Other relevant variables such as histology, ECOG PS, Baseline CA-125, primary debulking surgery, FIGO stage, were not included in the matching due to various limitations which is acceptable. The results of the comparison showed evidence of clear benefit of Elahere over melphalan. Differences in the unmatched variables suggest subjects in the Conteduca study had worse health status compared to those in study 0416 (e.g. 10.7% of subjects had non-serous histology vs none in Study 0416, and 10.7% of subjects had ECOG status of 2 vs none in Study 0416).

The COMP concluded that considering the limitations regarding the data available on the efficacy of melphalan among patients with ovarian cancer, the significant benefit of mirvetuximab soravtansin (Elahere) versus melphalan (Phelinun) is considered uncertain. However, this uncertainty is due to lack of relevant efficacy data supporting the use of melphalan, which, moreover, does not represent a state-of-the art approach to ovarian cancer treatment. Given that superior efficacy of Elahere is shown versus currently used and registered standard-of-care therapies, COMP does not regard the uncertainty of the comparison versus melphalan as decisive. In conclusion, the significant benefit of mirvetuximab soravtansin (Elahere) versus melphalan (Phelinun) is agreed.

2. The subgroup analyses of the efficacy results based on the Investigator's choice treatment: pegylated liposomal doxorubicin, topotecan and paclitaxel separately taking into account the treatment lines.

   The sponsor provided the efficacy results of the subgroup analyses that compares MIRV to each individual non-platinum single agent in patients who have received 1 to 3 prior lines of therapy.

   Comparison of MIRV vs non-platinum single agents in patients who received 1 to 3 prior lines of therapy

   Study 0416 was not designed to formally test MIRV against each individual IC chemotherapy; results of the requested analyses are presented in 9 for MIRV compared with paclitaxel, table 10 for pegylated liposomal doxorubicin and Table 11 for topotecan. According to the sponsor, efficacy

results (OS, PFS and ORR) align with results from the ITT analysis set, in which MIRV provided an efficacy advantage compared with all IC chemotherapies combined. Forest plot presentation of the results by IC therapy supports the comparison.

Table 9. PFS, OS, and ORR Among Patients Randomized to MIRV or Paclitaxel (Intent-to-Treat Population)

Parameter	**MIRV**	**Paclitaxel**
Total N[a]	93	92
Median PFS in months (95% CI)	5.55 (4.04, 6.87)	5.29 (4.04, 5.62)
PFS Hazard Ratio (95% CI)	0.78 (0.556, 1.082)	
Median OS in months (95% CI)	16.07 (12.12, 19.94)	13.01 (11.37, 16.69)
OS Hazard Ratio (95% CI)	0.85 (0.545, 1.315)	
ORR (%) [95% CI]	36 (38.7) [28.8, 49.4]	28 (30.4) [21.3, 40.9]
ORR Difference (95% CI)	0.08 (-0.054, 0.219)	

Abbreviations: CI = confidence interval; ORR = overall response rate; OS = overall survival; PFS = progression-free survival
a. Data for total population is from the MAA dossier submitted to the EMA

Table 10. PFS, OS, and ORR Among Patients Randomized to MIRV or Pegylated liposomal doxorubicin (Intent-to-Treat Population)

Parameter	**MIRV**	**Pegylated liposomal doxorubicin**
Total N[a]	82	81
Median PFS in months (95% CI)	6.44 (4.37, 8.11)	2.53 (1.61, 4.53)
PFS Hazard Ratio (95% CI)	0.53 (0.368, 0.769)	
Median OS in months (95% CI)	24.57 (12.75, ----)	13.31 (10.05, 16.36)
OS Hazard Ratio (95% CI)	0.60 (0.372, 0.960)	
ORR (%) [95% CI]	42 (51.2) [39.9, 62.4]	5 (6.2) [2.0, 13.8]
ORR Difference (95% CI)	0.45 (0.330, 0.571)	

Abbreviations: CI = confidence interval; ORR = overall response rate; OS = overall survival; PFS = progression-free survival
a. Data for total population is from the MAA dossier submitted to the EMA
Source tables available upon request

Table 11. PFS, OS, and ORR Among Patients Randomized to MIRV or Topotecan (Intent-to-Treat Population)

Parameter	**MIRV**	**Topotecan**
Total N[a]	52	53
Median PFS in months (95% CI)	4.24 (3.02, 5.85)	2.96 (1.64, 4.24)
PFS Hazard Ratio (95% CI)	0.67 (0.434, 1.044)	
Median OS in months (95% CI)	17.51 (11.43, ----)	8.74 (5.22, 15.90)
OS Hazard Ratio (95% CI)	0.50 (0.289, 0.874)	
ORR (%) [95% CI]	18 (34.6) [22.0, 49.1]	3 (5.7) [1.2, 15.7]
ORR Difference (95% CI)	0.29 (0.146, 0.433)	

Abbreviations: CI = confidence interval; ORR = overall response rate; OS = overall survival; PFS = progression-free survival
a. Data for total population is from the MAA dossier submitted to the EMA

Comparison of MIRV vs non-platinum single agents incorporating number of prior therapy lines

Additional analyses comparing MIRV vs each IC chemotherapy analysed by the number of prior therapy lines are provided based on the request from the COMP (Table 12, Table 13, Table 14). As noted previously, Study 0416 was not powered to evaluate the efficacy of MIRV against each individual chemotherapy agent, and analysis by lines of therapy further divides the total ITT analysis set (n=435), into 9 smaller subgroup analysis sets. In these smaller subgroups in which sample size ranges from n = 4 to n = 47, the point estimates show a positive trend in favour of MIRV; confidence intervals around these point estimates are wide, due to the sample size limitation. In this regard, results should be interpreted with caution. Overall, efficacy outcomes (OS, PFS and ORR) align with results from the ITT analysis set, in which MIRV provided an advantage over individual non-platinum single agents.

Table 12. PFS, OS, and ORR Among Patients Who Received MIRV or Paclitaxel by Number of Prior Therapy Lines (Intent-to-Treat Population)

Group **Parameter**	**MIRV**	**Paclitaxel**
Subjects with 1 prior line of therapy		
Total N	4	4
Median PFS in months (95% CI)	1.61 (1.31, ----)	2.86 (1.51, ----)
PFS Hazard Ratio (95% CI)	1.52 (0.245, 9.372)	
Median OS in months (95% CI)	11.33 (6.64, ----)	8.77 (2.46, ----)
OS Hazard Ratio (95% CI)	0.39 (0.036, 4.388)	
ORR (%) [95% CI]	0 (0) [0.0, 60.2]	1 (25.0) [0.6, 80.6]
ORR Difference (95% CI)	-25.0 (-67.4, 17.4)	
Subjects with 2 prior lines of therapy		
Total N	42	42
Median PFS in months (95% CI)	5.49 (4.01, 6.87)	5.42 (2.89, 6.21)
PFS Hazard Ratio (95% CI)	0.78 (0.475, 1.268)	
Median OS in months (95% CI)	15.11 (12.12, ----)	16.69 (11.07, 24.25)
OS Hazard Ratio (95% CI)	0.98 (0.491, 1.937)	
ORR (%) [95% CI]	17 (40.5) [25.6, 56.7]	12 (28.6) [15.7, 44.6]
ORR Difference (95% CI)	11.9 (-8.3, 32.1)	
Subjects with 3 prior lines of therapy		
Total N	47	46
Median PFS in months (95% CI)	5.82 (2.92, 8.15)	4.47 (3.98, 5.68)
PFS Hazard Ratio (95% CI)	0.71 (0.440, 1.142)	
Median OS in months (95% CI)	17.35 (9.07, ----)	13.01 (10.28, 15.44)
OS Hazard Ratio (95% CI)	0.81 (0.438, 1.514)	
ORR (%) [95% CI]	19 (40.4) [26.4, 55.7]	15 (32.6) [19.5, 48.0]
ORR Difference (95% CI)	7.8 (-11.7, 27.3)	

Abbreviations: CI = confidence interval; ORR = overall response rate; OS = overall survival; PFS = progression-free survival

Table 13. PFS, OS, and ORR Among Patients Who Received MIRV or Pegylated liposomal doxorubicin by Number of Prior Therapy **Lines (Intent-to-Treat Population)**

Group **Parameter**	**MIRV**	**Pegylated liposomal doxorubicin**
Subjects with 1 prior line of therapy		
Total N	25	25
Median PFS in months (95% CI)	7.06 (5.75, 11.04)	3.09 (1.45, 7.16)
PFS Hazard Ratio (95% CI)	0.38 (0.194, 0.753)	
Median OS in months (95% CI)	24.57 (10.28, ----)	13.31 (8.21, ----)
OS Hazard Ratio (95% CI)	0.54 (0.229, 1.259)	
ORR (%) [95% CI]	13 (52.0) [31.3, 72.2]	2 (8.0) [1.0, 26.0]
ORR Difference (95% CI)	44.0 (21.7, 66.3)	
Subjects with 2 prior lines of therapy		
Total N	32	32
Median PFS in months (95% CI)	5.78 (4.04, 8.51)	2.15 (1.61, 7.16)
PFS Hazard Ratio (95% CI)	0.70 (0.381, 1.273)	
Median OS in months (95% CI)	16.46 (9.66, ----)	16.00 (10.78, ----)
OS Hazard Ratio (95% CI)	0.93 (0.407, 2.133)	
ORR (%) [95% CI]	18 (56.3) [37.7, 73.6]	2 (6.3) [0.8, 20.8]
ORR Difference (95% CI)	50.0 (30.9, 69.1)	
Subjects with 3 prior lines of therapy		
Total N	25	24
Median PFS in months (95% CI)	4.11 (2.79, ----)	1.64 (1.41, 2.83)
PFS Hazard Ratio (95% CI)	0.50 (0.247, 1.005)	
Median OS in months (95% CI)	14.03 (8.71, ----)	7.79 (4.57, 16.20)
OS Hazard Ratio (95% CI)	0.44 (0.193, 1.015)	
ORR (%) [95% CI]	11 (44.0) [24.4, 65.1]	1 (4.2) [0.1, 21.1]
ORR Difference (95% CI)	39.8 (18.8, 60.9)	

Abbreviations: CI = confidence interval; ORR = overall response rate; OS = overall survival; PFS = progression-free survival

Table 14. PFS, OS, and ORR Among Patients Who Received MIRV or Topotecan by Number of Prior Therapy Lines (Intent-to-Treat Population)

Group **Parameter**	**MIRV**	**Topotecan**
Subjects with 1 prior line of therapy		
Total N	2	3
Median PFS in months (95% CI)	--	5.75 (1.51, ----)
PFS Hazard Ratio (95% CI)	0.00	
Median OS in months (95% CI)	--	-- (3.09, ----)
OS Hazard Ratio (95% CI)	0.00	
ORR (%) [95% CI]	2 (100.0) [15.8, 100.0]	0 [0.0, 70.8]
ORR Difference (95% CI)	100.0 (100.0, 100.0)	
Subjects with 2 prior lines of therapy		
Total N	17	17

Group Parameter	MIRV	Topotecan
Median PFS in months (95% CI)	4.11 (2.30, 8.48)	3.02 (1.45, 4.27)
PFS Hazard Ratio (95% CI)	0.51 (0.227, 1.144)	
Median OS in months (95% CI)	15.41 (7.23, ----)	7.56 (4.60, 15.90)
OS Hazard Ratio (95% CI)	0.40 (0.151, 1.067)	
ORR (%) [95% CI]	6 (35.3) [14.2, 61.7]	1 (5.9) [0.1, 28.7]
ORR Difference (95% CI)	29.4 (4.1, 54.7)	
Subjects with 3 prior lines of therapy		
Total N	33	33
Median PFS in months (95% CI)	4.24 (3.02, 5.85)	2.60 (1.64, 5.82)
PFS Hazard Ratio (95% CI)	0.82 (0.467, 1.426)	
Median OS in months (95% CI)	17.51 (10.91, ----)	9.63 (4.86, 22.90)
OS Hazard Ratio (95% CI)	0.62 (0.309, 1.228)	
ORR (%) [95% CI]	10 (30.3) [15.6, 48.7]	2 (6.1) [0.7, 20.2]
ORR Difference (95% CI)	24.2 (6.6, 41.9)	

Abbreviations: CI = confidence interval; ORR = overall response rate; OS = overall survival; PFS = progression-free survival

COMP conclusion

The results of the requested separate comparisons of Elahere vs each of the non-platinum single agents (paclitaxel, pegylated liposomal doxorubicin and topotecan) in all three endpoints (PFS, OS and ORR) showed relatively large effects of Elahere compared to pegylated liposomal doxorubicin and topotecan. The benefits over paclitaxel are more modest and the same trends are shown in the results of the additional subgroup analyses by prior number of lines of therapy (1, 2 or 3), although these results should be interpreted with caution given the limited sample sizes.

The COMP considered that despite the uncertainties regarding the precise value of the increase in the median PFS as primary endpoint of Elahere, there was still an improvement in the OS versus paclitaxel. This is clinically relevant for 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.

Based on the above the COMP concluded that the significant benefit of mirvetuximab soravtansine versus standard of care treatment (consisting in paclitaxel, pegylated liposomal doxorubicin and topotecan) is considered justified based on improved efficacy.

4. COMP position adopted on date

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of ovarian cancer (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 4.6 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to pain, weight loss, ascites and vaginal bleeding, and life-threatening with reduced life expectancy;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the claim that Elahere is of significant benefit to those affected by the orphan condition is established. The sponsor provided clinical data which showed improved efficacy of Elahere versus the authorised medicinal products.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Elahere, humanised anti-folate receptor 1 monoclonal antibody conjugated to maytansinoid DM4, mirvetuximab soravtansine for treatment of ovarian cancer (EU/3/15/1458) is not removed from the Community Register of Orphan Medicinal Products.