Mirvetuximab soravtansine (ovarian cancer)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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Patient and family involvement

The questionnaire on the disease and its treatment was answered by Dr. Annette Fischer, Regina Kühn and Bettina Onnasch.

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Part I: Benefit assessment

I Table of contents

Page

I List of tables I.3
I List of abbreviations I.5
I 1 Executive summary of the benefit assessment I.7
I 2 Research question I.17
I 3 Information retrieval and study pool I.18
I 3.1 Studies included I.18
I 3.2 Study characteristics I.19
I 4 Results on added benefit I.43
I 4.1 Outcomes included I.43
I 4.2 Risk of bias I.47
I 4.3 Results I.48
I 4.4 Subgroups and other effect modifiers I.57
I 5 Probability and extent of added benefit I.62
I 5.1 Assessment of added benefit at outcome level I.62
I 5.2 Overall conclusion on added benefit I.65
I 6 References for English extract I.69

I List of tables[2]

Page

Table 2: Research question for the benefit assessment of mirvetuximab soravtansine..... I.7
Table 3: Mirvetuximab soravtansine – probability and extent of added benefit..... I.16
Table 4: Research question for the benefit assessment of mirvetuximab soravtansine..... I.17
Table 5: Study pool – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice I.18
Table 6: Characteristics of the included studies – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice I.19
Table 7: Characteristics of the intervention – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice I.22
Table 8: Planned duration of follow-up – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice I.30
Table 9: Characteristics of the study populations as well as study/treatment discontinuation – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice I.32
Table 10: Information on the course of the study – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice..... I.36
Table 11: Information on subsequent antineoplastic therapies – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice (MIRASOL) I.38
Table 12: Information on subsequent antineoplastic therapies – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice (FORWARD 1) I.39
Table 13: Risk of bias across outcomes (study level) – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice..... I.41
Table 14: Matrix of outcomes – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice I.44
Table 15: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice..... I.47
Table 16: Results (mortality, side effects) – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice I.49
Table 17: Results (morbidity, health-related quality of life) – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice..... I.54
Table 18: Subgroups (mortality, side effects) – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice I.58

[2] Table numbers start with '2' as numbering follows that of the full dossier assessment.

Table 19: Extent of added benefit at outcome level: mirvetuximab soravtansine vs. chemotherapy of physician's choice I.63
Table 20: Positive and negative effects from the assessment of mirvetuximab soravtansine compared with chemotherapy of physician's choice I.66
Table 21: Mirvetuximab soravtansine – probability and extent of added benefit I.68

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BRCA	breast cancer-associated gene
CTCAE	Common Terminology Criteria for Adverse Events
DGHO	Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (German Society for Haematology and Medical Oncology)
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique
FOSI	Functional Assessment of Cancer Therapy-Ovarian Symptom Index
FRα	folate receptor-alpha
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model with repeated measures
PARP	poly(adenosine diphosphate [ADP]-ribose) polymerase
PGIS	Patient Global Impression of Severity
PLD	pegylated liposomal doxorubicin
PS2+	positive staining 2+
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-OV28	Quality of Life Questionnaire-Ovarian Cancer 28
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	summary of product characteristics
SMQ	Standardized MedDRA Query
SOC	System Organ Class
VAS	visual analogue scale

Abbreviation	Meaning
VEGF	vascular endothelial growth factor

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug mirvetuximab soravtansine. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the 'company'). The dossier was sent to IQWiG on 28 January 2026.

Research question

The aim of this report is to assess the added benefit of mirvetuximab soravtansine in comparison with the appropriate comparator therapy (ACT) in patients with folate receptor-alpha (FRα)-positive, platinum-resistant high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received 1 to 3 prior systemic treatment regimens.

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of mirvetuximab soravtansine

Therapeutic indication	**ACT[a]**
Adult patients with FRα-positive, platinum-resistant[b] high grade serous epithelial ovarian cancer[c] who have received 1 to 3 prior systemic treatment regimens	▪ paclitaxel (with or without bevacizumab for bevacizumab-naïve patients[d]) or ▪ pegylated liposomal doxorubicin (with or without bevacizumab for bevacizumab-naïve patientsd) or ▪ topotecan (with or without bevacizumab for bevacizumab-naïve patientsd)
a. Presented is the ACT specified by the G-BA. b. According to the G-BA, it is assumed that platinum-resistant, relapsed ovarian cancer involves a response to a prior platinum-containing therapy with a relapse-free interval of less than 6 months. This also includes platinum-refractory ovarian cancer, which does not respond to platinum-containing chemotherapy or progresses within 4 weeks of the end of treatment. c. This term also includes fallopian tube and primary peritoneal cancer. d. In accordance with the treatment recommendations set out in guidelines, for patients who have not yet received treatment containing bevacizumab, or who have received treatment with another VEGF inhibitor or a substance targeting the VEGF receptor, on-label treatment with a combination therapy of bevacizumab with paclitaxel, topotecan or liposomal doxorubicin may be indicated, provided that bevacizumab is suitable for the patients. ACT: appropriate comparator therapy; FRα: folate receptor-alpha; G-BA: Federal Joint Committee; VEGF: vascular endothelial growth factor	

The company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used to derive the added benefit. This concurs with the inclusion criterion of the company.

Study pool and study design

The MIRASOL and FORWARD 1 studies were used for the benefit assessment. Both studies are completed, open-label, multicentre RCTs comparing mirvetuximab soravtansine with a chemotherapy of investigator's choice from paclitaxel, pegylated liposomal doxorubicin (PLD) or topotecan. They included adult patients with FRα-positive, platinum-resistant high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer, which are hereinafter referred to with the umbrella term 'ovarian cancer'. In accordance with the summary of product characteristics (SmPC), in MIRASOL, a positive FRα status was defined as the immunohistochemistry confirmation of ≥75% of viable tumour cells exhibiting moderate (2+) and/or strong (3+) membrane staining intensity (positive staining 2+ [PS2+] scoring). The FORWARD 1 study protocol also stipulated the determination of the FRα status using the PS2+ scoring system. Deviating from this, a different method was applied in the study, however. As a consequence, the company presented a subpopulation from the FORWARD 1 study in which the PS2+ scoring was applied retrospectively.

In both studies, patients were required to have previously received 1 to 3 prior systemic lines of therapy and be in good general condition according to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1. Patients with primary platinum-refractory ovarian cancer were excluded from both studies.

MIRASOL enrolled a total of 453 patients, randomized in a 1:1 ratio either to treatment with mirvetuximab soravtansine (N = 227) or to treatment with a chemotherapeutic regimen previously chosen by the investigator (N = 226).

FORWARD 1 enrolled a total of 366 patients, randomized in a 2:1 ratio either to treatment with mirvetuximab soravtansine (N = 248) or to treatment with a chemotherapeutic regimen previously chosen by the investigator (N = 118).

In both studies, treatment with mirvetuximab soravtansine in the intervention arm was administered largely in compliance with the SmPC. The doses of the chemotherapeutic agents used did not correspond to the relevant SmPCs, but were nevertheless regarded as appropriate in the German health care context (see below for further details). Furthermore, the study protocols for both studies did not provide for mandatory premedication with corticosteroids, antihistamines and H_2 antagonists to prevent hypersensitivity reactions caused by paclitaxel. In both studies, treatment continued until the occurrence of unacceptable toxicity, disease progression, withdrawal of consent, the end of the study or death. The option of switching treatments had been included in the FORWARD 1 study via

protocol amendments, but was removed again before it became an option for any patients. A treatment switch was not planned at any stage in the MIRASOL study. In both studies, subsequent therapies were permitted without restriction for patients in both study arms following disease progression.

The primary outcome in both studies was progression-free survival. Moreover, overall survival as well as outcomes in the categories morbidity and health-related quality of life as well as adverse events (AEs) were recorded in both studies.

Presented subpopulation of the FORWARD 1 study

According to the SmPC, the therapeutic indication of mirvetuximab soravtansine includes patients with FRα-positive ovarian cancer, defined as ≥75% of viable tumour cells with moderate (2+) and/or strong (3+) membrane staining intensity demonstrated by immunohistochemistry (PS2+ scoring). In FORWARD 1, a tumour was considered FRα-positive if ≥50% of tumour cells showed membrane staining visible at ≤10X microscope objective. Following the completion of the study, the FRα status of the patients' tumours was retrospectively reclassified in accordance with the SmPC as part of an exploratory analysis. The company referred to a congress presentation, according to which 333 of the 366 patients in total were reclassified. It was unclear why 33 patients (9%) of the total population in the FORWARD 1 study were not reclassified. No information was available on this aspect. This uncertainty was taken into account when assessing the certainty of conclusions. Based on the reclassification, the company presented a subpopulation of 116 patients whose tumours had a FRα-positive status in accordance with the specifications set out in the SmPC.

Implementation of the ACT

Lack of combination therapy with bevacizumab

The G-BA designated paclitaxel, PLD or topotecan – each with or without bevacizumab – as ACTs for bevacizumab-naïve patients. In MIRASOL and FORWARD 1, combination therapy with bevacizumab was not an option for the control arm in either study. According to the S3 guideline recommendations, the combination of bevacizumab with paclitaxel, PLD or topotecan may be used in this therapeutic indication. According to the SmPC, bevacizumab, in combination with the aforementioned chemotherapeutic agents, is approved for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian cancer who received no more than 2 prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other vascular endothelial growth factor (VEGF) inhibitors or VEGF receptor–targeted agents. The company argued that chemotherapy in combination with bevacizumab would only have been an option for a small proportion of patients, and that the patients in the MIRASOL and FORWARD 1 studies were treated in accordance with the German health care context. It is understandable that, based on the specifications in the SmPC, bevacizumab combination therapy would have been an option for a maximum of 27% of

patients (across both studies) at the time of enrolment. Clear criteria for or against the use of bevacizumab cannot be derived from the SmPC. It was assumed that the decision for or against treatment with bevacizumab must be weighed up on an individual basis, taking comorbidities into account. Correspondingly, it was assumed that bevacizumab was not an option for some patients due to comorbidities. However, it was not possible to assess this retrospectively on the basis of the medical history of the study populations; consequently, the proportion of these patients was non-quantifiable. Overall, it was assumed that a relevant proportion – though no more than 27% – of the patients would have been eligible for bevacizumab combination therapy at baseline. This uncertainty was taken into account when assessing the certainty of conclusions.

Based on the results of MIRASOL and FORWARD 1, conclusions regarding the added benefit of mirvetuximab soravtansine can only be drawn for those patients for whom monotherapy with paclitaxel, PLD or topotecan is a suitable treatment.

Use of alternative chemotherapy dosing regimens in the control arm

In both studies, the administration of paclitaxel, PLD and topotecan differed from the SmPCs. To prove that the dosing regimens used in the studies correspond to everyday clinical practice in Germany, the company submitted various documents. The guidelines do not provide any explicit dosage recommendations for the drugs. The primary literature cited in each of the guidelines specifies both the on-label dosages and those used in the studies in question. The German Society for Haematology and Medical Oncology also recommends the dosages used in the studies and, for paclitaxel and PLD, additionally the dosages specified in the SmPCs. On this basis, the dosages of paclitaxel, PLD and topotecan used in the studies were considered appropriate.

Pretreatment to prevent hypersensitivity reactions caused by mirvetuximab soravtansine and paclitaxel

According to the SmPCs, premedication to prevent hypersensitivity reactions is required for both treatment with mirvetuximab soravtansine and treatment with paclitaxel. However, the study documents only explicitly state the requirement for premedication in relation to mirvetuximab soravtansine, but not for paclitaxel. No precise details were available regarding the extent to which premedication for paclitaxel in compliance with the SmPC was administered; an approximation of these details can only be derived for the MIRASOL study, based on the information on concomitant treatments. This uncertainty was taken into account in the risk of bias in the results regarding side effects.

Data cuts

MIRASOL

For the benefit assessment, the results from the third data cut of 26 September 2024 were used, which was the final analysis after at least 300 deaths.

FORWARD 1

For the benefit assessment, the results from the second data cut of 18 March 2020 were used, which was the final analysis one year after the first data cut-off.

Meta-analytical summary of MIRASOL and FORWARD 1

The company conducted a meta-analytical summary of the results of MIRASOL and FORWARD 1 on the basis of individual patient data. This meta-analysis was used for this benefit assessment.

Risk of bias

The risk of bias across outcomes was rated as low for both studies.

With regard to the results for the overall survival outcome in the MIRASOL study, there was a high risk of bias due to the high, differing proportions of study discontinuations at the patient's request (4% versus 10%) and, in particular, the unclear, differing proportions of early censorings (6% versus 10%) for potentially informative reasons. It was unclear to what extent these data also included patients who did not receive treatment. Here, too, there was a difference in proportions of 4% versus 8%. For FORWARD 1, the risk of bias for the results on overall survival was assessed as low. The results for the outcomes in the side effects category each had a high risk of bias. For serious AEs (SAEs) and severe AEs, this was attributable to shortened observations for potentially informative reasons in the presence of different observation periods. For the results relating to non-severe/non-serious outcomes in the category of side effects, there was a high risk of bias due to the unblinded study design, involving subjective outcome recording / subjective decisions to discontinue treatment, as well as incomplete observations for potentially informative reasons in the presence of different observation periods. In principle, the uncertainty associated with premedication to prevent hypersensitivity reactions during treatment with paclitaxel must also be taken into account for the outcomes in the side effects category. Due to the wide range of symptoms of hypersensitivity reactions, they cannot be clearly assigned to specific System Organ Classes (SOCs) or Preferred Terms (PTs). Overall, this uncertainty contributed to the high risk of bias in the results of the overall AE rates as well as specific AEs such as skin and subcutaneous tissue disorders or dyspnoea.

No suitable data were available for the outcomes of symptoms, health status and health-related quality of life. Therefore, the risk of bias was not assessed for these outcomes.

Summary assessment of the certainty of conclusions

Irrespective of the assessment of the risk of bias, there were relevant uncertainties for the MIRASOL and FORWARD 1 studies regarding the absence of an additional treatment option with bevacizumab in the control arm. For FORWARD 1, there was additional uncertainty because the FRα status was not reclassified for all patients. Overall, the certainty of conclusions for both studies was limited. Based on the results of the meta-analysis of 2 studies with limited certainty of conclusions, no more than an indication, for example of an added benefit, could therefore be derived.

Results

Mortality

Overall survival

For the outcome of overall survival, the meta-analysis of MIRASOL and FORWARD 1 showed a statistically significant difference in favour of mirvetuximab soravtansine compared with chemotherapy of physician's choice. There was an effect modification by the characteristic 'BRCA status'. There is an indication of an added benefit of mirvetuximab soravtansine compared with the ACT both for patients with a positive BRCA status and for patients with a negative/unknown BRCA status, albeit of different extents. However, there were uncertainties regarding the delineation of the subgroups due to a lack of data on patients with unknown BRCA status. Consequently, the results of the subgroup analysis were not used for the remainder of the benefit assessment.

Morbidity

Symptoms (EORTC QLQ-C30, QLQ-OV28, PGIS and FOSI)

No suitable data were available for the symptom outcomes, as assessed using the EORTC QLQ-C30, QLQ-OV28, PGIS and FOSI. In each case, there is no hint of an added benefit of mirvetuximab soravtansine in comparison with the ACT; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

No suitable data were available for the health status outcome, as assessed using the EQ-5D VAS. There is no hint of an added benefit of mirvetuximab soravtansine in comparison with the ACT; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30 and QLQ-OV28

No suitable data were available for the health-related quality of life outcomes, as assessed using the EORTC QLQ-C30 and QLQ-OV28. In each case, there is no hint of an added benefit of

mirvetuximab soravtansine in comparison with the ACT; an added benefit is therefore not proven.

Side effects

SAEs

For the outcome of SAEs, the meta-analysis of MIRASOL and FORWARD 1 showed a statistically significant difference in favour of mirvetuximab soravtansine compared with chemotherapy of physician's choice. There is an indication of lesser harm of mirvetuximab soravtansine in comparison with the ACT.

Severe AEs

For the outcome of severe AEs, the meta-analysis of MIRASOL and FORWARD 1 showed a statistically significant difference in favour of mirvetuximab soravtansine compared with chemotherapy of physician's choice. There is therefore an indication of lesser harm of mirvetuximab soravtansine in comparison with the ACT.

Discontinuation due to AEs

For the outcome of discontinuation due to AEs, the meta-analysis, taking into account the total population, showed a statistically significant difference in favour of mirvetuximab soravtansine compared with chemotherapy of physician's choice. There was an effect modification by the characteristic 'age'. For patients ≥65 years, there is an indication of lesser harm of mirvetuximab soravtansine in comparison with the ACT. For patients <65 years, there is no hint of greater or lesser harm of mirvetuximab soravtansine in comparison with the ACT; greater or lesser harm is therefore not proven for this group.

Eye disorders (AEs, severe AEs) and pneumonitis (AEs)

For each of the outcomes of eye disorders (AEs and severe AEs) and pneumonitis (AEs), the meta-analysis of MIRASOL and FORWARD 1 showed a statistically significant difference to the disadvantage of mirvetuximab soravtansine compared with chemotherapy of physician's choice. In each case, there is therefore an indication of greater harm of mirvetuximab soravtansine in comparison with the ACT.

Given the prophylactic administration of steroid-containing eye drops, it was not ruled out that, had they been administered in accordance with the SmPC (only after the onset of an AE), eye disorders would have occurred on a larger scale and with greater severity. In the situation at hand, however, this had no consequence for the derivation of the added benefit, because, in the overall assessment and based on the available data on eye disorders (AEs and severe AEs), greater harm of the highest extent was already determined.

Dyspnoea (AEs)

For the outcome of dyspnoea (AEs), the meta-analysis, taking into account the total population, showed a statistically significant difference in favour of mirvetuximab soravtansine compared with chemotherapy of physician's choice. There were effect modifications by the characteristics of age and BRCA status. These effect modifications cannot be assessed without examining for cross-interactions. Furthermore, the limitations described apply to the analyses according to BRCA status. The added benefit is therefore derived based on the results of the total population. There is an indication of lesser harm of mirvetuximab soravtansine in comparison with the ACT.

Stomatitis (AE) and skin and subcutaneous tissue disorders (AEs)

For each of the outcomes of stomatitis (AE) and skin and subcutaneous tissue disorders (AEs), the meta-analysis of MIRASOL and FORWARD 1 showed a statistically significant difference in favour of mirvetuximab soravtansine compared with chemotherapy of physician's choice. In each case, there is therefore an indication of lesser harm of mirvetuximab soravtansine in comparison with the ACT.

Small intestinal obstruction (SAEs), blood and lymphatic system disorders (severe AEs), and fatigue (severe AEs)

For each of the outcomes of small intestinal obstruction (SAEs), blood and lymphatic system disorders (severe AEs) and fatigue (severe AEs), the meta-analysis of MIRASOL and FORWARD 1 showed a statistically significant difference in favour of mirvetuximab soravtansine compared with chemotherapy of physician's choice. In each case, there is therefore an indication of lesser harm of mirvetuximab soravtansine in comparison with the ACT.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the probability and extent of the added benefit of the drug mirvetuximab soravtansine versus the ACT was assessed as follows:

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) 'proof', (2) 'indication', (3) 'hint', or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or lesser benefit). For further details see [1,2].

Patients for whom monotherapy with paclitaxel, PLD or topotecan is a suitable therapy

Overall, there are predominantly positive effects of mirvetuximab soravtansine in comparison with chemotherapy of physician's choice. Data across the entire observation period were only available for overall survival. All other effects referred exclusively to the shortened observation period (until 30 days after the end of treatment). There were no suitable data for the outcome categories of morbidity and health-related quality of life.

On the side of positive effects, there is an indication of an added benefit of major extent for the outcome overall survival. In addition, there are several positive effects of a major or considerable extent for outcomes in the side effects category; this applies to both the overall rates and individual specific AEs. Decisive are the positive effects of major extent in the overall rates of severe AEs and SAEs. In contrast to these positive effects, there are individual negative effects in the outcome category of side effects, particularly in severe eye disorders (extent: major). Overall, the positive effects clearly outweigh the negative ones.

In summary, there is an indication of a major added benefit of mirvetuximab soravtansine versus the ACT for adult patients with FRα-positive, platinum-resistant high grade serous epithelial ovarian cancer who have received 1 to 3 prior systemic treatment regimens, and for whom monotherapy with paclitaxel, PLD or topotecan is a suitable therapy.

Patients for whom combination therapy with bevacizumab is a suitable therapy

No data were available to assess the added benefit of mirvetuximab soravtansine versus the ACT for adult patients with FRα-positive, platinum-resistant high grade serous epithelial ovarian cancer who have received 1 to 3 prior systemic treatment regimens, and for whom combination therapy with bevacizumab is a suitable therapy. An added benefit for these patients is not proven.

Table 3 summarizes the probability and extent of added benefit of mirvetuximab soravtansine.

Table 3: Mirvetuximab soravtansine – probability and extent of added benefit

Therapeutic indication	**Appropriate comparator therapy (ACT)[a]**	**Probability and extent of added benefit**
Adult patients with FRα-positive, platinum-resistant[b] high grade serous epithelial ovarian cancer[c] who have received 1 to 3 prior systemic treatment regimens	▪ paclitaxel (with or without bevacizumab for bevacizumab-naïve patients[d]) or ▪ pegylated liposomal doxorubicin (with or without bevacizumab for bevacizumab-naïve patientsd) or ▪ topotecan (with or without bevacizumab for bevacizumab-naïve patientsd)	▪ Patients for whom monotherapy with paclitaxel, PLD or topotecan is a suitable therapy: indication of a major added benefit[e, f] ▪ Patients for whom combination therapy with bevacizumab is a suitable therapy: added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, it is assumed that platinum-resistant, relapsed ovarian cancer involves a response to a prior platinum-containing therapy with a relapse-free interval of less than 6 months. This also includes platinum-refractory ovarian cancer, which does not respond to platinum-containing chemotherapy or progresses within 4 weeks of the end of treatment.
c. This term also includes fallopian tube and primary peritoneal cancer.
d. In accordance with the treatment recommendations set out in guidelines, for patients who have not yet received treatment containing bevacizumab, or who have received treatment with another VEGF inhibitor or a substance targeting the VEGF receptor, on-label treatment with a combination therapy of bevacizumab with paclitaxel, topotecan or liposomal doxorubicin may be indicated, provided that bevacizumab is suitable for the patients.
e. MIRASOL and FORWARD 1 included only patients with an ECOG PS of 0 or 1. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥2.
f. No patients with primary platinum-refractory tumours were included in MIRASOL and FORWARD 1. It remains unclear whether the observed effects can be transferred to patients with primary platinum-refractory ovarian cancer.

ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FRα: folate receptor-alpha; G-BA: Federal Joint Committee; VEGF: vascular endothelial growth factor

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of mirvetuximab soravtansine in comparison with the appropriate comparator therapy (ACT) in patients with folate receptor-alpha (FRα)-positive, platinum-resistant high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received 1 to 3 prior systemic treatment regimens.

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of mirvetuximab soravtansine

Therapeutic indication	**ACT[a]**
Adult patients with FRα-positive, platinum-resistant[b] high grade serous epithelial ovarian cancer[c] who have received 1 to 3 prior systemic treatment regimens	▪ paclitaxel (with or without bevacizumab for bevacizumab-naïve patients[d]) or ▪ pegylated liposomal doxorubicin (with or without bevacizumab for bevacizumab-naïve patients[d]) or ▪ topotecan (with or without bevacizumab for bevacizumab-naïve patients[d])
a. Presented is the ACT specified by the G-BA. b. According to the G-BA, it is assumed that platinum-resistant, relapsed ovarian cancer involves a response to a prior platinum-containing therapy with a relapse-free interval of less than 6 months. This also includes platinum-refractory ovarian cancer, which does not respond to platinum-containing chemotherapy or progresses within 4 weeks of the end of treatment. c. This term also includes fallopian tube and primary peritoneal cancer. d. In accordance with the treatment recommendations set out in guidelines, for patients who have not yet received treatment containing bevacizumab, or who have received treatment with another VEGF inhibitor or a substance targeting the VEGF receptor, on-label treatment with a combination therapy of bevacizumab with paclitaxel, topotecan or liposomal doxorubicin may be indicated, provided that bevacizumab is suitable for the patients. ACT: appropriate comparator therapy; FRα: folate receptor-alpha; G-BA: Federal Joint Committee; VEGF: vascular endothelial growth factor	

The company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used to derive the added benefit. This concurs with the inclusion criterion of the company.

I 3 Information retrieval and study pool

The study pool for the assessment was compiled on the basis of the following information:

Sources used by the company in the dossier:

- Study list on mirvetuximab soravtansine (status: 17 November 2025)
- Bibliographical literature search on mirvetuximab soravtansine (last search on 17 November 2025)
- Search of trial registries / trial results databases for studies on mirvetuximab soravtansine (last search on 17 November 2025)
- Search on the G-BA website for mirvetuximab soravtansine (last search on 17 November 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on mirvetuximab soravtansine (last search on 10 February 2026); for search strategies, see I Appendix A of the full dossier assessment

The search did not identify any additional relevant studies.

I 3.1 Studies included

The studies listed in the following table were included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice[a]

Study	Study category			Available sources		
	Study for the marketing authorization of the drug to be assessed (yes/no)	Sponsored study[b] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[c] (yes/no [citation])	Publication and other sources[d] (yes/no [citation])
IMGN853-0416 (MIRASOL[e])	Yes	Yes[f]	No	Yes [3,4]	Yes [5-7]	Yes [8-10]
IMGN853-0403 (FORWARD 1[e])	Yes	Yes[f]	No	Yes [11,12]	Yes [13,14]	Yes [8,10,15]

a. With a choice of paclitaxel, pegylated liposomal doxorubicin or topotecan prior to randomization.
b. Study sponsored by the company.
c. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
d. Other sources: documents from the search on the G-BA website and other publicly available sources.
e. In the following tables, the study is referred to by this acronym.
f. The study was sponsored by ImmunoGen. ImmunoGen has been part of the AbbVie Group since February 2024.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The MIRASOL and FORWARD 1 studies were used for the benefit assessment. The study pool was consistent with that selected by the company.

I 3.2 Study characteristics

Table 6 and Table 7 describe the studies used for the benefit assessment.

Table 6: Characteristics of the included studies – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice[a] (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
MIRASOL	RCT, open-label, parallel	Adult female patients with FRα-positive[c], platinum-resistant[d], high-grade serous epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer, with ▪ 1 to 3 prior systemic lines of therapy ▪ ECOG PS ≤ 1	mirvetuximab soravtansine (N = 227) chemotherapy[a] (N = 226)	Screening: up to 28 days Treatment: until disease progression, unacceptable toxicity, withdrawal of consent, death or end of study[e] Follow-up[f]: outcome-specific, at most until death, withdrawal of consent or end of the study[e]	136 study centres in: Australia, Belgium, Bulgaria, Canada, China, Czech Republic, France, Germany, Israel, Italy, Netherlands, Poland, Portugal, Russia, Serbia, South Korea, Spain, Taiwan, United Kingdom, United States 2/2020–9/2024 Data cuts: 6 March 2023 (prespecified final PFS analysis)[g] 27 October 2023 (EMA request) 26 September 2024 (prespecified final OS analysis at the end of the study[e])	Primary: PFS (assessed by investigator) Secondary: overall survival, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the included studies – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice[a] (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
FORWARD 1[h]	RCT, open-label, parallel	Adult female patients with FRα-positive[c], platinum-resistant[i], advanced epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer, with ▪ 1 to 3 prior systemic lines of therapy ▪ ECOG PS ≤ 1	mirvetuximab soravtansine (N = 248) chemotherapy[a] (N = 118) Relevant subpopulation thereof[j]: mirvetuximab soravtansine (n = 82) chemotherapy[a] (n = 34)	Screening: up to 28 days Treatment: until disease progression, unacceptable toxicity, withdrawal of consent, death or end of study[k] Follow-up[f]: outcome-specific, at most until death, withdrawal of consent or end of the study[k]	101 centres in: Belgium, Canada, Czech Republic, France, Ireland, Italy, Russia, Serbia, Spain, Ukraine, United Kingdom and United States 1/2017–3/2020 Data cuts: 19 February 2019[l] (prespecified final PFS analysis) 18 March 2020 (final analysis at the end of the study[k])	Primary: PFS (according to BICR) Secondary: overall survival, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the included studies – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice[a] (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]

a. With a choice of paclitaxel, pegylated liposomal doxorubicin or topotecan prior to randomization.
b. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
c. Using the Ventana FOLR1 (FOLR1-2.1) CDx assay. In the MIRASOL study, a tumour was considered FRα-positive if ≥75% of viable tumour cells exhibited moderate (2+) and/or strong (3+) membrane staining, analogous to the definition in the SmPC. In the FORWARD 1 study, however, a tumour was considered FRα-positive if ≥50% of tumour cells showed membrane staining visible at ≤10X microscope objective.
d. For patients with only one line of platinum-based therapy: patients must have shown a partial or complete response after ≥4 cycles of platinum, and then progressed between 3 months and 6 months after the date of the last dose of platinum. Patients with a platinum-refractory tumour during the first treatment, defined as disease that did not respond to or progressed within 3 months of the last dose of platinum, were excluded. Patients who had received 2 or 3 lines of platinum therapy must have progressed on or within 6 months after the date of the last dose of platinum.
e. The study was scheduled to end after the final analysis of overall survival, prespecified after ≥300 deaths.
f. Outcome-specific information is provided in Table 8.
g. Prespecified after ≥330 PFS events
h. Initially the FORWARD 1 study was a 2-stage, phase 2 study (March 2016) to determine the appropriate dosing for mirvetuximab soravtansine (Stage 1) and to compare the efficacy of mirvetuximab soravtansine with chemotherapy of physician's choice in patients with platinum-resistant ovarian cancer. Following an IDMC review, protocol amendment 5 (17 August 2016) closed enrolment to Stage 1, the final dosing for mirvetuximab soravtansine was selected on the basis of the IMGN853-0401 study results, and the design was changed from phase 2 to a phase 3 study. The following information relates to phase 3 of the study.
i. Defined as progression within 6 months from completion of ≥4 cycles of platinum-containing therapy (time since the last dose). Patients with disease progression during or within 4 weeks after completing their first platinum-containing therapy (primary platinum-refractory) were excluded.
j. Patients who, according to the reclassification of the FRα expression level using the PS2+ scoring method, are FRα-positive based on the presence of ≥75% of viable tumour cells with moderate (2+) and/or strong (3+) membrane staining, analogous to the definition in the SmPC.
k. The study was scheduled to end 1 year after the final PFS analysis.
l. Prespecified after 236 PFS events

AE: adverse event; BICR: blinded independent central review; CDx: Companion diagnostics; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EMA: European Medicines Agency; FOLR1: folate receptor 1; FRα: folate receptor-alpha; ICH: immunohistochemistry; IDMC: independent data monitoring committee; n: relevant subpopulation; N: number of randomized patients; OS: overall survival; PFS: progression-free survival; PS2+: positive staining 2+; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice[a] (multipage table)

Study	Intervention	Comparison
MIRASOL, FORWARD 1	mirvetuximab soravtansine 6 mg/kg AIBW IV on Day 1 of each 3-week cycle	Chemotherapy of physician's choice: ▪ paclitaxel: 80 mg/m² IV on Days 1, 8, 15 and 22 of each 4-week cycle ▪ pegylated liposomal doxorubicin: 40 mg/m² IV on Day 1 of each 4-week cycle ▪ topotecan: 4 mg/m² IV on Days 1, 8 and 15 of each 4-week cycle or 1.25 mg/m² IV on Days 1–5 of each 3-week cycle
	Dose modifications: ▪ Interruption of treatment in the case of treatment-related AEs ▪ Gradual dose reduction to 5 mg/kg and 4 mg/kg AIBW respectively[b]	▪ All drugs: interruption of treatment in the event of treatment-related AEs; ▪ paclitaxel: gradual dose reduction[b, c] to 70 mg/m² and 60 mg/m² respectively ▪ pegylated liposomal doxorubicin: gradual dose reduction[b] to 30 mg/m² and 20 mg/m² respectively ▪ topotecan: gradual dose reduction to 3.5 mg/m², or 3 mg/m² for weekly dosing, or to 1.0 mg/m², or 0.75 mg/m² for dosing every 3 weeks[b]
	Required prior treatment ▪ 1–3 lines of systemic cancer therapy[d] **Disallowed prior treatment** ▪ Wide-field radiotherapy affecting at least 20% of the bone marrow ▪ Treatment with mirvetuximab soravtansine[e] **Allowed concomitant treatment** ▪ Premedication required for mirvetuximab soravtansine[f]: paracetamol (oral or IV), dexamethasone IV and diphenhydramine (IV or oral) ▪ Premedication for chemotherapy: at the discretion of the investigator or according to institutional guidelines ▪ Required for mirvetuximab soravtansine: corticosteroid eye drops (1% prednisolone or equivalent)[g] and daily lubricating eye drops ▪ Antiemetic and antidiarrhoeal drugs[h] ▪ Continuation of prior treatment with haematopoietic growth factors ▪ Anticoagulants ▪ Prophylactic administration of steroids and antihistamines to prevent infusion reactions ▪ Palliative radiotherapy[i] **Disallowed concomitant treatment** ▪ Antineoplastic therapy ▪ Folate-containing dietary supplements	

Table 7: Characteristics of the intervention – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice[a] (multipage table)

Study	Intervention	Comparison
a. With a choice of paclitaxel, pegylated liposomal doxorubicin or topotecan prior to randomization. b. In the MIRASOL study, dose re-escalation was explicitly prohibited for all drugs; in the FORWARD 1 study, dose re-escalation was explicitly prohibited only for topotecan. c. Instead of a second dose reduction, 70 mg/m^2 could be maintained if one weekly dose was omitted within one cycle. d. Adjuvant ± neoadjuvant therapy are regarded as a single line of treatment. Maintenance therapies (e.g. bevacizumab, PARP inhibitors) are considered as part of the preceding line of therapy. Hormonal therapies were counted as a separate line of treatment unless they were administered as maintenance therapy (the latter was described for the FORWARD 1 study as a protocol amendment (amendment 8) dated 8 May 2017, but is not specified in the inclusion criteria). The MIRASOL study also stipulated that therapy changed due to AEs (in the absence of progression) should not be considered a separate line of treatment. e. In MIRASOL, other FRα-targeting drugs were also not permitted. f. In MIRASOL the concomitant treatment with antiemetics was additionally recommended. g. On Days 1–8 of each cycle; in MIRASOL, additionally one day before the start of the cycle. h. In FORWARD 1 not allowed for prophylaxis. i. Allowed only in FORWARD 1 and only after discussion with the sponsor; the patient was censored in the PFS analysis from the time this therapy was performed. AE: adverse event; AIBW: adjusted ideal body weight; IV: intravenous; RCT: randomized controlled trial; VEGF: vascular endothelial growth factor		

Study design of MIRASOL and FORWARD 1

MIRASOL and FORWARD 1 are completed, open-label, multicentre RCTs comparing mirvetuximab soravtansine with a chemotherapy of investigator's choice from paclitaxel, pegylated liposomal doxorubicin (PLD) or topotecan. Initially the FORWARD 1 study was a phase 2 dose-finding study. Following new scientific findings, the study was redesigned as a phase 3 study a few months after its start. Only phase 3 of the FORWARD 1 study was relevant to this benefit assessment.

Both studies included adult patients with FRα-positive, platinum-resistant high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer, which are hereinafter referred to with the umbrella term 'ovarian cancer'.

In FORWARD 1, the inclusion criteria were not explicitly restricted to high-grade serous ovarian cancer; instead, patients with advanced epithelial ovarian cancer were included. Patients with clear cell, mucinous histology, mixed histology with mucinous component, sarcoma, sarcomatous component, or low grade ovarian cancer were excluded. In FORWARD 1, 98% of the total population had high-grade serous tumours. The study population therefore largely corresponded to the therapeutic indication in question.

In MIRASOL, a positive FRα status was defined as the immunohistochemistry confirmation of ≥75% of viable tumour cells exhibiting moderate (2+) and/or strong (3+) membrane staining

intensity (positive staining 2+ [PS2+] scoring) [16]. This concurs with the definition in the summary of product characteristics (SmPC). The FORWARD 1 study protocol also stipulated the determination of the FRα status using the PS2+ scoring system. In Module 4 A, however, the company stated that a different method was applied. As a consequence, the company presented a subpopulation from the FORWARD 1 study in which the PS2+ scoring was applied retrospectively (see section below).

In both studies, patients were required to have previously received 1 to 3 prior systemic lines of therapy and be in good general condition according to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1. In MIRASOL, platinum resistance was defined on the basis of the number of lines of platinum-based therapy received. Patients who had received only one line of platinum-based therapy, after at least 4 cycles of platinum-containing therapy must have had a partial or complete response and then progressed between 3 months and 6 months after the date of the last dose of platinum. Patients who had received 2 or 3 lines of platinum therapy were required to have progressed on or within 6 months after the date of the last dose of platinum. In FORWARD 1, platinum resistance was defined as progression within 6 months from completion of ≥4 cycles of platinum-containing therapy, regardless of the number of previous lines of platinum-based therapy. Patients with primary platinum-refractory ovarian cancer were excluded from both studies. In MIRASOL this was defined as no response or disease progression within 3 months; and in FORWARD 1 as disease progression during or within 4 months after the last dose of the first platinum-containing therapy.

MIRASOL enrolled a total of 453 patients, randomized in a 1:1 ratio either to treatment with mirvetuximab soravtansine (N = 227) or to treatment with a chemotherapeutic regimen previously chosen by the investigator (N = 226). Randomization was stratified according to the number of prior lines of therapy (1 versus 2 versus 3) and the chemotherapy (paclitaxel versus PLD versus topotecan) chosen prior to randomization.

FORWARD 1 enrolled a total of 366 patients, randomized in a 2:1 ratio either to treatment with mirvetuximab soravtansine (N = 248) or to treatment with a chemotherapeutic regimen previously chosen by the investigator (N = 118). Randomization was stratified according to the number of prior lines of therapy (1 or 2 versus 3), the chemotherapy (paclitaxel versus PLD versus topotecan) chosen prior to randomization, and FRα status (≥75% of tumour staining versus ≥50% and <75% of tumour staining).

In both studies, treatment with mirvetuximab soravtansine in the intervention arm was administered largely in compliance with the SmPC [16]. Contrary to the SmPC, steroid-containing eye drops were to be administered not after the onset of Common Terminology Criteria for Adverse Events (CTCAE) grade ≥2 corneal side effects, but prophylactically before

(only in MIRASOL) and after (in both studies) each dose. This aspect was taken into account when interpreting the results regarding side effects.

In both studies, the dosages of the chemotherapeutic agents used did not correspond to the relevant SmPCs [17-19]. However, they were nonetheless consistent with the German health care context and were regarded as appropriate (see section on the implementation of the ACT). Furthermore, the study protocols for both studies did not explicitly provide for mandatory premedication with corticosteroids, antihistamines and H_2 antagonists to prevent hypersensitivity reactions caused by paclitaxel (see section on the implementation of the ACT).

In both studies, treatment continued until the occurrence of unacceptable toxicity, disease progression, withdrawal of consent, the end of the study or death. In the FORWARD 1 study, protocol amendment 5 introduced the option for patients in the control arm to switch to treatment with mirvetuximab soravtansine following disease progression. However, this option was removed prior to the enrolment of the first patient via protocol amendment 7, meaning that, in practice, no patient had the option of switching treatment. A switch to mirvetuximab soravtansine was not planned at any stage in the MIRASOL study. In both studies, subsequent therapies were permitted without restriction for patients in both study arms following disease progression (an overview of subsequent antineoplastic therapies can be found in Table 11 and Table 12).

The primary outcome in both studies was progression-free survival. Moreover, overall survival as well as outcomes in the categories morbidity and health-related quality of life as well as adverse events (AEs) were recorded in both studies.

Presented subpopulation of the FORWARD 1 study

According to the SmPC, the therapeutic indication of mirvetuximab soravtansine includes patients with FRα-positive ovarian cancer, defined as ≥75% of viable tumour cells with moderate (2+) and/or strong (3+) membrane staining intensity demonstrated by immunohistochemistry (PS2+ scoring) [16]. In the FORWARD 1 study, FRα status was determined using a different method, according to which a tumour was considered FRα-positive if ≥50% of tumour cells showed membrane staining visible at ≤10X microscope objective. Following the completion of the study, the FRα status of the patients' tumours was retrospectively reclassified in accordance with the SmPC as part of an exploratory analysis. This was based on digital tumour images taken during the study prior to randomization, which were re-assessed by an independent, blinded pathologist. The company referred to a congress presentation [20], according to which 333 of the 366 patients in total were reclassified. On this basis, the company presented a subpopulation of 116 patients whose tumours had a FRα-positive status in accordance with the specifications set out in the SmPC. Of the 116 patients,

82 patients were allocated to the intervention arm and 34 to the control arm. The company's approach to the reclassification in accordance with SmPC was regarded as appropriate, and the presented subpopulation was used for the benefit assessment. However, it was unclear why 33 patients (9%) of the total population in the FORWARD 1 study were not reclassified. No information was available on this aspect. This uncertainty was taken into account when assessing the certainty of conclusions (see Section I 4.2).

Implementation of the ACT

Lack of combination therapy with bevacizumab

The G-BA designated paclitaxel, PLD or topotecan – each with or without bevacizumab – as ACTs for bevacizumab-naïve patients. In MIRASOL and FORWARD 1, combination therapy with bevacizumab was not an option for the control arm in either study. According to the S3 guideline recommendations, the combination of bevacizumab with paclitaxel, PLD or topotecan may be used in this therapeutic indication [21]. According to the SmPC, bevacizumab, in combination with the aforementioned chemotherapeutic agents, is approved for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian cancer who received no more than 2 prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other vascular endothelial growth factor (VEGF) inhibitors or VEGF receptor–targeted agents [22]. The company argued that chemotherapy in combination with bevacizumab would only have been an option for a small proportion of patients, and that the patients in the MIRASOL and FORWARD 1 studies were treated in accordance with the German health care context. It based its argumentation on the fact that the S3 guideline already recommends maintenance therapy with bevacizumab in previous lines of treatment, meaning that most patients without comorbidities should therefore already have received bevacizumab in previous lines of treatment [21]. It went on to state that 27% of patients (across both studies) had not yet received bevacizumab before study start and had received no more than 2 previous lines of treatment, which could be assumed to be chemotherapeutic regimens. This proportion, for whom bevacizumab would formally have been an option, could be reduced even further by identifying relevant comorbidities in the patients' medical history, the company added. In its reasoning, the company further referred to the proportion of around 18% of patients (across both studies) who received bevacizumab as any subsequent therapy; however, some of these patients did not meet the formal criteria for treatment with bevacizumab. According to the company, this means that only 7% of patients treated with bevacizumab as part of subsequent therapy would have been eligible to receive this treatment at baseline in accordance with the specifications in the SmPC.

It is understandable that, based on the specifications in the SmPC, bevacizumab combination therapy would have been an option for a maximum of 27% of patients (across both studies) at the time of enrolment, even though the inclusion criteria did not distinguish between chemotherapy and other treatments regarding the number of prior treatments. The

S3 guideline recommends only chemotherapy for previous lines of treatment [21], so it can be assumed that the number of previous lines of treatment largely corresponds to the number of previous chemotherapeutic regimens. Clear criteria for or against the use of bevacizumab cannot be derived from the SmPC; rather, this is a decision that must be weighed up on an individual basis, taking comorbidities into account. It was assumed that bevacizumab was not an option for some patients due to comorbidities. However, it was not possible to assess this retrospectively on the basis of the medical history of the study populations; consequently, the proportion of these patients was non-quantifiable. It was not appropriate to use the patients who received bevacizumab as subsequent therapy as a basis for assessing the treatment situations at baseline, as the treatment situations at baseline and at the end of the study were different.

Overall, it was assumed that a relevant proportion – though no more than 27% – of the patients would have been eligible for bevacizumab combination therapy at baseline. This uncertainty was taken into account when assessing the certainty of conclusions (see Section I 4.2).

Furthermore, based on the results of MIRASOL and FORWARD 1, conclusions regarding the added benefit of mirvetuximab soravtansine can only be drawn for those patients for whom monotherapy with paclitaxel, PLD or topotecan is a suitable treatment.

Use of alternative chemotherapy dosing regimens in the control arm

In both studies, the administration of paclitaxel, PLD and topotecan differed (see Table 6) from the SmPCs [17-19]. To prove that the dosing regimens used in the studies correspond to everyday clinical practice in Germany, the company submitted various documents: an exploratory search of the dosing recommendations for paclitaxel, PLD and topotecan in the treatment of platinum-resistant ovarian cancer within the context of German and European clinical practice, a search regarding the comparability of alternative topotecan dosages in the treatment of platinum-resistant ovarian cancer, and an extract from a registry containing dosage data from clinical practice [23-25]. It compared the dosages cited in the identified literature with those used in the MIRASOL and FORWARD 1 studies and concluded that the study results were transferable to the German health care context.

The guidelines do not provide any explicit dosage recommendations for paclitaxel, PLD and topotecan; however, for paclitaxel, weekly administration is consistently recommended, contrary to the SmPCs [21,26-29]. The primary literature cited in each of the guidelines specifies both the on-label dosages and those used in the studies in question. The German Society for Haematology and Medical Oncology (DGHO) also recommends the dosages used in the studies and, for paclitaxel and PLD, additionally the dosages specified in the SmPCs [30]. On this basis, the dosages of paclitaxel, PLD and topotecan used in the studies were

considered appropriate. This is also in line with the discussion at the oral hearing of the previous benefit assessment procedure [31].

Pretreatment to prevent hypersensitivity reactions caused by mirvetuximab soravtansine and paclitaxel

According to the SmPCs, premedication to prevent hypersensitivity reactions is required for both treatment with mirvetuximab soravtansine and treatment with paclitaxel [16,19], whilst premedication for PLD should be administered only as needed, and the SmPC for topotecan contains no details on this matter [17,18]. However, the study documents only explicitly state the requirement for premedication in relation to mirvetuximab soravtansine, but not for paclitaxel. For all drugs used in the control arm, any premedication was to be given at the discretion of the investigator or according to institutional guidelines. No precise details were available regarding the extent to which premedication for paclitaxel in compliance with the SmPC, which stipulates the use of corticosteroids, antihistamines and H_2 antagonists, was administered; an approximation of these details can only be derived for the MIRASOL study, based on the information on concomitant treatments. No data were available for the relevant subpopulation in the FORWARD 1 study. Overall, during the MIRASOL study, 34% of patients treated with paclitaxel received corticosteroids and 33% received antihistamines. No separate data were available for H_2 antagonists. Consequently, based on this information, a relevant proportion of patients treated with paclitaxel did not receive premedication in accordance with the SmPC. This uncertainty was taken into account in the risk of bias in the results regarding side effects.

Data cuts

MIRASOL

The study is completed and 3 data cuts were available:

- First data-cut (6 March 2023): prespecified final analysis of progression-free survival, planned after at least 330 progression events
- Second data cut (27 October 2023): requested by the European Medicines Agency (EMA)
- Third data-cut (26 September 2024): prespecified final analysis of overall survival, planned after at least 300 deaths

The results from the third data cut of 26 September 2024 were used for the benefit assessment. This concurred with the company's approach.

FORWARD 1

The study is completed and 2 data cuts were available:

- First data-cut (19 February 2019): prespecified final analysis of progression-free survival, planned after 236 progression events
- Second data cut (18 March 2020): final analysis, planned 1 year after the first data cut-off

This benefit assessment used the results from the second data cut of 18 March 2020. This concurred with the company's approach.

Planned duration of follow-up

Table 8 shows the planned duration of follow-up observation of patients for the individual outcomes.

Table 8: Planned duration of follow-up – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice[a]

Study **Outcome category** **Outcome**	**Planned follow-up**
MIRASOL	
Mortality	
Overall survival	Until death, withdrawal of consent or end of study[b]
Morbidity	
Symptoms (EORTC QLQ-C30, EORTC QLQ-OV28, PGIS[c])	Until disease progression or the start of new anticancer therapy
Health status (EQ-5D VAS)	Until disease progression or the start of new anticancer therapy
Health-related quality of life	
EORTC QLQ-C30, EORTC QLQ-OV28	Until disease progression or the start of new anticancer therapy
Side effects	
All outcomes in the side effects category	30 days after the last dose of the study medication
FORWARD 1	
Mortality	
Overall survival	Until death, withdrawal of consent or end of study[d]
Morbidity	
Symptoms (EORTC QLQ-C30, EORTC QLQ-OV28, FOSI)	Until the last dose of the study drug or disease progression
Health status (EQ-5D VAS)	Until the first visit following disease progression
Health-related quality of life	
EORTC QLQ-C30, EORTC QLQ-OV28	Until the last dose of the study drug or disease progression
Side effects	
All outcomes in the side effects category	30 days after the last dose of the study medication

a. With a choice of paclitaxel, pegylated liposomal doxorubicin or topotecan prior to randomization.
b. The study was scheduled to end after the final analysis of overall survival, prespecified after ≥300 deaths.
c. The PGIS was not introduced until protocol amendment 2 in December 2020.
d. The study was scheduled to end one year after the final PFS analysis.

EORTC: European Organisation for Research and Treatment of Cancer; FOSI: Functional Assessment of Cancer Therapy-Ovarian Symptom Index; PGIS: Patient Global Impression of Severity; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-OV28: Quality of Life Questionnaire-Ovarian Cancer 28; RCT: randomized controlled trial; VAS: visual analogue scale

In both studies, overall survival was followed-up until the end of the study, provided that informed consent had not been withdrawn. In MIRASOL, patient-reported outcomes relating to morbidity and health-related quality of life were recorded until disease progression or the start of a new anticancer therapy. In FORWARD 1, these outcomes were recorded until the

last dose of the study medication or until disease progression; the EQ-5D visual analogue scale (VAS) was recorded up to the first visit following disease progression. In both studies, the outcomes in the side effects category were recorded until 30 days after the last dose of the study medication.

The observation periods for the outcomes of morbidity, health-related quality of life and side effects were systematically shorter compared with the observation period for overall survival in both studies, as recording was linked to the end of treatment or disease progression. However, to draw a reliable conclusion on the total study period or the time to patient death, it would also be necessary to record these outcomes for the total period, as was done for survival.

Patient characteristics

Table 9 shows the characteristics of the patients in the studies included.

Table 9: Characteristics of the study populations as well as study/treatment discontinuation – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice[a] (multipage table)

Study	MIRASOL		FORWARD 1	
Characteristic Category	mirvetuximab soravtansine	Chemotherapy[a]	mirvetuximab soravtansine	Chemotherapy[a]
	N[b] = 227	N[b] = 226	N[b] = 82	N[b] = 34
Age [years], mean (SD)	63 (10)	62 (9)	63 (9)	60 (12)
Family origin, n (%)				
White	156 (69)	145 (64)	81 (99)	31 (91)
Asian	28 (12)	25 (11)	0 (0)	2 (6)
Black or African American	8 (4)	5 (2)	0 (0)	1 (3)
Other[c]	3 (1)	2 (1)	1 (1)	0 (0)
Missing	32 (14)	49 (22)	0 (0)	0 (0)
Geographical region, n (%)				
Asia-Pacific	25 (11)	26 (12)	0 (0)	0 (0)
Europe	127 (56)	123 (54)	50 (61)	26 (76)
Middle East	1 (<1)	8 (4)	0 (0)	0 (0)
North America	74 (33)	69 (31)	32 (39)	8 (24)
Baseline weight [kg], mean (SD)[d]	68.5 (15.3)	69.2 (15.7)	71.1 (17.1)	67.8 (13.3)
Baseline AIBW [kg], mean (SD)[d]	59.1 (8.3)	–	60.4 (8.5)	–
Primary tumour site, n (%)				
Epithelial ovarian	182 (80)	182 (81)	68 (84)	31 (91)
Fallopian tube	27 (12)	23 (10)	6 (7)	1 (3)
Primary peritoneal	16 (7)	20 (9)	7 (9)	2 (6)
Other	2 (1)	1 (0)	1 (1)	0 (0)
FIGO stage, n (%)				
Stage I	4 (2)	1 (<1)	0 (0)	0 (0)
Stage II	5 (2)	8 (4)	2 (2)	0 (0)
Stage III	137 (60)	147 (65)	52 (63)	25 (74)
Stage IV	76 (33)	65 (29)	27 (33)	9 (26)
Missing	5 (2)	5 (2)	1 (1)	0 (0)
Any BRCA mutations[e], n (%)				
Positive	29 (13)	36 (16)	11 (13)	3 (9)
BRCA1	24 (11)	29 (13)	8 (10)	3 (9)
BRCA2	9 (4)	7 (3)	3 (4)	0 (0)
Negative/unknown	198 (87)	190 (84)	71 (87)	31 (91)
Time since initial diagnosis to randomization [months][d]				
Mean (SD)	33.4 (20.1)	34.9 (22.3)	27.3 (18.4)	34.0 (25.5)
Median [min; max]	28.5 [9.1; 164.2]	29.2 [8.7; 131.5]	23.9 [8.2; 128.1]	30.6 [7.2; 119.3]

Table 9: Characteristics of the study populations as well as study/treatment discontinuation – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice[a] (multipage table)

Study	MIRASOL		FORWARD 1	
Characteristic Category	mirvetuximab soravtansine	Chemotherapy[a]	mirvetuximab soravtansine	Chemotherapy[a]
	N[b] = 227	N[b] = 226	N[b] = 82	N[b] = 34
Prior lines of treatment, n (%)				
1	29 (13)	34 (15)	53 (65)[f]	20 (59)[f]
2	90 (40)	88 (39)		
3	108 (48)	104 (46)	29 (35)	14 (41)
Prior treatment, n (%)				
PARP inhibitors	124 (55)	127 (56)	13 (16)	4 (12)
taxanes	227 (100)	224 (99)	77 (94)	34 (100)
doxorubicin / pegylated liposomal doxorubicin	130 (57)	133 (59)	35 (43)	12 (35)
topotecan	1 (<1)	2 (1)	0 (0)	0 (0)
bevacizumab	138 (61)	143 (63)	41 (50)	18 (53)
Platinum-free interval, n (%)				
≤3 months	88 (39)	99 (44)	32 (39)	15 (44)
>3 to ≤6 months	138 (61)	124 (55)	46 (56)	17 (50)
>6 months	1 (<1)	3 (1)	4 (5)	2 (6)
ECOG PS, n (%)				
0	130 (57)	120 (53)	47 (57)	21 (62)
1	97 (43)	101 (45)	34 (41)	13 (38)
2	0 (0)	3 (1)	0 (0)	0 (0)
Missing	0 (0)	2 (1)	1 (1)	0 (0)
FRα PS2+ score, [%]				
Mean (SD)	85.6 (8.97)	86.2 (8.54)	ND	ND
Median [min; max]	85 [70; 100]	85 [75; 100]	ND	ND
Histology, n (%)				
High-grade serous	227 (100)	225 (100)	ND[g]	ND[g]
Endometrioid	0 (0)	1 (<1)	ND	ND
Chemotherapy selected prior to randomization, n (%)				
paclitaxel	–	92 (41[h])	–	13 (38[h])
pegylated liposomal doxorubicin	–	81 (36[h])	–	15 (44[h])
topotecan	–	53 (23[h])	–	6 (18[h])
Treatment discontinuation, n (%)	217 (96)[i]	225 (100)[i]	79 (96)[j]	34 (100)[j]
Study discontinuation, n (%)	149 (66)[k]	180 (80)[k]	79 (96)[l]	34 (100)[l]

Table 9: Characteristics of the study populations as well as study/treatment discontinuation – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice[a] (multipage table)

Study Characteristic Category	MIRASOL		FORWARD 1	
	mirvetuximab soravtansine	Chemotherapy[a]	mirvetuximab soravtansine	Chemotherapy[a]
	N[b] = 227	N[b] = 226	N[b] = 82	N[b] = 34

a. With a choice of paclitaxel, pegylated liposomal doxorubicin or topotecan prior to randomization.
b. Number of randomized patients who received at least one dose of the respective treatment. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
c. Institute's calculation, pooled from the categories 'native Americans or Alaskans' and 'others'.
d. The figures are based on different patient numbers. Weight: MIRASOL: 213 vs. 198 patients, FORWARD 1: 79 vs. 32 patients; AIBW: MIRASOL: 218 patients, FORWARD 1: 79 patients; time since initial diagnosis to randomization: MIRASOL: 208 vs. 208 patients, FORWARD 1: 73 vs. 33 patients.
e. BRCA status was recorded solely on the basis of medical history and was not systematically assessed.
f. No separate data regarding the first or second prior lines of treatment.
g. In the total population of FORWARD 1, the proportion of patients with high-grade serous histology was 99% vs. 97%.
h. Institute's calculation.
i. Frequent reasons for treatment discontinuation in the intervention arm vs. the control arm (percentages based on randomized patients): disease progression (76% vs. 66%), AEs (11% vs. 12%), withdrawal of consent (2% vs. 5%). This includes 4% vs. 8% of patients who never started treatment. The data also include patients who died during treatment with the study medication (intervention arm: 1% vs. control arm: <1%).
j. Frequent reasons for treatment discontinuation in the intervention arm vs. the control arm (percentages based on randomized patients): disease progression (77% vs. 71%), AEs (11% vs. 9%), withdrawal of consent (2% vs. 3%). This includes 4% vs. 6% of patients who never started treatment. The data also include patients who died during treatment with the study medication (intervention arm: 2% vs. control arm: 3%).
k. Most frequent reason for study discontinuation in the intervention vs. control arm (percentages refer to randomized patients): withdrawal of consent (4% vs. 10%). The data also include patients who died during the course of the study (intervention arm: 56% vs. control arm: 66%).
l. Frequent reasons for study discontinuation in the intervention arm vs. the control arm (percentages based on randomized patients): investigator decision (28% vs. 18%), withdrawal of consent (2% vs. 3%). The data also include patients who died during the course of the study (intervention arm: 62% vs. control arm: 74%).

AIBW: adjusted ideal body weight; BRCA: breast cancer associated gene; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FIGO: Fédération Internationale de Gynécologie et d'Obstétrique; FRα: folate receptor-alpha; n: number of patients in the category; N: number of randomized patients; ND: no data; PARP: poly(adenosine diphosphate [ADP]-ribose) polymerase; PS2+: positive staining 2+; RCT: randomized controlled trial; SD: standard deviation

The demographic and clinical characteristics of the patients were largely comparable both between the treatment arms of the studies and between the 2 studies. On average, the patients were 63 (MIRASOL) and 62 (FORWARD 1) years old at baseline. The majority of patients were initially diagnosed with epithelial ovarian cancer. In the MIRASOL study, all but one patient had high-grade serous histology. No information was available on this for the subpopulation of the FORWARD 1 study; in the overall population, the figures were 99%

versus 97%. In MIRASOL, the majority of patients (approximately 87%) had received 2 or 3 prior lines of therapy. No separate data were available for FORWARD 1 on patients who received 1 or 2 prior lines of therapy. The proportion of patients who had received 3 prior lines of therapy was 37% in the FORWARD 1 study, which was slightly lower than in the MIRASOL study (47%). However, the proportions between the different study arms were comparable in each study. The proportion of patients with tumours with a positive mutation status for the breast cancer-associated gene (BRCA) 1 or 2 was comparable in both studies. However, BRCA status was recorded solely on the basis of medical history and was not systematically recorded (see also Section I 4.4). A look at previous treatments revealed differences in the proportion of patients who had previously received poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors. In the MIRASOL study, the proportion in both arms (55% versus 56%) was higher than in the FORWARD 1 study (16% versus 12%). According to the company, this can be explained by the fact that, at the start of the FORWARD 1 study, marketing authorization for the PARP inhibitors olaparib and niraparib had only recently been granted for the treatment of ovarian cancer. With regard to prior therapy with PARP inhibitors, the MIRASOL study thus was a better representation of the current health care standard in Germany than the FORWARD 1 study. In the subpopulation of the FORWARD 1 study, differences were observed in the proportion of patients with Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) Stage III between the intervention arm (63%) and the control arm (74%), as well as in the time since initial diagnosis (intervention arm: median 23.9 months; control arm: median 30.6 months).

In both studies, all patients in the control arm and 96% of those in the intervention arm discontinued treatment. The most common reason was disease progression (76% versus 66% [MIRASOL], and 77% versus 71% [FORWARD 1]). The majority of patients in MIRASOL discontinued the study, and almost all patients in FORWARD 1 discontinued the study. These figures also include patients who died during the course of the study (56% versus 66% [MIRASOL] and 62% versus 74% [FORWARD 1]). In the MIRASOL study, the most common reason for study discontinuation was withdrawal of consent (4% versus 10%), whilst in the FORWARD 1 study it was investigator decision (28% versus 18%).

As neither study was intended to include patients with an ECOG PS ≥2 or patients with primary platinum-refractory tumours, it remained unclear whether the study results were transferable to these patients, who are also covered by the therapeutic indication under assessment.

Information on the course of the study

Table 10 shows the mean and median treatment durations of the patients as well as the mean and median observation periods for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice[a]

Study **Duration of the study phase** **Outcome category** **Outcome**	**MIRASOL** **(data cut-off: 26 September 2024)**		**FORWARD 1** **(data cut-off: 18 March 2020)**	
	mirvetuximab soravtansine **N[b] = 227**	**Chemotherapy[a]** **N[b] = 226**	**mirvetuximab soravtansine** **N[b] = 82**	**Chemotherapy[a]** **N[b] = 34**
Treatment duration [weeks]	N = 218	N = 207	N = 79	N = 32
Median [min; max]	21.6 [3.0; 158.3]	12.9 [2.0; 120.0]	ND[c]	ND[c]
Mean (SD)	30.3 (26.5)	17.7 (15.1)	ND[c]	ND[c]
Number of cycles				
Median [min; max]	7.0 [1; 51]	3.0 [1; 30]	8.0 [1.0; 42.0]	3.5 [1.0; 16.0]
Mean (SD)	9.2 (7.9)	4.5 (3.8)	10.5 (9.1)	5.0 (4.0)
Observation period [weeks]				
Overall survival[d]				
Median [min; max]	65.6 [0.1; 194.7]	49.1 [0.1; 172.9]	67.8 [0.3; 134.4]	47.8 [0.6; 108.9]
Mean (SD)	73.3 (49.3)	57.3 (43.2)	63.2 (38.0)	50.3 (36.2)
Morbidity				
Symptoms (EORTC QLQ-C30, QLQ-OV28, PGIS, FOSI)	No suitable data[e]		No suitable data[e]	
Health status (EQ-5D VAS)	No suitable data[e]		No suitable data[e]	
Health-related quality of life (EORTC QLQ-C30, QLQ-OV28)	No suitable data[e]		No suitable data[e]	
Side effects (all AEs)[f]				
Median [min; max]	23.5 [1.7; 160.1]	15.9 [2.3; 120.8]	ND	ND
Mean (SD)	32.1 (26.5)	20.1 (15.1)	ND	ND

a. With a choice of paclitaxel, pegylated liposomal doxorubicin or topotecan prior to randomization.
b. Number of randomized patients.
c. No data are available for the subpopulation presented in the dossier.
d. The median observation period, determined using the inverse Kaplan-Meier method, is available in Module 5 only for the intervention arm: 132.6 [125.0; 146.4] (conversion from months to weeks by the Institute); the observation periods shown were therefore calculated on the basis of the observed time for all patients.
e. For an explanation, see Section I 4.1.
f. No information is available on how the observation period was calculated.

EORTC: European Organisation for Research and Treatment of Cancer; FOSI: Functional Assessment of Cancer Therapy-Ovarian Symptom Index; M: max; min: minimum; N: number of analysed patients; ND: no data; PGIS: Patient Global Impression of Severity; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-OV28: Quality of Life Questionnaire-Ovarian Cancer 28; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

No information on the treatment duration was available for the subpopulation of the FORWARD 1 study. A comparison with the MIRASOL study was only possible on the basis of the number of treatment cycles. This showed that, in both studies, patients in the intervention

arm underwent more than twice as many treatment cycles – a median of 7.0 (MIRASOL) and 8.0 (FORWARD 1) – than in the control arm (3.0 [MIRASOL] and 3.5 cycles [FORWARD 1]).

The median observation periods for overall survival were comparable between the studies for the respective study arms, and were longer in the intervention arms than in the control arms. No suitable data were available for any of the morbidity and health-related quality of life outcomes (see Section I 4.1); consequently, no information is provided here regarding the observation periods for these outcomes. For the outcome category of side effects, no information was available on the mean or median observation period for the FORWARD 1 study. As the observation period for side effects was linked to the end of treatment (plus 30 days) and there was a relevant difference between the 2 study arms in the number of treatment cycles administered, it was also assumed that there was a relevant difference in the observation period for side effects. In MIRASOL, the observation period for side effects was longer in the intervention arm than in the control arm (a median of 23.5 versus 15.9 weeks).

Table 11 and Table 12 show the subsequent therapies that patients received after discontinuing the study medication in MIRASOL and FORWARD 1.

Table 11: Information on subsequent antineoplastic therapies – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice[a] (MIRASOL)

Drug class	Patients with subsequent therapy n (%)	
	mirvetuximab soravtansine N = 227	Chemotherapy[a] N = 226
Patients with first subsequent therapy[b]	140 (61.7)	136 (60.2)
Other (including study drugs)	15 (10.7)	14 (10.3)
Anthracyclines	40 (28.6)	13 (9.6)
Chemotherapy (other)	12 (8.6)	26 (19.1)
gemcitabine	20 (14.3)	28 (20.6)
Hormonal therapy	0 (0)	2 (1.5)
Kinase inhibitors	3 (2.1)	5 (3.7)
mirvetuximab soravtansine	0 (0)	5 (3.7)
PARP inhibitors	6 (4.3)	3 (2.2)
PD-1/PD-L1 inhibitors	4 (2.9)	8 (5.9)
Platinum-based therapy	23 (16.4)	16 (11.8)
Taxanes	52 (37.1)	35 (25.7)
Topoisomerase inhibitors	3 (2.1)	7 (5.1)
VEGF-targeted therapy	21 (15)	21 (15.4)
Patients with any subsequent therapy[b]	152 (67.0)	147 (65.0)
Other	22 (14.5)	24 (16.3)
Anthracyclines	57 (37.5)	21 (14.3)
bevacizumab	42 (27.6)	35 (23.8)
Chemotherapy (other)	50 (32.9)	56 (38.1)
gemcitabine	54 (35.5)	58 (39.5)
Hormonal therapy	7 (4.6)	5 (3.4)
Kinase inhibitors	12 (7.9)	10 (6.8)
mirvetuximab soravtansine	2 (1.3)	16 (10.9)
PARP inhibitors	10 (6.6)	7 (4.8)
PD-1/PD-L1 inhibitors	14 (9.2)	16 (10.9)
Platinum-based therapy	42 (27.6)	42 (28.6)
Taxanes	80 (52.6)	59 (40.1)
topotecan	20 (13.2)	24 (16.3)

a. With a choice of paclitaxel, pegylated liposomal doxorubicin or topotecan prior to randomization.
b. The following percentages are based on the number of patients with subsequent therapy; Institute's calculation.

n: number of patients with subsequent therapy; N: number of analysed patients; PARP: poly(adenosine diphosphate [ADP]-ribose) polymerase; PD-1: programmed cell death protein 1; PD-L1: programmed cell death-ligand 1; RCT: randomized controlled trial; VEGF: vascular endothelial growth factor

Table 12: Information on subsequent antineoplastic therapies – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice[a] (FORWARD 1)

Drug class	Patients with subsequent therapy, n (%)	
	mirvetuximab soravtansine N = 82	Chemotherapy[a] N = 34
Patients with first subsequent therapy[b]	44 (53.7)	17 (50.0)
Other (including study drugs)	4 (9.1)	6 (35.3)
Anthracyclines	12 (27.3)	3 (17.6)
Chemotherapy (other)	1 (2.3)	2 (11.8)
gemcitabine	9 (20.5)	3 (17.6)
Hormonal therapy	1 (2.3)	0 (0)
Kinase inhibitors	1 (2.3)	0 (0)
PARP inhibitors	1 (2.3)	1 (5.9)
Platinum-based therapy	8 (18.2)	3 (17.6)
Taxanes	12 (27.3)	4 (23.5)
VEGF-targeted therapy	11 (25.0)	2 (11.8)
Patients with any subsequent therapy[b]	44 (53.7)	17 (50.0)
Other (including study drugs)	8 (18.2)	6 (35.3)
Anthracyclines	18 (40.9)	3 (17.6)
Chemotherapy (other)	4 (9.1)	4 (23.5)
gemcitabine	15 (34.1)	5 (29.4)
Hormonal therapy	4 (9.1)	0 (0)
Kinase inhibitors	1 (2.3)	0 (0)
PARP inhibitors	3 (6.8)	1 (5.9)
Platinum-based therapy	11 (25.0)	4 (23.5)
Taxanes	20 (45.5)	8 (47.1)
topotecan	4 (9.1)	1 (5.9)
VEGF-targeted therapy	17 (38.6)	5 (29.4)

a. With a choice of paclitaxel, pegylated liposomal doxorubicin or topotecan prior to randomization.
b. The following percentages are based on the number of patients with subsequent therapy; Institute's calculation.

n: number of patients with subsequent therapy; N: number of analysed patients; PARP: poly(adenosine diphosphate [ADP]-ribose) polymerase; PD-1: programmed cell death protein 1; PD-L1: programmed cell death-ligand 1; RCT: randomized controlled trial; VEGF: vascular endothelial growth factor

In both studies, treatment with the study medication was conducted until disease progression, unacceptable toxicity, withdrawal of consent, death or the end of the study. In both studies, subsequent antineoplastic therapy was possible without restriction.

In MIRASOL, 190 (84%) in the intervention arm versus 158 (70%) in the control arm experienced disease progression (excluding deaths) during the course of the study, compared

with 61 (74%) versus 25 (74%) patients in FORWARD 1. From these patients, 140 (74%) in the intervention arm versus 136 (86%) in the control arm of MIRASOL received a first subsequent therapy, compared with 44 (72%) versus 17 (68%) patients in FORWARD 1. Thus, the majority of patients for whom subsequent therapy was, in principle, indicated due to disease progression did receive such therapy. The same picture emerged for the FORWARD 1 study with regard to any subsequent therapies. It was unclear why the proportion of patients with first subsequent therapy in the MIRASOL study was lower than the proportion of patients with any subsequent therapy.

The majority of patients in MIRASOL and FORWARD 1 received taxanes, anthracyclines, VEGF-targeted therapies, gemcitabine or other chemotherapies (including platinum-based therapies) as their first subsequent therapy. The distribution of the drugs or classes of drugs used in any subsequent therapies (all subsequent therapies beyond the first subsequent therapy) was comparable to the first subsequent therapies. In MIRASOL, 3.7% of patients in the control arm received mirvetuximab soravtansine as their first subsequent therapy (based on the proportion of patients receiving first subsequent therapy). When considering all subsequent therapies (beyond the first subsequent therapy), the proportion of patients treated with mirvetuximab soravtansine in the MIRASOL study increased to 10.9% in the control arm, whilst in the intervention arm there was an additional 1.3% of patients who received mirvetuximab soravtansine (based on the proportion of patients receiving any subsequent therapy).

The S3 guideline does not make any specific treatment recommendations for subsequent lines of treatment [21]. Analogous to the treatment situation at baseline, the DGHO recommends subsequent therapy with paclitaxel, PLD or topotecan, either as monotherapy or in combination with bevacizumab, followed, where appropriate, by bevacizumab and additionally treosulfan [26]. At the time both studies were conducted, mirvetuximab soravtansine was not an approved treatment option. Given the small proportion of patients who received mirvetuximab soravtansine as subsequent therapy, this had no consequence for the benefit assessment. Overall, given the lack of clear recommendations regarding the later lines of treatment for this condition, the use of subsequent therapies was considered to be largely appropriate.

Meta-analytical summary of MIRASOL and FORWARD 1

The company conducted a meta-analytical summary of the results of MIRASOL and FORWARD 1 based on individual patient data. It justified this on the basis of the close similarity of the study protocols, the largely identical inclusion criteria, the same operationalization of the outcomes, and the identical research questions and interventions. It added that the demographic and disease-specific characteristics of the patients included in both studies were comparable, but that there was a difference in the proportion of patients who had been

previously treated with PARP inhibitors. According to the company, this can be explained by the fact that, at the start of the FORWARD 1 study, marketing authorization for the PARP inhibitors olaparib and niraparib had only recently been granted for the treatment of ovarian cancer. According to the company, this difference had no impact on the high degree of comparability between the 2 study populations.

The company's reasoning was appropriate. In addition, the company conducted interaction tests for heterogeneity between the studies as part of the meta-analysis. No significant results were observed for the outcomes relevant to the benefit assessment. Analogous to the company's approach, the results of the meta-analysis were used for this benefit assessment.

Risk of bias across outcomes (study level)

Table 13 shows the risk of bias across outcomes (risk of bias at study level).

Table 13: Risk of bias across outcomes (study level) – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice[a]

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
MIRASOL	Yes	Yes	No	No	Yes	Yes	Low
FORWARD 1	Yes	Yes	No	No	Yes	Yes	Low

a. With a choice of paclitaxel, pegylated liposomal doxorubicin or topotecan prior to randomization.
RCT: randomized controlled trial

The risk of bias across outcomes was rated as low for both studies.

Limitations resulting from the open-label study design are described in Section I 4.2 under outcome-specific risk of bias.

Transferability of the study results to the German health care context

According to the company, the study populations are comparable to patients in the German health care context in terms of prior therapies, the proportion of patients with BRCA1 mutation, the location of the primary tumour, the FIGO stage at the time of the initial diagnosis, and the European family origin of most patients. With regard to the dosages of chemotherapy used, which deviated from the SmPC information, the company stated that evidence from guidelines, practice guidelines and studies, which it had identified through a systematic and exploratory search, confirmed that the dosages and dosing regimens used

concurred with the German health care context (see also the Section on the implementation of the ACT). Furthermore, the company stated that the treatment options in the control arms of the studies are transferable to the German health care context. It explained that, given the open recommendation on this matter in the S3 guideline and the specifications set out in the SmPC, combination therapy with bevacizumab, which was not an option in the studies, could only be considered for a selected patient population. According to the company, it could be assumed that most patients who met the requirements set out in the SmPC and who had neither contraindications nor an increased risk of comorbidity had already been treated with bevacizumab as part of previous treatment regimens.

The company did not provide any further information on the transferability of the study results to the German health care context. For the transferability of the study results, see also the information on the implementation of the ACT in Section I 3.2.

I 4 Results on added benefit

I 4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - Overall survival
- Morbidity
  - Symptoms
    - recorded using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), EORTC QLQ-Ovarian Cancer 28 (OV28), Patient Global Impression of Severity (PGIS) and Functional Assessment of Cancer Therapy-Ovarian Symptom Index (FOSI)
  - Health status
    - recorded using the EQ-5D VAS
- Health-related quality of life
  - recorded using the EORTC QLQ-C30 and QLQ-OV28
- Side effects
  - Serious AEs (SAEs)
  - Severe AEs (CTCAE grade ≥3)
  - Discontinuation due to AEs
  - Eye disorders (System Organ Class [SOC], AEs and severe AEs [CTCAE grade ≥3])
  - Pneumonitis (Preferred Term [PT] collection, AEs)
  - Other specific AEs, if any

The selection of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A).

Table 14 shows for which outcomes data were available in the included studies.

Table 14: Matrix of outcomes – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice[a]

Study	Outcomes												
	Overall survival	Symptoms (EORTC QLQ-C30, EORTC QLQ-OV28)	Symptoms (PGIS)	Symptoms (FOSI)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-OV28)	SAEs	Severe AEs[b]	Discontinuation due to AEs	Eye disorders (SOC, AEs)	Eye disorders (SOC, severe AEs[b])	Pneumonitis (PT collection, AEs)[c]	Further specific AEs[d]
MIRASOL	Yes	No[e]	No[e]	No[f]	No[e]	No[e]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
FORWARD 1	Yes	No[e]	No[f]	No[e]	No[e]	No[e]	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. With a choice of paclitaxel, pegylated liposomal doxorubicin or topotecan prior to randomization.
b. Severe AEs are operationalized as CTCAE grade ≥3 AEs.
c. The operationalization of the adverse event of special interest (AESI) from the MIRASOL study is used, which includes the PTs 'interstitial lung disease', 'organizing pneumonia', 'pneumonitis', 'pulmonary fibrosis' and 'respiratory failure'.
d. The following events (coded according to MedDRA) are considered: dyspnoea (PT, AEs), stomatitis (PT, AEs), skin and subcutaneous tissue disorders (SOC, AEs), small intestinal obstruction (PT, SAEs), blood and lymphatic system disorders (SOC, severe AEs[b]) and fatigue (PT, severe AEs[b]).
e. No suitable data available; see the following text section for reasons.
f. Outcome not recorded.

AE: adverse event; AESI: adverse event of special interest; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; FOSI: Functional Assessment of Cancer Therapy-Ovarian Symptom Index; MedDRA: Medical Dictionary for Regulatory Activities; PGIS: Patient Global Impression of Severity; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-OV28: Quality of Life Questionnaire-Ovarian Cancer 28; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Patient-reported outcomes on morbidity and health-related quality of life

In Module 4 A and H, the company presented the mean change from baseline as a mixed-effects model with repeated measures (MMRM) analysis for the patient-reported outcomes in the categories of morbidity and health-related quality of life (EORTC QLQ-C30, QLQ-OV28, PGIS, FOSI and EQ-5D VAS). The PGIS was only recorded in MIRASOL and the FOSI only in FORWARD 1, so results were presented only for the respective studies. In the MIRASOL study, the PRO instruments were initially recorded every 9 (+/–1) weeks until disease progression or the end of treatment. From protocol amendment 2 onwards, recording was carried out on Day 1 of each treatment cycle (3 or 4 weeks) up to Week 24, and then every 3 months until disease progression or the start of a new anticancer therapy. In the FORWARD 1 study, the EQ-5D VAS was also recorded on Day 1 of each treatment cycle up to the first post-progression

visit. The other PRO instruments in FORWARD 1 were recorded every 8 weeks in patients with a 4-week treatment cycle (paclitaxel, PLD and topotecan on a 4-week regimen), and every 9 weeks in patients on a 3-week treatment cycle (mirvetuximab soravtansine and topotecan on a 3-week regimen), until disease progression. Due to the differences in the timepoints of recording between the studies, the company used only the results from MIRASOL to derive the added benefit for all patient-reported outcomes except the EQ-5D VAS. The company combined the recordings, which took place at different times between the study arms and within the control arm, using a 'windowing' method. The interval between the planned recordings was to be as short as possible and no longer than one week. Recordings for which no corresponding recording from the other treatment arm – with a maximum time interval of one week – could be identified were excluded from the analyses. In addition to the main analyses, the company presented sensitivity analyses for the MIRASOL study regarding the EORTC QLQ-C30, QLQ-OC28 and EQ-5D VAS outcomes, which included only those patients enrolled from protocol amendment 2 onwards.

Timepoints of recording and method of analysis

The company's approach, in the given situation, to use only the results from the MIRASOL study for the analyses of the EORTC QLQ-C30 and QLQ-OV28 was considered appropriate. The method employed by the company to combine different timepoints of recording between the study arms and within the control arm was considered appropriate in the given situation. In principle, where treatments with different cycle lengths are being compared, very frequent recordings should be conducted.

Return rates

For the EORTC QLQ-C30 and the QLQ-OV28 (data refer to the MIRASOL study) and the EQ-5D VAS (data refer to the meta-analysis), a high proportion of patients – in each case exceeding 20% – were found to have missing values at baseline; these patients were therefore not included in the analyses of the mean change from baseline. Furthermore, sharp declines in return rates were already seen at early timepoints of recording, with some variation between the study arms. The return rates for the EORTC QLQ-C30, the QLQ-OV28 and the EQ-5D VAS fell below 70% as early as the first subsequent recording. These return rates rose slightly again at the second subsequent recording, before falling continuously. This short-term increase was attributable to the more frequent recording introduced in the MIRASOL study under protocol amendment 2. For the PGIS (recorded only in the MIRASOL study), the return rates were already below 60% at baseline. No separate figures on return rates were available for the FOSI. The analyses presented in Module 4 H showed that, as early as the first scheduled subsequent recording (Weeks 8/9), fewer than 70% of patients in the control arm responded, and that the return rate dropped sharply in subsequent recordings. It was unclear why, contrary to the planned approach, more frequent recordings took place for the FOSI in some instances. It was planned to carry out recordings every 8/9 weeks; however, the company provided analyses

based on more frequent recording intervals. The low return rates described were found in both the main analyses and the sensitivity analyses (where return rates were below 70% for the EQ-5D VAS at the first subsequent recording, and for the EORTC QLQ-C30 and the QLQ-OV28 at the second subsequent recordings), which only included patients from the MIRASOL study who were enrolled from protocol amendment 2 onwards. The analyses presented by the company for the outcomes EORTC QLQ-C30, QLQ-OV28, PGIS, FOSI and EQ-5D VAS were therefore not suitable for inclusion in the benefit assessment.

Side effects

Frequent adverse events

The company provided information in the dossier on frequent AEs in the individual studies and the meta-analysis. A comparison of the tables showed that the list of frequent AEs in the meta-analysis was incomplete, as not all AEs that occurred in at least 10 patients in the meta-analysis population were included in the relevant table. The proportion of potentially missing AEs was assessed to be small, and this was of no consequence for the benefit assessment.

Eye disorders

The recording of eye disorders without defining their operationalization was prespecified in both studies. In the MIRASOL study, the operationalization via the SOC 'eye disorders' was determined post hoc. In Module 4 A, the company presented analyses for the individual studies and based on the meta-analysis. The operationalization of eye disorders using the SOC 'eye disorders' was considered to be appropriate. Contrary to the SmPC, steroid-containing eye drops were to be administered not after the onset of CTCAE grade ≥2 corneal side effects [16], but prophylactically before (only in MIRASOL) and after (in both studies) each dose (see Section I 3.2). It was unclear whether this had any impact on the occurrence of eye disorders in MIRASOL and FORWARD 1 in terms of their frequency and severity. This was taken into account when interpreting the results regarding this outcome.

Operationalization of pneumonitis

For the specific AEs pneumonitis, the Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) 'interstitial lung disease' (narrow scope) was considered a sufficient approximation to represent the AE. In Module 4 A, the company presented analyses for pneumonitis based on a PT collection for the individual studies and based on the meta-analysis. This PT collection was defined post hoc for the MIRASOL study and comprised the PTs interstitial lung disease, organizing pneumonia, pneumonitis, pulmonary fibrosis and respiratory failure. By comparing the AEs that occurred with the SMQ 'interstitial lung disease' (narrow scope), it was possible to use the PT collection presented by the company as a suitable operationalization for this benefit assessment.

I 4.2 Risk of bias

Table 15 describes the risk of bias for the results of the relevant outcomes.

Table 15: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice[a]

Study	Study level	Outcomes												
		Overall survival	Symptoms (EORTC QLQ-C30, EORTC QLQ-OV28)	Symptoms (PGIS)	Symptoms (FOSI)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-OV28)	SAEs	Severe AEs[b]	Discontinuation due to AEs	Eye disorders (SOC, AEs)	Eye disorders (SOC, severe AEs[b])	Pneumonitis (PT collection, AEs)[c]	Further specific AEs[d]
MIRASOL	L	H[e]	–[f]	–[f]	–[g]	–[f]	–[f]	H[e]	H[e]	H[h]	H[e, i]	H[e]	H[e, i]	H[e, i]
FORWARD 1	L	L	–[f]	–[g]	–[f]	–[f]	–[f]	H[e]	H[e]	H[h]	H[e, i]	H[e]	H[e, i]	H[e, i]

a. With a choice of paclitaxel, pegylated liposomal doxorubicin or topotecan prior to randomization.
b. Severe AEs are operationalized as CTCAE grade ≥3 AEs.
c. The operationalization of the adverse event of special interest (AESI) from the MIRASOL study is used, which includes the PTs 'interstitial lung disease', 'organizing pneumonia', 'pneumonitis', 'pulmonary fibrosis' and 'respiratory failure'.
d. The following events (coded according to MedDRA) are considered: dyspnoea (PT, AEs), stomatitis (PT, AEs), skin and subcutaneous tissue disorders (SOC, AEs), small intestinal obstruction (PT, SAEs), blood and lymphatic system disorders (SOC, severe AEs[b]) and fatigue (PT, severe AEs[b]).
e. Incomplete observations for potentially informative reasons.
f. No suitable data available; see Section I 4.1 for the reasoning.
g. Outcome not recorded.
h. Lack of blinding in the presence of subjective decision on treatment discontinuation.
i. Lack of blinding in subjective recording of outcomes; for the other specific AEs, this applies only to non-serious or non-severe AEs.

AE: adverse event; AESI: adverse event of special interest; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; FOSI: Functional Assessment of Cancer Therapy-Ovarian Symptom Index; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PGIS: Patient Global Impression of Severity; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 28; QLQ-OV28: Quality of Life Questionnaire-Ovarian Cancer 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

With regard to the results for the overall survival outcome in the MIRASOL study, there was a high risk of bias due to the high, differing proportions of study discontinuations at the patient's request (4% versus 10%) and, in particular, the unclear, differing proportions of early censorings (6% versus 10%) for potentially informative reasons. It was unclear to what extent these data also included patients who did not receive treatment. Here, too, there was a

difference in proportions of 4% versus 8%. For FORWARD 1, the risk of bias of the results on overall survival was assessed as low. However, notable were the high proportions of study discontinuations based on the decision of the investigator (28% versus 18%). No information was available as to the reasons behind this decision. However, these study discontinuations only occurred late in the study (after the first data cut-off) and did not call the observed treatment effect into question.

The results for the outcomes in the side effects category each had a high risk of bias. For SAEs (overall rate, other specific AEs) and severe AEs (overall rate, eye disorders, other specific AEs), this was attributable to shortened observations for potentially informative reasons in the presence of different observation periods. These result from the fact that the recording of side effects was linked to the end of the study medication (see Table 8). For the results relating to all other outcomes in the category of side effects that are non-severe/non-serious, there was a high risk of bias due to the unblinded study design, involving subjective outcome recording / subjective decisions to discontinue treatment, as well as incomplete observations for potentially informative reasons in the presence of different observation periods. In principle, the uncertainty associated with premedication to prevent hypersensitivity reactions during treatment with paclitaxel must also be taken into account for the outcomes in the side effects category (see Section I 3.2). Due to the wide range of symptoms of hypersensitivity reactions, they cannot be clearly assigned to specific SOCs or PTs. Overall, this uncertainty contributed to the high risk of bias in the results of the overall AE rates (severe AEs, SAEs, discontinuation due to AEs) as well as specific AEs such as skin and subcutaneous tissue disorders or dyspnoea.

No suitable data were available for the outcomes relating to symptoms, health status and health-related quality of life; therefore, the risk of bias was not assessed for these outcomes.

Summary assessment of the certainty of conclusions

Irrespective of the assessment of the risk of bias, there were relevant uncertainties for the MIRASOL and FORWARD 1 studies regarding the absence of an additional treatment option with bevacizumab in the control arm (see Section I 3.2). For FORWARD 1, there was additional uncertainty because the FRα status was not reclassified for all patients (see Section I 3.2). Overall, the certainty of conclusions for both studies was limited. Based on the results of the meta-analysis of 2 studies with limited certainty of conclusions, no more than an indication, for example of an added benefit, could therefore be derived.

I 4.3 Results

Table 16 and Table 17 summarize the results of the comparison between mirvetuximab soravtansine and the ACT in adult patients with FRα-positive, platinum-resistant high grade serous epithelial ovarian cancer who have received 1 to 3 prior systemic treatment regimens. Where necessary, calculations conducted by the Institute are provided in addition to the data

from the company's dossier. For the outcome eye disorders (severe AEs) with 0 events in the control arm, no data were available for the effect estimate of the time-to-event analyses. One way to obtain point and interval estimates for time-to-event analyses in such situations is to use the Firth correction to the Cox model [32-35] in combination with profile likelihood methods for the 95% confidence intervals.

The Kaplan-Meier curves for the time-to-event analyses of the individual studies are presented in I Appendix B of the full dossier assessment. Results on common AEs, SAEs, severe AEs as well as discontinuations due to AEs are presented in I Appendix C of the full dossier assessment.

Table 16: Results (mortality, side effects) – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice[a] (multipage table)

Outcome category **Outcome** **Study**	**mirvetuximab soravtansine**		**Chemotherapy[a]**		**mirvetuximab soravtansine vs. chemotherapy[a]**
	N	**Median time to event in weeks [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in weeks [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value[b]**
Mortality					
Overall survival					
MIRASOL	227	73.3 [62.4; 86.0][c] 162 (71)	226	58.0 [49.4; 65.9][c] 177 (78)	0.67 [0.54; 0.84]; <0.001
FORWARD 1	82	71.4 [54.0; 89.1][c] 51 (62)	34	49.6 [26.6; 78.7][c] 25 (74)	0.66 [0.40; 1.08]; 0.104
Total[d]					0.67 [0.55; 0.82]; <0.001

Table 16: Results (mortality, side effects) – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice[a] (multipage table)

Outcome category Outcome Study	mirvetuximab soravtansine		Chemotherapy[a]		mirvetuximab soravtansine vs. chemotherapy[a]
	N	Median time to event in weeks [95% CI] Patients with event n (%)	N	Median time to event in weeks [95% CI] Patients with event n (%)	HR [95% CI]; p-value[b]
Side effects					
AEs (supplementary information)					
MIRASOL	218	0.5 [0.3; 0.9] 211 (97)	207	1.0 [0.9; 1.1] 194 (94)	–
FORWARD 1	79	0.4 [0.3; 0.6] 79 (100)	32	0.5 [0.3; 1.0] 32 (100)	–
SAEs					
MIRASOL	218	NA [59.9; NC] 55 (25)	207	33.7 [28.6; NC] 69 (33)	0.55 [0.38; 0.79]; 0.001
FORWARD 1	79	97.3 [97.3; NC] 22 (28)	32	30.7 [7.6; NC] 13 (41)	0.44 [0.21; 0.92]; 0.033
Total[d]					0.51 [0.37; 0.71]; 0.001
Severe AEs[e]					
MIRASOL	218	31.6 [21.1; 47.7] 97 (44)	207	14.1 [9.7; 17.7] 113 (55)	0.54 [0.41; 0.72]; <0.001
FORWARD 1	79	31.9 [19.0; NC] 37 (47)	32	9.0 [3.1; 10.4] 20 (62)	0.44 [0.25; 0.79]; 0.008
Total[d]					0.51 [0.40; 0.66]; <0.001
Discontinuation due to AEs					
MIRASOL	218	NA [73.9; NC] 25 (11)	207	79.1 [55.3; NC] 31 (15)	0.44 [0.25; 0.78]; 0.004
FORWARD 1	79	NA [61.1; NC] 11 (14)	32	NA [18.7; NC] 7 (22)	0.41 [0.15; 1.11]; 0.089
Total[d]					0.44 [0.27; 0.73]; 0.001

Table 16: Results (mortality, side effects) – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice[a] (multipage table)

Outcome category Outcome Study	mirvetuximab soravtansine		Chemotherapy[a]		mirvetuximab soravtansine vs. chemotherapy[a]
	N	Median time to event in weeks [95% CI] Patients with event n (%)	N	Median time to event in weeks [95% CI] Patients with event n (%)	HR [95% CI]; p-value[b]
Eye disorders (SOC, AEs)					
MIRASOL	218	9.3 [8.1; 13.3] 125 (57)	207	NA 18 (9)	7.48 [4.54; 12.34]; <0.001
FORWARD 1	79	8.14 [5.1; 15.9] 51 (65)	32	NA [23.6; NC] 6 (19)	4.51 [1.91; 10.61]; <0.001
Total[d]					6.73 [4.37; 10.38]; <0.001
Eye disorders (SOC, severe AEs[e])					
MIRASOL	218	100.7 [98.4; NC] 34 (16)	207	NA 0 (0)	ND[f]; <0.001
FORWARD 1	79	106.0 [44.7; NC] 11 (14)	32	NA 0 (0)	ND[f]; 0.183
Total[d]					ND[f, g]; <0.001
Pneumonitis (PT collection[h], AEs)					
MIRASOL	218	NA [56.7; NC] 26 (12)	207	NA 1 (0.5)	12.37 [1.65; 92.88]; <0.001
FORWARD 1	79	84.14 [71.6; NC] 11 (14)	32	NA 2 (6)	1.25 [0.27; 5.83]; 0.770
Total[d]					4.62 [1.38; 15.42]; 0.003
Dyspnoea (PT, AEs)					
MIRASOL	218	NA 17 (8)	207	NA 27 (13)	0.32 [0.16; 0.65]; <0.001
FORWARD 1	79	NA 10 (13)	32	NA [18.7; NC] 5 (16)	0.58 [0.18; 1.81]; 0.357
Total[d]					0.38 [0.21; 0.67]; <0.001

Table 16: Results (mortality, side effects) – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice[a] (multipage table)

Outcome category **Outcome** **Study**	**mirvetuximab soravtansine**		**Chemotherapy[a]**		**mirvetuximab soravtansine vs. chemotherapy[a]**
	N	**Median time to event in weeks [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in weeks [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value[b]**
Stomatitis (PT, AEs)					
MIRASOL	218	NA 8 (4)	207	NA [51.6; NC] 23 (11)	0.18 [0.08; 0.44]; <0.001
FORWARD 1	79	NA 4 (5)	32	NA [11.4; NC] 9 (28)	0.15 [0.04; 0.48]; <0.001
Total[d]					0.18 [0.09; 0.35]; <0.001
Skin and subcutaneous tissue disorders (SOC, AEs)					
MIRASOL	218	134.1 [88.1; NC] 37 (17)	207	18.3 [13.4; 27.1] 76 (37)	0.29 [0.19; 0.44]; <0.001
FORWARD 1	79	NA [30.9; NC] 16 (20)	32	10.3 [6.3; 17.0] 18 (56)	0.15 [0.07; 0.33]; <0.001
Total[d]					0.24 [0.17; 0.35]; <0.001
Small intestinal obstruction (PT, SAEs)					
MIRASOL	218	NA 4 (2)	207	NA 10 (5)	0.24 [0.07; 0.76]; 0.010
FORWARD 1	79	NA 0 (0)	32	NA 2 (6)	NA; 0.016
Total[d]					0.18 [0.06; 0.56]; 0.001
Blood and lymphatic system disorders (SOC, severe AEs[e])					
MIRASOL	218	NA 6 (3)	207	NA 51 (25)	0.07 [0.03; 0.17]; <0.001
FORWARD 1	79	NA 4 (5)	32	34.3 [6.3; NC] 9 (28)	0.06 [0.01; 0.28]; <0.001
Total[d]					0.07 [0.03; 0.15]; <0.001

Table 16: Results (mortality, side effects) – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice[a] (multipage table)

Outcome category Outcome Study	mirvetuximab soravtansine		Chemotherapy[a]		mirvetuximab soravtansine vs. chemotherapy[a]
	N	Median time to event in weeks [95% CI] Patients with event n (%)	N	Median time to event in weeks [95% CI] Patients with event n (%)	HR [95% CI]; p-value[b]
Fatigue (PT, severe AEs[e])					
MIRASOL	218	NA 5 (2)	207	NA 11 (5)	0.31 [0.11; 0.90]; 0.024
FORWARD 1	79	NA 2 (3)	32	74.71 [NC] 2 (6)	0.27 [0.04; 1.98]; 0.213
Total[d]					0.30 [0.12; 0.78]; 0.010

a. With a choice of paclitaxel, pegylated liposomal doxorubicin or topotecan prior to randomization.
b. Cox proportional hazards model adjusted for stratification variables: number of previous lines of treatment (1 or 2 vs. 3) and chemotherapy option as covariables; for the meta-analysis, additionally study indicator; p-value from the log-rank test.
c. Institute's calculation from data in months.
d. Calculated from IPD meta-analysis (fixed-effect model).
e. Operationalized as CTCAE grade ≥3.
f. The company stated that an HR cannot be calculated for outcomes for which no events occurred in a study arm. One way of obtaining point and interval estimates for time-to-event analyses in such situations is to use the Firth correction to the Cox model in combination with profile likelihood methods for the 95% confidence interval.
g. The company did not present any information on the HR (including 95% CI). In the given data constellation, with an event rate of 16 vs. 14% (n = 34 [MIRASOL] und n = 11 [FORWARD 1]) in the intervention arms vs. 0% (n = 0 [MIRASOL] und n = 0 [FORWARD 1]) in the comparator arms, and with Kaplan-Meier curves clearly separating early in the course of the study (see Figure 13 and Figure 14 of the full dossier assessment), a statistically significant difference to the disadvantage of mirvetuximab soravtansine can be assumed.
h. Concurs with the operationalization of the adverse event of special interest (AESI) from the MIRASOL study, which includes the PTs 'interstitial lung disease', 'organizing pneumonia', 'pneumonitis', 'pulmonary fibrosis' and 'respiratory failure'.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; NC: not calculable; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 17: Results (morbidity, health-related quality of life) – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice[a]

Outcome category Outcome	mirvetuximab soravtansine			Chemotherapy[a]			mirvetuximab soravtansine vs. chemotherapy[a]
	N	Values at baseline mean (SD)	Mean change in the course of the study mean (SE)	N	Values at baseline mean (SD)	Mean change in the course of the study mean (SE)	MD [95% CI]; p-value
Morbidity							
Symptoms (EORTC QLQ-C30)	No suitable data[b]						
Symptoms (EORTC QLQ-OV28)	No suitable data[b]						
Symptoms (PGIS)[c]	No suitable data[b]						
Symptoms (FOSI)[c]	No suitable data[b]						
Health status (EQ-5D VAS)	No suitable data[b]						
Health-related quality of life							
EORTC QLQ-C30	No suitable data[b]						
EORTC QLQ-OV28	No suitable data[b]						

a. With a choice of paclitaxel, pegylated liposomal doxorubicin or topotecan prior to randomization.
b. No suitable data are available, for justification, see Section I 4.1.
c. The PGIS was not recorded in the FORWARD 1 study. The FOSI was not recorded only in the MIRASOL study.

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; FOSI: Functional Assessment of Cancer Therapy-Ovarian Symptom Index; MD: mean difference; N: number of analysed patients; PGIS: Patient Global Impression of Severity; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-OV28: Quality of Life Questionnaire-Ovarian Cancer 28; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

Based on the available information, no more than indications, e.g. of an added benefit, can be determined for all outcomes. The reasons for this are set out in Section I 4.2.

Mortality

Overall survival

For the outcome of overall survival, the meta-analysis of MIRASOL and FORWARD 1 showed a statistically significant difference in favour of mirvetuximab soravtansine compared with chemotherapy of physician's choice. There was an effect modification by the characteristic 'BRCA status' (see Section I 4.4). There is an indication of an added benefit of mirvetuximab soravtansine compared with the ACT both for patients with a positive BRCA status and for patients with a negative/unknown BRCA status, albeit of different extents. However, there were uncertainties regarding the delineation of the subgroups due to a lack of data on patients

with unknown BRCA status (see Section I 4.4). Consequently, the results of the subgroup analysis were not used for the remainder of the benefit assessment.

Morbidity

Symptoms (EORTC QLQ-C30, QLQ-OV28, PGIS and FOSI)

No suitable data were available for the symptom outcomes, as assessed using the EORTC QLQ-C30, QLQ-OV28, PGIS and FOSI (see Section I 4.1). In each case, there is no hint of an added benefit of mirvetuximab soravtansine in comparison with the ACT; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

No suitable data were available for the health status outcome, as assessed using the EQ-5D VAS (see Section I 4.1). There is no hint of an added benefit of mirvetuximab soravtansine in comparison with the ACT; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30 and QLQ-OV28

No suitable data were available for the health-related quality of life outcomes, as assessed using the EORTC QLQ-C30 and QLQ-OV28 (see Section I 4.1). In each case, there is no hint of an added benefit of mirvetuximab soravtansine in comparison with the ACT; an added benefit is therefore not proven.

Side effects

SAEs

For the outcome of SAEs, the meta-analysis of MIRASOL and FORWARD 1 showed a statistically significant difference in favour of mirvetuximab soravtansine compared with chemotherapy of physician's choice. There is an indication of lesser harm of mirvetuximab soravtansine in comparison with the ACT.

Severe AEs

For the outcome of severe AEs, the meta-analysis of MIRASOL and FORWARD 1 showed a statistically significant difference in favour of mirvetuximab soravtansine compared with chemotherapy of physician's choice. There is therefore an indication of lesser harm of mirvetuximab soravtansine in comparison with the ACT.

Discontinuation due to AEs

For the outcome of discontinuation due to AEs, the meta-analysis, taking into account the total population, showed a statistically significant difference in favour of mirvetuximab soravtansine compared with chemotherapy of physician's choice. There was an effect modification by the characteristic 'age' (see Section I 4.4). For patients ≥65 years, there is an

indication of lesser harm of mirvetuximab soravtansine in comparison with the ACT. For patients <65 years, there is no indication of greater or lesser harm of mirvetuximab soravtansine in comparison with the ACT; greater or lesser harm is therefore not proven for this group.

Eye disorders (AEs, severe AEs) and pneumonitis (AEs)

For each of the outcomes of eye disorders (AEs and severe AEs) and pneumonitis (AEs), the meta-analysis of MIRASOL and FORWARD 1 showed a statistically significant difference to the disadvantage of mirvetuximab soravtansine compared with chemotherapy of physician's choice. In each case, there is therefore an indication of greater harm of mirvetuximab soravtansine in comparison with the ACT.

Given the prophylactic administration of steroid-containing eye drops, it was not ruled out that, had they been administered in accordance with the SmPC (only after the onset of an AE), eye disorders would have occurred on a larger scale and with greater severity. In the situation at hand, however, this had no consequence for the derivation of the added benefit, because, in the overall assessment and based on the available data on eye disorders (AEs and severe AEs), greater harm of the highest extent was already determined.

Dyspnoea (AEs)

For the outcome of dyspnoea (AEs), the meta-analysis, taking into account the total population, showed a statistically significant difference in favour of mirvetuximab soravtansine compared with chemotherapy of physician's choice. There were effect modifications by the characteristics of age and BRCA status (see Section I 4.4). These effect modifications cannot be assessed without examining for cross-interactions. Furthermore, the limitations described apply to the analyses according to BRCA status (see Section I 4.4). The added benefit is therefore derived based on the results of the total population. There is an indication of lesser harm of mirvetuximab soravtansine in comparison with the ACT.

Stomatitis (AE) and skin and subcutaneous tissue disorders (AEs)

For each of the outcomes of stomatitis (AE) and skin and subcutaneous tissue disorders (AEs), the meta-analysis of MIRASOL and FORWARD 1 showed a statistically significant difference in favour of mirvetuximab soravtansine compared with chemotherapy of physician's choice. In each case, there is therefore an indication of lesser harm of mirvetuximab soravtansine in comparison with the ACT.

Small intestinal obstruction (SAEs), blood and lymphatic system disorders (severe AEs), and fatigue (severe AEs)

For each of the outcomes of small intestinal obstruction (SAEs), blood and lymphatic system disorders (severe AEs) and fatigue (severe AEs), the meta-analysis of MIRASOL and

FORWARD 1 showed a statistically significant difference in favour of mirvetuximab soravtansine compared with chemotherapy of physician's choice. In each case, there is therefore an indication of lesser harm of mirvetuximab soravtansine in comparison with the ACT.

I 4.4 Subgroups and other effect modifiers

The following potential effect modifiers were considered for this assessment:

- Age (<65 years versus ≥65 years)
- BRCA status (positive versus negative/unknown)
- Disease stage at diagnosis (I–III versus IV)

BRCA status was planned as a subgroup characteristic in both studies; however, the status was not systematically recorded for all patients, and no information was available on the number of patients with unknown BRCA status. It was therefore not possible to assess the extent to which the results for the group with a negative/unknown BRCA status provided valid conclusions for patients with a negative BRCA status. In the meta-analysis, the proportion of patients with a positive BRCA status was 13% versus 15%. Sometimes higher proportions are described in the literature; it cannot therefore be ruled out that the subgroup with a negative or unknown BRCA status may also include patients with a positive BRCA status [26,27,29]. In order to interpret the results with sufficient certainty, it would be necessary to divide them into 3 subgroups (positive versus negative versus unknown). Due to the uncertainties described, the results regarding the effect modification by the characteristic of BRCA status are presented, but were not used for the remainder of the benefit assessment.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value <0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup. Subgroup results where the extent does not differ between subgroups are not presented.

In accordance with the described methods, no relevant effect modification by the characteristic 'stage at diagnosis' was identified for the outcomes for which suitable data were available.

The results for the subgroup characteristics of age and BRCA status are presented in Table 18. The Kaplan-Meier curves for the subgroup analyses of the meta-analysis are presented in

I Appendix B.3 of the full dossier assessment. The company did not provide any Kaplan-Meier curves for the individual studies.

Table 18: Subgroups (mortality, side effects) – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice[a] (multipage table)

Outcome Characteristic Study Subgroup	mirvetuximab soravtansine N	mirvetuximab soravtansine Median time to event in weeks [95% CI] Patients with event n (%)	Chemotherapy[a] N	Chemotherapy[a] Median time to event in weeks [95% CI] Patients with event n (%)	mirvetuximab soravtansine vs. chemotherapy[a] HR [95% CI][b]	mirvetuximab soravtansine vs. chemotherapy[a] p-value[c]
Overall survival						
BRCA status						
MIRASOL						
Positive	29	71.6 [51.4; 87.4][d] 18 (62)	36	44.7 [32.1; 58.0][d] 33 (92)	0.42 [0.24; 0.76]	0.003
Negative/unknown	198	73.3 [61.3; 86.7][d] 144 (73)	190	60.3 [53.7; 71.6][d] 144 (76)	0.73 [0.58; 0.93]	0.001
FORWARD 1						
Positive		NC[e, f]		NC[e, f]		
Negative/unknown		NC[e, f]		NC[e, f]		
Total[g]					Interaction:	0.038[h]
Positive					0.38 [0.22; 0.68]	<0.001
Negative/unknown					0.74 [0.60; 0.92]	0.006
Side effects						
Discontinuation due to AEs						
Age						
MIRASOL						
<65 years	115	NA [60.3; NC] 13 (11)	119	NA 12 (10)	0.68 [0.30; 1.53]	0.352
≥65 years	103	NA [73.9; NC] 12 (12)	88	55.3 [55.3; NC] 19 (22)	0.30 [0.14; 0.64]	0.001
FORWARD 1						
<65 years		ND[f]		ND[f]		
≥65 years		ND[f]		ND[f]		
Total[g]					Interaction:	0.028[h]
<65 years					0.66 [0.33; 1.35]	0.260
≥65 years					0.28 [0.14; 0.54]	<0.001

Table 18: Subgroups (mortality, side effects) – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice[a] (multipage table)

Outcome Characteristic Study Subgroup	mirvetuximab soravtansine N	mirvetuximab soravtansine Median time to event in weeks [95% CI] Patients with event n (%)	Chemotherapy[a] N	Chemotherapy[a] Median time to event in weeks [95% CI] Patients with event n (%)	mirvetuximab soravtansine vs. chemotherapy[a] HR [95% CI][b]	mirvetuximab soravtansine vs. chemotherapy[a] p-value[c]
Dyspnoea (PT, AE)						
Age						
MIRASOL						
<65 years	115	NA [59.0; NC] 12 (10)	119	NA 12 (10)	0.62 [0.27; 1.41]	0.254
≥65 years	103	NA 5 (5)	88	NA 15 (17)	0.21 [0.08; 0.59]	0.001
FORWARD 1						
<65 years		ND[f]		ND[f]		
≥65 years		ND[f]		ND[f]		
Total[g]					Interaction:	0.012[h]
<65 years					0.75 [0.37; 1.54]	0.441
≥65 years					0.22 [0.1; 0.52]	<0.001
BRCA status						
MIRASOL						
Positive	27	NA 0 (0)	35	NA [14.71; NC] 7 (20)	ND	0.008
Negative/unknown	191	NA 17 (9)	172	NA 20 (12)	0.51 [0.26; 0.99]	0.046
FORWARD 1						
Positive		ND[f]		ND[f]		
Negative/unknown		ND[f]		ND[f]		
Total[g]					Interaction:	0.01[h]
Positive					0.06 [0.01; 0.57]	0.002
Negative/unknown					0.58 [0.33; 1.02]	0.060

Table 18: Subgroups (mortality, side effects) – RCT, direct comparison: mirvetuximab soravtansine vs. chemotherapy of physician's choice[a] (multipage table)

Outcome Characteristic Study Subgroup	mirvetuximab soravtansine N Median time to event in weeks [95% CI] Patients with event n (%)	Chemotherapy[a] N Median time to event in weeks [95% CI] Patients with event n (%)	mirvetuximab soravtansine vs. chemotherapy[a] HR [95% CI][b] p-value[c]
a. With a choice of paclitaxel, pegylated liposomal doxorubicin or topotecan prior to randomization. b. HR and CI based on Cox proportional hazards model adjusted for stratification variables: number of previous lines of treatment (1 or 2 vs. 3) and chemotherapy option as covariables; for the meta-analysis, additionally study indicator. c. p-value is based on log-rank test. d. Institute's calculation from data in months. e. Not calculated, as the subgroup contains either too few patients or too few events. f. The study was taken into account in the calculation of a pooled interaction test. g. Calculation by means of an IPD meta-analysis (fixed-effect model). h. In interaction tests, the interaction between the subgroup characteristic and the treatment was included in the model and the corresponding p-value was reported. AE: adverse event; BRCA: breast cancer-associated gene; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; NC: not calculable; ND: no data; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event			

Mortality

Overall survival

There is a statistically significant effect modification by the characteristic of BRCA status for the outcome of overall survival. For both patients with a positive BRCA status and those with a negative or unknown BRCA status, there is a statistically significant difference in favour of mirvetuximab soravtansine compared with chemotherapy of physician's choice. There is therefore an indication of an added benefit of mirvetuximab soravtansine compared with the ACT both for patients with a positive BRCA status and for patients with a negative/unknown BRCA status, albeit of different extents. Due to the uncertainties regarding the delineation of the subgroups – due to the lack of data on patients with unknown BRCA status – the results of the subgroup analysis were not used for the remainder of the benefit assessment.

Side effects

Discontinuation due to AEs

There was a statistically significant effect modification for the characteristic age for the outcome of discontinuation due to AEs. For patients ≥65 years, there was a statistically significant difference in favour of mirvetuximab soravtansine compared with chemotherapy

of physician's choice. For patients ≥65 years, there is an indication of lesser harm of mirvetuximab soravtansine in comparison with the ACT.

There was no statistically significant difference between the treatment arms for patients <65 years. For this subgroup, there is no hint of lesser or greater harm of mirvetuximab soravtansine in comparison with the ACT for any of the outcomes; greater or lesser harm is therefore not proven.

Dyspnoea (AEs)

For the outcome of dyspnoea, there was an effect modification by each of the characteristics of age and BRCA status. These effect modifications cannot be assessed without examining for cross-interactions. Furthermore, the limitations described apply to the analyses according to BRCA status. The added benefit is therefore derived based on the results of the total population.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG General Methods [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Chapter I 4 (see Table 19).

Determination of the outcome category for the outcomes on side effects

It was not clear from the dossier whether the following outcome was serious/severe or non-serious/non-severe. The classification of this outcome is explained below.

Discontinuation due to AEs

For the outcome discontinuation due to AEs, the dossier did not contain any information on the severity of the events that occurred. Module 5 showed that 60.7% of the events recorded in the MIRASOL study were severe. There was no corresponding data for the subpopulation of the FORWARD 1 study. Based on the events in the MIRASOL study, the proportion of severe AEs in the meta-analysis was already at least 46%. Given the comparable, high frequency of severe AEs in both studies (see Table 16), it was assumed that the proportion of severe AEs contributing to the outcome ‘discontinuation due to AEs’ was over 50% in the meta-analysis. The outcome was therefore allocated to the category of severe/serious side effects.

Table 19: Extent of added benefit at outcome level: mirvetuximab soravtansine vs. chemotherapy of physician's choice[a] (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**mirvetuximab soravtansine vs. chemotherapy[a]** **Median time to event (weeks)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Outcomes with observation over the entire study duration		
Mortality		
Overall survival		
	71.4–73.3 vs. 49.6–58.0 weeks[d] HR: 0.67 [0.55; 0.82]; p<0.001 Probability: indication	Outcome category: mortality CI_u<0.85 Added benefit, extent: major
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30, QLQ-OV28, PGIS, FOSI)	No suitable data[e]	Lesser benefit not proven / added benefit not proven
Health status (EQ-5D VAS)	No suitable data[e]	Lesser benefit not proven / added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 and QLQ-OV28	No suitable data[e]	Lesser benefit not proven / added benefit not proven
Side effects		
SAEs	NA / 97.3 vs. 30.7–33.7 weeks[d] HR: 0.51 [0.37; 0.71]; p = 0.001 Probability: indication	Outcome category: serious/severe side effects CI_u<0.75, risk ≥5% Lesser harm, extent: major
Severe AEs	31.6–31.9 vs. 9.0–14.1 weeks[d] HR: 0.52 [0.40; 0.66]; p<0.001 Probability: indication	Outcome category: serious/severe side effects CI_u<0.75, risk ≥5% Lesser harm, extent: major
Discontinuation due to AEs		
Age		
<65 years	NA/ND vs. NA/ND[d] HR: 0.66 [0.33; 1.35]; p = 0.260	Greater/lesser harm not proven
≥65 years	NA/ND vs. 55.3 weeks / ND[d] HR: 0.28 [0.14; 0.54]; p<0.001 Probability: indication	Outcome category: serious/severe side effects CI_u<0.75, risk ≥5% Lesser harm, extent: major

Table 19: Extent of added benefit at outcome level: mirvetuximab soravtansine vs. chemotherapy of physician's choice[a] (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**mirvetuximab soravtansine vs. chemotherapy[a]** **Median time to event (weeks)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Eye disorders (AEs)	8.14–9.3 weeks vs. NA[d.] HR: 6.73 [4.37; 10.39] HR: 0.15 [0.10; 0.23][g]; p<0.001 Probability: indication	Outcome category: non-serious/non-severe side effects CI_u<0.80 Greater harm, extent: considerable
Eye disorders (severe AEs)	100.7–106.0 weeks vs. NA[d.] HR: ND; p<0.001 Probability: indication	Outcome category: serious/severe side effects Greater harm, extent: major[f]
Pneumonitis (AEs)	NA vs. 84.14 weeks vs. NA[d.] HR: 4.62 [1.38; 15.42] HR: 0.22 [0.06; 0.72][g]; p = 0.003 Probability: indication	Outcome category: non-serious/non-severe side effects CI_u<0.80 Greater harm, extent: considerable
Dyspnoea (AEs)	NA vs. NA[d] HR: 0.18 [0.09; 0.35]; p<0.001 Probability: indication	Outcome category: non-serious/non-severe side effects CI_u<0.80 Lesser harm, extent: considerable
Stomatitis (AEs)	NA vs. NA[d] HR: 0.18 [0.09; 0.35]; p<0.001 Probability: indication	Outcome category: non-serious/non-severe side effects CI_u<0.80 Lesser harm, extent: considerable
Skin and subcutaneous tissue disorders (AEs)	134.1/NA vs. 10.3–18.3 weeks[d] HR: 0.24 [0.17; 0.35]; p<0.001 Probability: indication	Outcome category: non-serious/non-severe side effects CI_u<0.80 Lesser harm, extent: considerable
Small intestinal obstruction (SAEs)	NA vs. NA[d] HR: 0.18 [0.06; 0.56]; p = 0.001 Probability: indication	Outcome category: serious/severe side effects CI_u<0.75, risk ≥5% Lesser harm, extent: major
Blood and lymphatic system disorders (severe AEs)	NA vs. NA/34.3 weeks[d] HR: 0.07 [0.03; 0.15]; p<0.001 Probability: indication	Outcome category: serious/severe side effects CI_u<0.75, risk ≥5% Lesser harm, extent: major

Table 19: Extent of added benefit at outcome level: mirvetuximab soravtansine vs. chemotherapy of physician's choice[a] (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**mirvetuximab soravtansine vs. chemotherapy[a]** **Median time to event (weeks)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Fatigue (severe AEs)	NA vs. NA/74.71 weeks[d] HR: 0.30 [0.12; 0.78]; p = 0.010 Probability: indication	Outcome category: serious/severe side effects 0.75≤ CI_u <0.90 Lesser harm, extent: considerable

a. With a choice of paclitaxel, pegylated liposomal doxorubicin or topotecan prior to randomization.
b. Probability provided if statistically significant differences are present.
c. Depending on the outcome category, estimations of effect size use different limits based on the upper limit of the confidence interval (CI_u).
d. Minimum and maximum median time to event per treatment arm in the included studies.
e. See Section I 4.1 for reasons.
f. The company did not present any information on the HR (including 95% CI). Based on the p-value, there is a statistically significant difference. In the given data constellation, with an event rate of 16 vs. 14% (n = 34 [MIRASOL] und n = 11 [FORWARD 1]) in the intervention arms vs. 0% (n = 0 [MIRASOL] und n = 0 [FORWARD 1]) in the comparator arms, and with Kaplan-Meier curves clearly separating early in the course of the study (see Figure 13 and Figure 14 of the full dossier assessment), the extent is assessed as major.
g. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; HR: hazard ratio; ND: no data; SAE: serious adverse event

I 5.2 Overall conclusion on added benefit

Table 20 summarizes the results taken into account for the overall conclusion on the extent of the added benefit.

Table 20: Positive and negative effects from the assessment of mirvetuximab soravtansine compared with chemotherapy of physician's choice[a]

Positive effects	Negative effects
Outcomes with observation over the entire study duration	
Mortality ▪ Overall survival: indication of an added benefit – extent: major	–
Outcomes with shortened observation period	
Non-serious/non-severe side effects ▪ Dyspnoea (AEs): indication of lesser harm – extent: considerable ▪ Stomatitis (AEs): indication of lesser harm – extent: considerable ▪ Skin and subcutaneous tissue disorders (AEs): indication of lesser harm – extent: considerable	Non-serious/non-severe side effects ▪ Pneumonitis: indication of greater harm – extent considerable
Serious/severe side effects ▪ SAEs: indication of lesser harm – extent: major ▪ Severe AEs: indication of lesser harm – extent: major ▪ Discontinuation due to AEs ▫ Age (≥65 years): indication of lesser harm – extent: major ▪ Small intestinal obstruction (SAEs): indication of lesser harm – extent: major ▪ Blood and lymphatic system disorders (severe AEs) – indication of lesser harm: major ▪ Fatigue (severe AEs): indication of lesser harm – extent: considerable	Serious/severe side effects ▪ Eye disorders (represented in AEs and severe AEs): indication of greater harm – extent: major
No suitable data were available for the outcomes on morbidity and health-related quality of life.	
a. With a choice of paclitaxel, pegylated liposomal doxorubicin or topotecan prior to randomization. AE: adverse event; SAE: serious adverse event	

In this benefit assessment, based on the MIRASOL and FORWARD 1 studies, conclusions regarding the added benefit of mirvetuximab soravtansine can only be drawn for those patients for whom monotherapy with paclitaxel, PLD or topotecan is a suitable treatment (see Section I 3.2).

Patients for whom monotherapy with paclitaxel, PLD or topotecan is a suitable therapy

Overall, there are predominantly positive effects of mirvetuximab soravtansine in comparison with chemotherapy of physician's choice. Data across the entire observation period were only available for overall survival. All other effects referred exclusively to the shortened observation period (until 30 days after the end of treatment). There were no suitable data for the outcome categories of morbidity and health-related quality of life.

On the side of positive effects, there is an indication of an added benefit of major extent for the outcome overall survival. In addition, there are several positive effects of a major or considerable extent for outcomes in the side effects category; this applies to both the overall rates and individual specific AEs. Decisive are the positive effects of major extent in the overall rates of severe AEs and SAEs. In contrast to these positive effects, there are individual negative effects in the outcome category of side effects, particularly in severe eye disorders (extent: major). Overall, the positive effects clearly outweigh the negative ones.

In summary, there is an indication of a major added benefit of mirvetuximab soravtansine versus the ACT for adult patients with FRα-positive, platinum-resistant high grade serous epithelial ovarian cancer who have received 1 to 3 prior systemic treatment regimens, and for whom monotherapy with paclitaxel, PLD or topotecan is a suitable therapy.

Patients for whom combination therapy with bevacizumab is a suitable therapy

No data were available to assess the added benefit of mirvetuximab soravtansine versus the ACT for adult patients with FRα-positive, platinum-resistant high grade serous epithelial ovarian cancer who have received 1 to 3 prior systemic treatment regimens, and for whom combination therapy with bevacizumab is a suitable therapy. An added benefit for these patients is not proven.

The result of the assessment of the added benefit of mirvetuximab soravtansine in comparison with the ACT is summarized in Table 21.

Table 21: Mirvetuximab soravtansine – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with FRα-positive, platinum-resistant[b] high grade serous epithelial ovarian cancer[c] who have received 1 to 3 prior systemic treatment regimens	▪ paclitaxel (with or without bevacizumab for bevacizumab-naïve patients[d]) or ▪ pegylated liposomal doxorubicin (with or without bevacizumab for bevacizumab-naïve patientsd) or ▪ topotecan (with or without bevacizumab for bevacizumab-naïve patientsd)	▪ Patients for whom monotherapy with paclitaxel, PLD or topotecan is a suitable therapy: indication of a major added benefit[e, f] ▪ Patients for whom combination therapy with bevacizumab is a suitable therapy: added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, it is assumed that platinum-resistant, relapsed ovarian cancer involves a response to a prior platinum-containing therapy with a relapse-free interval of less than 6 months. This also includes platinum-refractory ovarian cancer, which does not respond to platinum-containing chemotherapy or progresses within 4 weeks of the end of treatment.
c. This term also includes fallopian tube and primary peritoneal cancer.
d. In accordance with the treatment recommendations set out in guidelines, for patients who have not yet received treatment containing bevacizumab, or who have received treatment with another VEGF inhibitor or a substance targeting the VEGF receptor, on-label treatment with a combination therapy of bevacizumab with paclitaxel, topotecan or liposomal doxorubicin may be indicated, provided that bevacizumab is suitable for the patients.
e. MIRASOL and FORWARD 1 included only patients with an ECOG PS of 0 or 1. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥2.
f. No patients with primary platinum-refractory tumours were included in MIRASOL and FORWARD 1. It remains unclear whether the observed effects can be transferred to patients with primary platinum-refractory ovarian cancer.

ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FRα: folate receptor-alpha; G-BA: Federal Joint Committee; VEGF: vascular endothelial growth factor

The assessment described above differs from that of the company, which claimed proof of a major added benefit for all patients in the given therapeutic indication, regardless of the suitability of a combination therapy with bevacizumab.

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

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