IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Cobimetinib – Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Cobimetinib – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 11 March 2016). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AJCC	American Joint Committee on Cancer
BRAF	rapidly accelerated fibrosarcoma – isoform B
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LDH	lactate dehydrogenase
MMRM	mixed-effects model repeated measures
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire-Core 30
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) 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 cobimetinib. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 1 December 2015.

Research question

The aim of this report was to assess the added benefit of cobimetinib in comparison with vemurafenib as appropriate comparator therapy (ACT) in adult patients with unresectable or metastatic melanoma with a rapidly accelerated fibrosarcoma – isoform B (BRAF) V600 mutation. The drug is approved in combination with vemurafenib.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier.

Results

Study pool and study characteristics

The study coBRIM was included in the benefit assessment. This study was a randomized, double-blind, multicentre, active-controlled study on the comparison of cobimetinib in combination with vemurafenib (combination arm) and vemurafenib.

Adult patients with histologically confirmed unresectable (stage IIIc) or metastatic (stage IV) melanoma and confirmed BRAF V600 mutation were included in the study. The patients were not allowed to have received prior systemic anti-cancer treatment of the advanced melanoma. Treatment switch from the vemurafenib to the combination arm was not allowed. All patients had the option to start another treatment on disease progression.

Progression-free survival was the primary outcome of the study. Patient-relevant secondary outcomes were overall survival, symptoms, health status, health-related quality of life and adverse events (AEs).

Risk of bias

The risk of bias at study level for the coBRIM study was rated as low.

The risk of bias for the outcome "overall survival" was rated as low. The risk of bias for the outcomes from the areas of morbidity and health-related quality of life was rated as potentially high because of the high proportion of missing values in the analysis (> 10%). There was a high risk of bias also for the outcomes from the area of AEs due to different observation periods with potentially informative censoring.

Results

Mortality

Treatment with cobimetinib in combination with vemurafenib resulted in a statistically significant prolongation of overall survival in comparison with vemurafenib. This resulted in an indication of an added benefit of cobimetinib in combination with vemurafenib compared with the ACT.

Morbidity

- Symptoms

The morbidity of the patients was recorded using the symptom scales of the disease-specific questionnaire European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30).

A statistically significant difference in favour of cobimetinib in combination with vemurafenib was shown for the outcome **"pain"**. The 95% confidence interval (CI) of Hedges' g was not completely below the irrelevance threshold of -0.2. It can therefore not be inferred that the effect is relevant. In addition, there was proof of an effect modification by the characteristic "age". This resulted in a hint of an added benefit for patients under the age of 65 years; for older patients, there was no hint of an added benefit of cobimetinib in combination with vemurafenib in comparison with the ACT; an added benefit is therefore not proven for this subgroup.

A statistically significant difference in favour of cobimetinib in combination with vemurafenib was shown for the outcome **"insomnia"**. The 95% CI of Hedges' g was not completely below the irrelevance threshold of –0.2. It can therefore not be inferred that the effect is relevant. For the outcome "insomnia", this resulted in no hint of an added benefit of cobimetinib in combination with vemurafenib in comparison with the ACT; an added benefit is therefore not proven for this outcome.

A statistically significant difference to the disadvantage of cobimetinib in combination with vemurafenib was shown for the outcome **"diarrhoea"**. The 95% CI of Hedges' g was completely above the irrelevance threshold of 0.2. This was interpreted to be a relevant effect. There was a hint of lesser benefit of cobimetinib in combination with vemurafenib compared with the ACT for the outcome "diarrhoea".

A statistically significant difference to the disadvantage of cobimetinib in combination with vemurafenib was shown for the outcome **"nausea and vomiting"**. The 95% CI of Hedges' g was not completely above the irrelevance threshold of 0.2. It can therefore not be inferred that the effect is relevant. For the outcome "nausea and vomiting", there was no hint of an added benefit or of lesser benefit of cobimetinib in combination with vemurafenib in comparison with the ACT; an added benefit is therefore not proven for this outcome.

No statistically significant difference between the treatment options was shown for the outcomes **"dyspnoea", "fatigue", "appetite loss"** and **"constipation"**. This resulted in no hint of an added benefit of cobimetinib in combination with vemurafenib in comparison with the ACT; an added benefit is therefore not proven for these outcomes.

- Health status

A statistically significant difference in favour of cobimetinib in combination with vemurafenib was shown for the outcome "health status" recorded with the visual analogue scale (VAS) of the European Quality of Life-5 Dimensions (EQ-5D) questionnaire. The 95% CI of Hedges' g was not completely above the irrelevance threshold of 0.2. It can therefore not be inferred that the effect is relevant. For the outcome "health status", there was no hint of an added benefit of cobimetinib in combination with vemurafenib in comparison with the ACT; an added benefit is therefore not proven.

Health-related quality of life

- Functional scales

Aspects of health-related quality of life were recorded using the functional scales of the cancer-specific questionnaire EORTC QLQ-C30.

No statistically significant difference between the treatment options was shown for all 6 functional scales investigated (global health status, physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning). This resulted in no hint of an added benefit of cobimetinib in combination with vemurafenib in comparison with the ACT; an added benefit is therefore not proven for these outcomes.

Adverse events

- Serious adverse events and discontinuation due to adverse events

No statistically significant difference between the treatment options was shown for the outcomes "serious adverse events (SAEs)" and "discontinuation due to AEs". This resulted in no hint of greater or lesser harm of cobimetinib in combination with vemurafenib compared with the ACT for these outcomes; greater or lesser harm is therefore not proven for this outcome.

- Severe adverse events (CTCAE grade ≥ 3)

A statistically significant difference to the disadvantage of cobimetinib in combination with vemurafenib was shown for the outcome "severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)", and additionally proof of an effect modification by the characteristic "metastasis stage".

There was a hint of greater harm of cobimetinib in combination with vemurafenib for patients with metastasis stage IIIc, M1a or M1b. There was no hint of greater or lesser harm of

cobimetinib in combination with vemurafenib compared with the ACT for patients with metastasis stage M1c; greater or lesser harm is therefore not proven for this subgroup.

- Specific adverse events

A statistically significant difference to the disadvantage of cobimetinib in combination with vemurafenib was shown for the outcome **"photosensitivity reaction"**, and additionally proof of an effect modification by the characteristic "metastasis stage".

There was a hint of greater harm of cobimetinib in combination with vemurafenib for patients with metastasis stage M1c. There was no hint of greater harm of cobimetinib in combination with vemurafenib compared with the ACT for patients with metastasis stage IIIc, M1a or M1b; greater or lesser harm is therefore not proven for this subgroup.

A statistically significant difference in favour of cobimetinib in combination with vemurafenib was shown for each of the outcomes **"alopecia"** and **"hyperkeratosis"**. Despite the high risk of bias, there was an indication of lesser harm of cobimetinib in combination with vemurafenib for each of these outcomes. The certainty of results for these 2 outcomes was not downgraded because notably more events occurred in the vemurafenib arm, which had a shorter observation duration, and it was therefore not assumed that the observed direction of effect was caused by bias alone.

A statistically significant difference to the disadvantage of cobimetinib in combination with vemurafenib was shown for each of the following outcomes: **diarrhoea, nausea, vomiting** and **serous retinopathy/retinal detachment**. There was a hint of greater harm from cobimetinib for each of the outcomes "diarrhoea", "nausea" and "vomiting". There was an indication of greater harm of cobimetinib for the outcome "serous retinopathy/retinal detachment" despite the high risk of bias. Due to the effect size, which cannot be explained by the different observation periods and the potentially informative censorings alone, a high certainty of results could be assumed for this result.

- Further specific adverse events (neoplasms benign, malignant and unspecified [incl cysts and polyps])

Due to the different observation periods in the 2 study arms and the missing survival time analyses for this outcome, a qualitative interpretation was conducted on the basis of naive proportions. Overall, notably more events occurred in the vemurafenib arm, which had a shorter observation duration, so that it was not assumed that the observed direction of effect (in favour of cobimetinib in combination with vemurafenib) was caused by bias alone. An indication of lesser harm of cobimetinib in combination with vemurafenib was derived on the basis of this qualitative consideration.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

On the basis of the results presented, the extent and probability of the added benefit of the drug cobimetinib compared with the ACT is assessed as follows:

There are indications of an added benefit or of lesser harm of cobimetinib in combination with vemurafenib in the total population for the following outcomes: overall survival, neoplasms benign, malignant and unspecified (incl cysts and polyps), alopecia and hyperkeratosis. For patients < 65 years, a hint of an added benefit of cobimetinib in combination with vemurafenib was shown for the outcome "pain". An indication or hints of lesser benefit or greater harm were shown in the total population for the following outcomes: diarrhoea, nausea, vomiting and serous retinopathy/retinal detachment. Moreover, there were hints of greater harm for patients with metastasis stage IIIc, M1a and M1b for the outcome "severe AEs (AEs of CTCAE grade≥ 3)" and for patients with metastasis stage M1c for the outcome "photosensitivity reaction".

Overall, considerable positive and considerable negative effects remain. The certainty of results of the positive effects is higher than the one of the negative effects. Balancing these effects, the considerable positive effects were not outweighed by the negative effects, but downgraded in their extent.

In summary, there is an indication of a minor added benefit of cobimetinib in combination with vemurafenib compared with the ACT vemurafenib for patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

Table 2 presents a summary of the extent and probability of the added benefit of cobimetinib.

[4] 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, no added benefit, or less benefit). For further details see [1,2].

Table 2: Cobimetinib – extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation[b]	Vemurafenib	Indication of minor added benefit
a: Presentation of the ACT specified by the G-BA. b: According to the SPC, the administration of cobimetinib in combination with vemurafenib is approved for patients with unresectable or metastatic melanoma with a BRAF V600 mutation – without restriction of pretreatment [3]. The study population of the included study for the assessment of the added benefit (only treatment-naive patients) therefore does not completely cover the therapeutic indication. It remains unclear whether the observed effects can be transferred to patients who have already had treatment for their advanced melanoma. ACT: appropriate comparator therapy; BRAF: rapidly accelerated fibrosarcoma – isoform B; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics		

The G-BA decides on the added benefit.

2.2 Research question

The aim of this report was to assess the added benefit of cobimetinib in comparison with vemurafenib as ACT in adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. The drug is approved in combination with vemurafenib.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier.

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on cobimetinib (status: 13 November 2015)
- bibliographical literature search on cobimetinib (last search on 11 November 2015)
- search in trial registries for studies on cobimetinib (last search on 11 November 2015)

To check the completeness of the study pool:

- search in trial registries for studies on cobimetinib (last search on 17 December 2015)

No additional relevant study was identified from the check.

2.3.1 Studies included

The study listed in the following table was included in the benefit assessment.

Table 3: Study pool – RCT, direct comparison: cobimetinib + vemurafenib vs. vemurafenib

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
GO28141 (coBRIM)[b]	Yes	Yes	No

a: Study for which the company was sponsor.
b: In the following tables, the study is referred to with its abbreviated form.
RCT: randomized controlled trial; vs.: versus

The study pool for the benefit assessment of cobimetinib in combination with vemurafenib in comparison with vemurafenib consisted of the study coBRIM (GO28141) and concurred with that of the company. Hereinafter, the study is referred to as “coBRIM”.

Section 2.6 contains a reference list for the study included.

2.3.2 Study characteristics

Table 4 and Table 5 describe the study used for the benefit assessment.

Table 4: Characteristics of the study included – RCT, direct comparison: cobimetinib + vemurafenib vs. vemurafenib

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
coBRIM	RCT, double-blind, parallel	Treatment-naive[b] adult (≥ 18 years) patients with histologically confirmed unresectable (stage IIIc[c]) or metastatic (stage IV[c]) melanoma and confirmed BRAF V600 mutation; ECOG PS 0 or 1	Cobimetinib + vemurafenib (N = 247) placebo + vemurafenib (N = 248)	Screening: within 28 days prior to the start of treatment Treatment: until progression, death, unacceptable toxicity or withdrawal of consent Observation: outcome-specific, at most until death (for the outcome "overall survival")	133 centres in 19 countries in Australia and New Zealand, Europe, Israel, North America, Russia 1/2013–ongoing Data cut-offs: ▪ first data cut-off: 9 May 2014[d] ▪ second data cut-off: 19 Sep 2014[e] ▪ third data cut-off: 16 Jan 2015[f] ▪ fourth data cut-off: 28 Aug 2015[g]	Primary: progression-free survival Secondary: overall survival, symptoms, health status, health-related quality of life, AEs

(continued)

Table 4: Characteristics of the study included – RCT, direct comparison: cobimetinib + vemurafenib vs. vemurafenib (continued)

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: According to the inclusion criteria of the study, the patients were not allowed to have had prior systemic anti-cancer treatment for the treatment of the advanced melanoma (stage IIIc and IV). Prior treatment in the adjuvant setting (line of treatment before the advanced stage) including immunotherapy was allowed.
c: According to AJCC classification [4].
d: Final analysis on the outcome "PFS" (planned after about 206 events) as well as interim analysis on the outcome "overall survival".
e: Additional safety analysis on request of the FDA.
f: Additional efficacy analysis on request of EMA.
g: Final analysis on the outcome "overall survival" (Amendment 5 to the protocol from 24 February 2015): planned after 250 deaths, conducted after 255 deaths that actually occurred; it was originally planned to conduct an interim analysis after 256 deaths and the final analysis after 385 deaths.

AE: adverse event; AJCC: American Joint Committee on Cancer; BRAF: rapidly accelerated fibrosarcoma – isoform B; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EMA: European Medicines Agency; FDA: Food and Drug Administration; N: number of randomized patients; PFS: progression-free survival; RCT: randomized controlled trial; vs.: versus

Table 5: Characteristics of the intervention – RCT, direct comparison: cobimetinib + vemurafenib vs. vemurafenib

Study	Intervention	Comparison	Prior and concomitant medication
coBRIM	Day 1–21: cobimetinib 60 mg once daily, oral + vemurafenib 960 mg twice daily, oral	Day 1–21: vemurafenib 960 mg twice daily, oral + placebo for cobimetinib	**Pretreatment[b]:** ▪ no prior systemic anti-cancer treatment (prior treatment in the adjuvant setting including immunotherapy was allowed[c]) ▪ no pretreatment with a RAF inhibitor or a MEK inhibitor
	Day 22–28: vemurafenib 960 mg twice daily, oral	Day 22–28: vemurafenib 960 mg twice daily, oral	**Concomitant treatment:** Allowed concomitant treatment: ▪ Antiemetic and antidiarrhoeal drugs were not allowed to be given as prophylaxis before the first administration of the study medication; they were allowed for later administrations. Maintenance treatment could be continued. ▪ Analgesics were allowed to be given according to local practice. Non-permitted concomitant treatment: ▪ treatments for the advanced melanoma including chemotherapy, radiotherapy, immunotherapy or other investigational preparations ▪ palliative radiotherapy within 14 days prior to the administration of the study medication ▪ St. John's Wort
	Dose adjustments and treatment discontinuations or delays due to intolerance were allowed for both drugs[a]. Dose reductions below 480 mg vemurafenib twice daily or below 20 mg cobimetinib once daily were not allowed.		

a: In case of dose reduction or treatment discontinuation of one substance, continued treatment with the other substance was possible. Once a dose had been reduced it was not allowed to be increased again.
b: Prior treatment of the advanced disease (stage IIIc and IV).
c: 9.7% of the patients in total received adjuvant treatment.
MEK: mitogen-activated extracellular signal-regulated kinase; RAF: rapidly accelerated fibrosarcoma; RCT: randomized controlled trial; vs.: versus

Study design

The coBRIM study was a randomized, double-blind, multicentre, active-controlled study on the comparison of cobimetinib in combination with vemurafenib and vemurafenib.

Adult patients with histologically confirmed unresectable (stage IIIc) or metastatic (stage IV) melanoma and confirmed BRAF V600 mutation were included in the study. Treatment-naive patients without active central nervous system metastasis (see Section 2.7.2.4.1 of the full dossier assessment) and with good general health status (Eastern Cooperative Oncology Group Performance Status [ECOG PS] ≤ 1) were eligible for participation.

The patients were not allowed to have received prior systemic anti-cancer treatment of the advanced melanoma (stage IIIc or IV). Prior adjuvant treatment including immunotherapy

was allowed. According to the Summary of Product Characteristics (SPC) [3], the administration of cobimetinib in combination with vemurafenib is approved for patients with unresectable or metastatic melanoma with a BRAF V600 mutation; there is no restriction regarding pretreatment. The study population (only treatment-naive patients) therefore does not completely cover the therapeutic indication. It remains unclear whether the effects observed in the study can be transferred to patients who have already had treatment for the advanced stage (see Section 2.7.2.4.1 of the full dossier assessment).

495 patients were randomized in a ratio of 1:1, 247 patients to the combination arm (cobimetinib + vemurafenib) and 248 patients to the vemurafenib arm. Geographical region (North America/Europe/Australia/New Zealand and other) and the metastasis stage (M1c/IIIc, M1a and M1b) at the start of the study were stratification factors.

The drugs cobimetinib and vemurafenib used in the study were administered without relevant deviations from the SPC. The dose reductions envisaged in the study due to AEs did not completely comply with the specifications in the SPCs [3,5]. It appears unlikely, however, that the deviation had an important influence on the study results (see Section 2.7.2.3.2 of the full dossier assessment).

Treatment switch from the vemurafenib to the combination arm was not allowed. All patients had the option to start another treatment on disease progression.

Progression-free survival was the primary outcome of the study. Patient-relevant secondary outcomes were overall survival, disease-related symptoms, health status, health-related quality of life and AEs.

The study is continued until withdrawal of consent, death, or loss to follow-up of all patients or until the sponsor ends the study. The final analysis on overall survival has already been conducted, however. Treatment in both study arms is continued until disease progression, death, unacceptable toxicity or withdrawal of consent.

Follow-up and data cut-offs

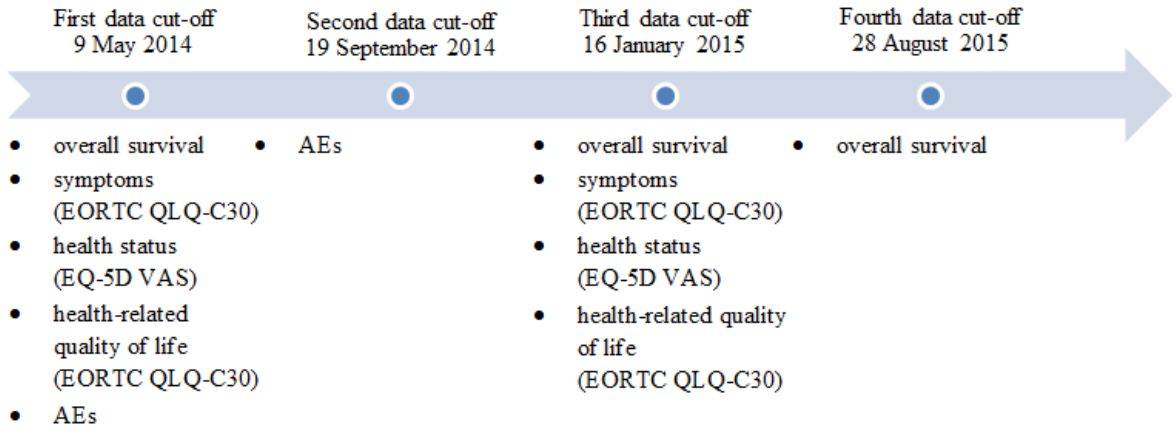
Table 6 shows the planned duration of follow-up of the patients for the individual outcomes.

Table 6: Planned duration of follow-up – RCT, direct comparison: cobimetinib + vemurafenib vs. vemurafenib

Study **Outcome category** **Outcome**	**Planned follow-up**
coBRIM	
Mortality	
Overall survival	Every 12 weeks until death
Morbidity	
Symptoms (measured with the EORTC QLQ-C30 symptom scales[a])	4 weeks after the last administration of the study medication
Health status (measured with the EQ-5D VAS[a])	4 and 12 weeks after the last administration of the study medication
Health-related quality of life	
Health-related quality of life (measured with the EORTC QLQ-C30 functional scales[a])	4 weeks after the last administration of the study medication
Adverse events	
AEs/SAEs	Up to 28 days after the last administration of the study medication or until the start of a subsequent antineoplastic treatment
a: According to Amendment 5 to the study protocol from 24 February 2015, no data on symptoms, health status and health-related quality of life were to be recorded after the final efficacy analysis (first data cut-off from 9 May 2014). AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus	

Of the outcomes included, only overall survival was recorded until death. The recording of other data was conducted outcome-specific beyond the end of treatment: AEs were recorded up to 28 days after the last treatment with the study medication or until the start of a subsequent antineoplastic treatment; data on the outcomes “symptoms” and “health-related quality of life” were recorded up to 4 weeks after the last administration of the study medication, and the outcome “health status” up to 12 weeks after the last administration of the study medication. The recording of the data on morbidity and health-related quality of life was stopped after Amendment 5 to the study protocol (24 February 2015).

A total of 4 data cut-offs were performed during the study. The following Figure 1 shows an overview of the data availability in the company’s dossier for the relevant outcomes (see Section 2.4.3 and Section 2.7.2.4.3 of the full dossier assessment for the choice of outcomes).



AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; QLQ-C30: Quality of Life Questionnaire-Core 30; VAS: visual analogue scale

Figure 1: Overview of the available outcomes at the 4 data cut-offs of the coBRIM study

The first data cut-off (9 May 2014) had been planned a priori as soon as about 206 events of the outcome "progression-free survival" have occurred. The company presented data on all relevant outcomes at this data cut-off.

The second data cut-off (19 September 2014) was conducted post hoc on request of the regulatory authority Food and Drug Administration (FDA) and comprised only data on AEs.

The third data cut-off (16 January 2015) was conducted post hoc on request of the regulatory authority European Medicines Agency (EMA) on the outcome "overall survival", among others. In addition, the company presented data on morbidity and health-related quality of life in the additional analyses for this data cut-off in the dossier.

The fourth data cut-off (28 August 2015) constituted a final analysis on the outcome "overall survival", which was introduced with Amendment 5 to the study protocol from 24 February 2015. The Amendment stipulated to conduct the final analysis on the outcome "overall survival" after 250 events. It was originally planned to conduct an interim analysis after 256 deaths, and the final analysis after 385 deaths.

Since only data on the outcome "overall survival" were available at the fourth data cut-off, but data on AEs, health-related quality of life, and morbidity were missing, the information at the fourth data cut-off were incomplete. Hence no adequate balancing of the positive and negative effects of cobimetinib was possible for this data cut-off. The fourth data cut-off was therefore not used for the benefit assessment. Due to the data availability in the dossier, the results of the third data cut-off were used for all outcomes except for the outcomes on AEs. An analysis of AEs based on the third data cut-off was not available. Due the comparatively short period between the second and the third data cut-off (about 4 months), the results of the

second data cut-off could be used for AEs (see Section 2.7.2.4.3 of the full dossier assessment).

Characteristics of the study population

Table 7 shows the characteristics of the patients in the study included.

Table 7: Characteristics of the study population – RCT, direct comparison: cobimetinib + vemurafenib vs. vemurafenib

Study Characteristics Category	**Cobimetinib + vemurafenib**	**Vemurafenib**
coBRIM	N[a] = 247	N[a] = 248
Age [years], mean (SD)	55 (14)	55 (14)
Sex [F/M], %	41/59	44/56
Baseline ECOG PS, n (%)[b]		
0	184 (76)	164 (67)
1	58 (24)	80 (33)
2	1 (0)	0
Ethnicity, n (%)		
White/Caucasian/European origin	227 (92)	235 (95)
Other	4 (2)	4 (2)
Unknown	16 (6)	9 (4)
BRAF mutation status, n (%)		
V600E	170 (69)	174 (70)
V600K	24 (10)	32 (13)
Unknown	53 (21)	42 (17)
Metastasis stage at screening, n (%)		
M0	21 (9)	13 (5)
M1a	40 (16)	40 (16)
M1b	40 (16)	42 (17)
M1c	146 (59)	153 (62)
Disease stage at screening[c], n (%)		
Stage IIIc	21 (9)	13 (5)
Stage IV	226 (91)[d]	235 (95)[d]
Treated brain metastases before the start of treatment, n (%)[e]	1 (0)	2 (1)

(continued)

Table 7: Characteristics of the study population – RCT, direct comparison: cobimetinib + vemurafenib vs. vemurafenib (continued)

Study Characteristics Category	**Cobimetinib + vemurafenib**	**Vemurafenib**
coBRIM	N[a] = 247	N[a] = 248
Baseline LDH, n (%)		
Increased	112 (45)	104 (42)
Normal	130 (53)	138 (56)
Unknown	5 (2)	6 (2)
Extent of metastases (number of locations), n (%)	ND	ND
Time since first diagnosis (months)[f], median [min; max]	28 [0; 421]	25 [0; 338]
Treatment discontinuation, n (%)[g, h, i]	102 (40)	138 (58)
Study discontinuation, n (%)[g]	48 (19)	67 (27)

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Information based on n = 243 in the cobimetinib + vemurafenib arm and n = 244 patients in the vemurafenib arm.
c: According to AJCC classification [4].
d: Institute's calculation.
e: Patients with brain metastases were included in the study only under certain conditions, see Section 2.7.2.4.1 of the full dossier assessment.
f: Information based on n = 240 in the cobimetinib + vemurafenib arm and n = 245 patients in the vemurafenib arm.
g: Data of the first data cut-off (9 May 2014); no information available for later data cut-offs.
h: Data of the safety population (n = 254 in the cobimetinib + vemurafenib arm and n = 239 patients in the vemurafenib arm).
i: Progression (24% of all patients in the combination arm and 47% of all patients in the vemurafenib arm) was the most common reason for treatment discontinuation.
AJCC: American Joint Committee on Cancer; BRAF: rapidly accelerated fibrosarcoma – isoform B; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; LDH: lactate dehydrogenase; M: male; max: maximum value; min: minimum value; n: number of patients in the category; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The demographic and disease-specific characteristics of the coBRIM study were mostly balanced between the treatment arms. The average age of the patients was 55 years, and they were mainly white, Caucasian or of European origin (intervention arm: 92%, comparator arm: 95%).

Over 90% of the patients had tumour stage IV according to the American Joint Committee on Cancer (AJCC) classification; the most frequent metastasis stage was M1c (about 60%). Just more than half of the patients had normal lactate dehydrogenase (LDH) levels.

Progression was the most common reason for treatment discontinuation: 24% of all patients in the combination arm and 47% of all patients in the vemurafenib arm discontinued treatment at

the first data cut-off due to progression. About 15% of the patients in the combination arm and 18% of the patients in the vemurafenib arm received subsequent treatments, most of them immunotherapy (about 5% in the combination arm and 7% in the vemurafenib arm). No information on later data cut-offs was available.

Duration of treatment and follow-up

Table 8 shows the median treatment duration of the patients and the follow-up period for individual outcomes.

Table 8: Information on the course of the study – RCT, direct comparison: cobimetinib + vemurafenib vs. vemurafenib

Study **Duration of the study phase** **Outcome category** **Data cut-off**	**Cobimetinib + vemurafenib**	**Vemurafenib**
coBRIM	N = 247	N = 248
Treatment duration [days]		
First data cut-off (9 May 2014)		
Cobimetinib or placebo median [min; max]	179 [4; 430][a]	155 [5; 486][a]
Vemurafenib median [min; max]	183 [9; 430][a]	155 [5; 387][a]
Second data cut-off (19 September 2014)		
Cobimetinib or placebo median [min; max]	267 [4; 563][b]	172.5 [5; 515][b]
Vemurafenib median [min; max]	279 [9; 563][b]	175 [5; 516][b]
Third data cut-off (16 January 2015)	ND	ND
Observation period [months]		
Overall survival		
First data cut-off (9 May 2014)		
Median [min; max]	7.4 [1.4, 14.7]	7.0 [0.5, 16.5]
Second data cut-off (19 September 2014)		
Median [min; max]	ND	ND
Third data cut-off (16 January 2015)		
Median [min; max]	14.9 [1.4; 22.5]	13.6 [0.5, 24.8]

(continued)

Table 8: Information on the course of the study – RCT, direct comparison: cobimetinib + vemurafenib vs. vemurafenib (continued)

Study **Duration of the study phase** **Outcome category** **Data cut-off**	**Cobimetinib + vemurafenib**	**Vemurafenib**
coBRIM	N = 247	N = 248
Morbidity, health-related quality of life, adverse events		
First data cut-off (9 May 2014)		
Median [min; max]	ND	ND
Second data cut-off (19 September 2014)		
Median [min; max]	ND	ND
Third data cut-off (16 January 2015)		
Median [min; max]	ND	ND

a: The data were only available for the safety population (254 patients with cobimetinib + vemurafenib and 239 patients with vemurafenib) and not for the ITT population.
b: The data were only available for the safety population (247 patients with cobimetinib + vemurafenib and 246 patients with vemurafenib) and not for the ITT population.
ITT: intention to treat; max: maximum; min: minimum; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; vs.: versus

The treatment duration in the coBRIM study differed between the 2 treatment arms. With 267 days cobimetinib treatment and 279 days vemurafenib treatment, the patients in the combination arm had received a substantially longer median treatment duration at the second data cut-off than in the vemurafenib arm, where the patients had received a median treatment duration of 172.5 days placebo and 175 days vemurafenib. There was no information on the median treatment duration with both substances (cobimetinib + vemurafenib or vemurafenib + placebo).

The observation period for the outcome “overall survival” did not differ substantially between the treatment arms. No information was available on the actual observation period for the outcomes from the areas of morbidity, health-related quality of life and AEs. Since the follow-up was based on the treatment duration (see Table 6), the observation duration for these outcomes presumably differed between the treatment arms.

The observation period for AEs can be estimated based on the information on the median treatment duration because AEs were predefined to be recorded up to 28 days after the last administration of the study medication or up to the start of a subsequent antineoplastic treatment. Assuming that all patients had exhausted the follow-up period of 28 days after the last administration of cobimetinib in the combination arm, and of placebo in the vemurafenib arm, this resulted in an approximate median observation period of 295 days in the

combination arm compared with 200.5 days in the vemurafenib arm (68% of the observation period of the combination arm). Due to the different observation periods, an analysis of the time to first event was used for AEs, if available.

For the other outcomes on morbidity and health-related quality of life, the mean change until cycle 8 using a mixed-effects model repeated measures (MMRM) analysis was used (see Section 2.7.2.4.3 of the full dossier assessment). The extent of the bias caused by the different observation periods in this analysis was unclear.

Risk of bias at study level

Table 9 shows the risk of bias at study level.

Table 9: Risk of bias at study level – RCT, direct comparison: cobimetinib + vemurafenib vs. vemurafenib

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
coBRIM	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level for the coBRIM study was rated as low. This concurs with the company's assessment.

Restrictions resulting from the different observation periods in the 2 treatment arms are described in Section 2.4.2 for the outcome-specific risk of bias.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - symptoms measured with the symptom scales of the EORTC QLQ-C30
  - health status measured with the EQ-5D VAS

- Health-related quality of life
  - measured with the functional scales of the EORTC QLQ-C30 questionnaire
- Adverse events
  - SAEs
  - discontinuation due to adverse events
  - severe AEs (CTCAE grade ≥ 3)
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.7.2.4.3 of the full dossier assessment).

Table 10 shows for which outcomes data were available in the study included.

Table 10: Matrix of outcomes – RCT, direct comparison: cobimetinib + vemurafenib vs. vemurafenib

Study	Outcomes							
	Overall survival	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Specific AEs[a]
coBRIM	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a: The following events (coded according to MedDRA) are considered: alopecia (PT), hyperkeratosis (PT), photosensitivity reaction (PT), diarrhoea (PT), nausea (PT), vomiting (PT), serous retinopathy/retinal detachment (AEGT) and neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC).

AE: adverse event; AEGT: Adverse Event Grouped Terms; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

2.4.2 Risk of bias

Table 11 shows the risk of bias for the relevant outcomes.

Table 11: Risk of bias at study and outcome level – RCT, direct comparison: cobimetinib + vemurafenib vs. vemurafenib

Study	Outcomes									
	Study level	Overall survival	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Specific AEs[a]	Neoplasms benign, malignant and unspecified (incl cysts and polyps)
coBRIM	L	L	H[b]	H[b]	H[b]	H[c]	H[c]	H[c]	H[c]	-[d]

a: Includes the following events (coded according to MedDRA): alopecia (PT), hyperkeratosis (PT), photosensitivity reaction (PT), diarrhoea (PT), nausea (PT), vomiting (PT), serous retinopathy/retinal detachment (AEGT).
b: Proportion of missing values in the analysis > 10%.
c: Different observation periods with potentially informative censoring.
d: Only qualitative interpretation of the results possible, see Section 2.7.2.4.2 of the full dossier assessment.
AE: adverse event; AEGT: Adverse Event Grouped Terms; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

The risk of bias for the outcome "overall survival" was rated as low. This concurs with the company's assessment.

The assessment of the risk of bias at outcome level deviates from that of the company for all other outcomes. The risk of bias for the outcomes from the areas of morbidity and health-related quality of life was rated as high because of the high proportion of missing values in the analysis (> 10%). There was a high risk of bias also for the outcomes from the area of AEs due to different observation periods with potentially informative censoring. There was no regular assessment of the risk of bias for the specific outcome "neoplasms benign, malignant and unspecified (incl cysts and polyps)". The results for this outcome were only interpretable in qualitative terms because the analysis was conducted on the basis of naive proportions despite different observation periods.

Detailed reasons for the assessment of the risk of bias can be found in Section 2.7.2.4.2 of the full dossier assessment.

2.4.3 Results

Table 12 to Table 17 summarize the results on the comparison of cobimetinib in combination with vemurafenib versus the ACT vemurafenib in patients with unresectable or metastatic

melanoma with a BRAF V600 mutation. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations. The Kaplan-Meier curve on the outcomes included was only available for the outcome "overall survival" and is presented in Appendix A of the full dossier assessment.

Table 12: Results (mortality) – RCT, direct comparison: cobimetinib + vemurafenib vs. vemurafenib

Study **Outcome**	**Cobimetinib + vemurafenib**		**Vemurafenib**		**Cobimetinib + vemurafenib vs. vemurafenib**
	N	**Median survival time in months [95% CI]** **Patients with event n (%)**	**N**	**Median survival time in months [95% CI]** **Patients with event n (%)**	**HR [95% CI][a]; p-value**
coBRIM					
Overall survival					
First data cut-off (9 May 2014)	247	NA [NA; NA] 34 (14)	248	NA [NA; NA] 51 (21)	0.64 [0.42; 1.00] 0.046
Third data cut-off (16 January 2015)	247	NA [20.7; NA] 79 (32)	248	17.0 [15.0; NA] 109 (44)	0.65 [0.49; 0.87] 0.003

a: Results form a Cox proportional hazards model adjusted for geographical region and metastasis stage.
CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; NA: not achieved; RCT: randomized controlled trial; vs.: versus

Table 13: Results (morbidity: symptoms, mean change until cycle 8, MMRM) – RCT, direct comparison: cobimetinib + vemurafenib vs. vemurafenib

Study Outcome Subscale	Cobimetinib + vemurafenib			Vemurafenib			Cobimetinib + vemurafenib vs. vemurafenib
	N[a]	Baseline values mean (SD)	Change until cycle 8 mean[b] (SE)	N[a]	Baseline values mean (SD)	Change until cycle 8 mean[b] (SE)	Mean difference[b] [95% CI]; p-value
coBRIM							
EORTC QLQ-C30 symptom scales [c, d]							
Dyspnoea	202	14.7 (23.0)	1.0 (1.4)	202	15.0 (23.8)	0.3 (1.4)	0.78 [–2.44; 3.99] 0.636
Fatigue	202	30.6 (24.1)	5.9 (1.4)	202	29.0 (26.0)	7.9 (1.4)	–2.08 [–5.34; 1.17] 0.209
Insomnia	202	31.2 (29.2)	–6.4 (1.5)	202	29.0 (28.5)	0.3 (1.6)	–6.74 [–10.35; –3.12] < 0.001 Hedges' g: –0.36 [–0.56; –0.17][e]
Pain	202	25.3 (26.9)	–2.2 (1.4)	202	24.3 (27.7)	2.8 (1.4)	–5.02 [–8.35; –1.7] 0.003 Hedges' g: –0.29 [–0.49; –0.10][e]
Appetite loss	202	18.5 (28.5)	1.8 (1.6)	202	17.3 (25.8)	4.6 (1.6)	–2.83 [–6.61; 0.95] 0.142
Diarrhoea	202	7.0 (16.5)	12.4 (1.2)	202	5.3 (14.3)	6.2 (1.2)	6.2 [3.34; 9.07] < 0.001 Hedges' g: 0.42 [0.22; 0.62][e]
Nausea and vomiting	202	8.3 (15.5)	3.7 (0.8)	202	6.4 (12.9)	1.4 (0.8)	2.25 [0.29; 4.2] 0.024 Hedges' g: 0.22 [0.03; 0.42][e]
Constipation	202	11.3 (21.9)	–2.0 (1.0)	202	9.4 (21.7)	–1.1 (1.1)	–0.85 [–3.3; 1.59] 0.494

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study (if applicable at other data cut-offs) may be based on other patient numbers.
b: Results from MMRM model adjusted for region and metastasis stage.
c: Results of the third data cut-off on 16 January 2015.
d: Lower (decreasing) values indicate improvement in the burden of symptoms; negative effects in the group comparison ([cobimetinib + vemurafenib] vs. vemurafenib) indicate an advantage of cobimetinib + vemurafenib.
e: Institute's calculation based on the mean difference and CI of the MMRM.
CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; MMRM: mixed-effects model repeated measures; N: number of analysed patients; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; vs.: versus

Table 14: : Results (morbidity: health status, mean change until cycle 8, MMRM) – RCT, direct comparison: cobimetinib + vemurafenib vs. vemurafenib

Study Outcome	Cobimetinib + vemurafenib			Vemurafenib			Cobimetinib + vemurafenib vs. vemurafenib
	N[a]	Baseline values mean (SD)	Change until cycle 8 mean[b] (SE)	N[a]	Baseline values mean (SD)	Change until cycle 8 mean[b] (SE)	Mean difference[b] [95% CI]; p-value
coBRIM							
Health status[c]							
EQ-5D VAS[d]	203	71.8 (20.3)	–0.5 (1.2)	199	72.8 (20.2)	–3.6 (1.2)	3.14 [0.34; 5.94] 0.028 Hedges' g: 0.22 [0.02; 0.41][e]

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study (if applicable at other data cut-offs) may be based on other patient numbers.
b: Results from MMRM model adjusted for region and metastasis stage.
c: Results of the third data cut-off on 16 January 2015.
d: Higher (increasing) values indicate better health status; positive effects in the group comparison ([cobimetinib + vemurafenib] vs. vemurafenib) indicate an advantage of cobimetinib + vemurafenib.
e: Institute's calculation based on the mean difference and CI of the MMRM.

CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale; vs.: versus

Table 15: Results (health-related quality of life, mean change until cycle 8, MMRM) – RCT, direct comparison: cobimetinib + vemurafenib vs. vemurafenib

Study Outcome Subscale	Cobimetinib + vemurafenib			Vemurafenib			Cobimetinib + vemurafenib vs. vemurafenib
	N[a]	Baseline values mean (SD)	Change until cycle 8 mean[b] (SE)	N[a]	Baseline values mean (SD)	Change until cycle 8 mean[b] (SE)	Mean difference[b] [95% CI]; p-value
coBRIM							
EORTC QLQ-C30 functional scales [c, d]							
Global health status	202	66.8 (21.4)	–4.2 (1.2)	202	68.1 (22.9)	–5.2 (1.3)	1.04 [–1.9; 3.97] 0.489
Physical functioning	202	82.7 (19.8)	–2.2 (1.1)	202	82.7 (20.8)	–4.5 (1.1)	2.28 [–0.28; 4.85] 0.080
Role functioning	202	78.8 (26.3)	–6.6 (1.6)	202	77.9 (28.7)	–9.1 (1.6)	2.59 [–1.18; 6.36] 0.177
Emotional functioning	202	71.8 (23.5)	3.6 (1.2)	202	73.3 (21.3)	2.6 (1.2)	1.06 [–1.67; 3.78] 0.446
Cognitive functioning	202	88.0 (17.9)	–3.4 (1.1)	202	88.8 (15.8)	–3.0 (1.1)	–0.32 [–2.85; 2.2] 0.801
Social functioning	202	77.5 (26.0)	–2.3 (1.5)	202	80.3 (26.6)	–4.9 (1.5)	2.61 [–0.9; 6.12] 0.144

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study (if applicable at other data cut-offs) may be based on other patient numbers.
b: Results from MMRM model adjusted for region and metastasis stage.
c: Results of the third data cut-off on 16 January 2015.
d: Lower (decreasing) values indicate worse global health status or functioning; negative effects in the group comparison ([cobimetinib + vemurafenib] – vemurafenib) indicate a disadvantage of cobimetinib + vemurafenib.

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; MMRM: mixed-effects model repeated measures; N: number of analysed patients; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; vs.: versus

Table 16: Results (AEs: time to first event) – RCT, direct comparison: cobimetinib + vemurafenib vs. vemurafenib

Study Outcome	Cobimetinib + vemurafenib		Vemurafenib		Cobimetinib + vemurafenib vs. vemurafenib
	N	Median time to event (months) [95% CI] Patients with event n (%)	N	Median time to event (months) [95% CI] Patients with event n (%)	HR[a] [95% CI]; p-value
coBRIM[b]					
AEs	247	ND 244 (99)	246	ND 240 (98)	--
SAEs	247	ND 85 (34)	246	ND 64 (26)	1.27 [0.91; 1.75] 0.154
Discontinuation due to AEs	247	ND 37 (15)	246	ND 20 (8)	1.71 [0.99; 2.94] 0.052
Severe AEs (CTCAE grade ≥ 3)	247	ND 176 (71)	246	ND 146 (59)	1.30 [1.04; 1.61] 0.019
Alopecia	247	ND 37 (15)	246	ND 73 (30)	0.41 [0.28; 0.61] < 0.001
Hyperkeratosis	247	ND 27 (11)	246	ND 75 (31)	0.28 [0.18; 0.44] < 0.001
Photosensitivity reaction	247	ND 82 (33)	246	ND 45 (18)	1.84 [1.28; 2.65] < 0.001
Diarrhoea	247	ND 148 (60)	246	ND 76 (31)	2.60 [1.97; 3.44] < 0.001
Nausea	247	ND 102 (41)	246	ND 62 (25)	1.80 [1.31; 2.47] < 0.001
Vomiting	247	ND 60 (24)	246	ND 31 (13)	2.03 [1.32; 3.13] 0.001
Serous retinopathy/retinal detachment	247	ND 63 (26)	246	ND 7 (3)	9.72 [4.45; 21.23] < 0.001

a: Results from an unadjusted Cox proportional hazards model.
b: Results of the second data cut-off on 19 September 2014.

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; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Table 17: Results (common AEs with potentially important differences between the treatment arms) – RCT, direct comparison: cobimetinib + vemurafenib vs. vemurafenib

Study Outcome	Cobimetinib + vemurafenib		Vemurafenib	
	N	Patients with event n (%)	N	Patients with event n (%)
coBRIM[a]				
Neoplasms benign, malignant and unspecified (incl cysts and polyps)[b]	247	60 (24)	246	107 (44)

a: Results of the second data cut-off on 19 September 2014.
b: The specific AE presented can only be interpreted in qualitative terms because of the differences in the median treatment duration in the 2 study arms.
AE: adverse event; N: number of analysed patients; n: number of patients with (at least one) event; RCT: randomized controlled trial; vs.: versus

Only one study (coBRIM) was available for the assessment of cobimetinib in combination with vemurafenib in comparison with the ACT vemurafenib. The available coBRIM study did not meet the particular requirements placed on the derivation of proof of an added benefit from a single study [1] (see Section 2.7.2.8.1 of the full dossier assessment). Hence at most indications, e.g. of an added benefit, could be derived from the data.

This deviates from the company's assessment, which considered the coBRIM study suitable for deriving proof.

Mortality

The third data cut-off was used for assessing the outcome "overall survival" (see Section 2.7.2.4.3 of the full dossier assessment). The results on the first data cut-off were presented as additional information only.

Treatment with cobimetinib in combination with vemurafenib resulted in a statistically significant prolongation of overall survival in comparison with vemurafenib. This resulted in an indication of an added benefit of cobimetinib in combination with vemurafenib compared with the ACT. This deviates from the company's assessment, which claimed proof of an added benefit for this outcome on the basis of the results of the fourth data cut-off.

Morbidity

Symptoms

The morbidity of the patients was recorded with the symptom scales of the disease-specific questionnaire EORTC QLQ-C30. Due to the high risk of bias (see Section 2.7.2.4.2 of the full dossier assessment), at most a hint of an added benefit or of lesser benefit could be derived for all outcomes in this category.

A statistically significant difference in favour of cobimetinib in combination with vemurafenib was shown for the outcome **"pain"** for the mean change up to cycle 8 using an

MMRM analysis. The 95% CI of Hedges' g was not completely below the irrelevance threshold of –0.2. It can therefore not be inferred that the effect is relevant.

In addition, there was proof of an effect modification by the characteristic "age" for the outcome "pain" (see Section 2.4.4). The results for patients who were younger than 65 years and for older patients were therefore interpreted separately. For the outcome "pain", this resulted in a hint of an added benefit for patients who are younger than 65 years; for older patients, there was no hint of an added benefit of cobimetinib in combination with vemurafenib in comparison with the ACT; an added benefit is therefore not proven for this subgroup. This deviates from the company's assessment, which used the responder analyses based on the first data cut-off for the derivation of the added benefit, considered the proof of an effect modification to be irrelevant, and overall derived proof of an added benefit on the basis of the total population.

A statistically significant difference in favour of cobimetinib in combination with vemurafenib was shown for the outcome **"insomnia"** for the mean change up to cycle 8 using an MMRM. The 95% CI of Hedges' g was not completely below the irrelevance threshold of –0.2. It can therefore not be inferred that the effect is relevant. For the outcome "insomnia", this resulted in no hint of an added benefit of cobimetinib in combination with vemurafenib in comparison with the ACT; an added benefit is therefore not proven for this outcome. This deviates from the company's assessment, which used the responder analyses based on the first data cut-off for the derivation of the added benefit, and derived proof of an added benefit for this outcome.

A statistically significant difference to the disadvantage of cobimetinib in combination with vemurafenib was shown for the outcome **"diarrhoea"** for the mean change up to cycle 8 using an MMRM. The 95% CI of Hedges' g was completely above the irrelevance threshold of 0.2. This was interpreted to be a relevant effect. There was a hint of lesser benefit of cobimetinib in combination with vemurafenib compared with the ACT for the outcome "diarrhoea". This deviates from the company's assessment, which used the responder analyses based on the first data cut-off for the derivation of the added benefit, and, despite a statistically significant difference to the disadvantage of cobimetinib, derived no lesser benefit from this.

A statistically significant difference to the disadvantage of cobimetinib in combination with vemurafenib was shown for the outcome **"nausea and vomiting"** for the mean change up to cycle 8 using an MMRM. The 95% CI of Hedges' g was not completely above the irrelevance threshold of 0.2. It can therefore not be inferred that the effect is relevant. For the outcome "nausea and vomiting", there was no hint of an added benefit or of lesser benefit of cobimetinib in combination with vemurafenib in comparison with the ACT; an added benefit is therefore not proven for this outcome. This concurs with the company's assessment, which used the responder analyses based on the first data cut-off for the derivation of the added benefit, however.

No statistically significant difference between the treatment options was shown for the mean change up to cycle 8 using an MMRM for each of the outcomes **"dyspnoea", "fatigue", "appetite loss"** and **"constipation"**. This resulted in no hint of an added benefit of cobimetinib in combination with vemurafenib in comparison with the ACT; an added benefit is therefore not proven for these outcomes. The company used the responder analyses based on the first data cut-off for the derivation of the added benefit of these outcomes. It derived proof of an added benefit for the outcome "fatigue"; it also considered the added benefit as not proven for the other outcomes.

Health status

A statistically significant difference in favour of cobimetinib in combination with vemurafenib was shown for the outcome "health status" recorded with the VAS of the EQ-5D for the mean change up to cycle 8 using an MMRM. The 95% CI of Hedges' g was not completely above the irrelevance threshold of 0.2. It can therefore not be inferred that the effect is relevant. For the outcome "health status", there was no hint of an added benefit of cobimetinib in combination with vemurafenib in comparison with the ACT; an added benefit is therefore not proven. This deviates from the company's assessment, which used the data of the first data cut-off and derived proof of an added benefit.

Health-related quality of life

Aspects of health-related quality of life were recorded using the functional scales of the cancer-specific questionnaire EORTC QLQ-C30. Due to the high risk of bias (see Section 2.7.2.4.2 of the full dossier assessment), at most a hint of an added benefit or of lesser benefit could be derived for all outcomes in this category.

No statistically significant difference between the treatment options was shown for the mean change up to cycle 8 using an MMRM for each of the following outcomes: **global health status, physical functioning, role functioning, emotional functioning, cognitive functioning** and **social functioning**. This resulted in no hint of an added benefit of cobimetinib in combination with vemurafenib in comparison with the ACT; an added benefit is therefore not proven for these outcomes. The company used the data of the first data cut-off based on the responder analyses for the derivation of the added benefit of these outcomes. The company derived proof of an added benefit for the outcomes "physical functioning" and "social functioning"; it also considered the added benefit as not proven for the other outcomes.

Adverse events

Due to the different observation periods in the 2 study arms, the time-adjusted analyses were used for the assessment. Based on the results of these analyses, due to the high risk of bias (see Section 2.7.2.4.2 of the full dossier assessment), at most a hint of lesser or greater harm can be derived for all outcomes except individual specific AEs, for which the derivation of an indication is justified below.

Serious adverse events

No statistically significant difference between the treatment options was shown for the outcome "SAEs" (time to first event). This resulted in no hint of greater or lesser harm of cobimetinib in combination with vemurafenib compared with the ACT for SAEs; greater or lesser harm is therefore not proven for this outcome. This concurs with the company's assessment.

Discontinuation due to AEs

No statistically significant difference between the treatment options was shown for the outcome "discontinuation due to AEs (time to first event). This resulted in no hint of greater or lesser harm of cobimetinib in combination with vemurafenib compared with the ACT for discontinuation due to AEs; greater or lesser harm is therefore not proven for this outcome. This concurs with the company's assessment.

Severe adverse events (CTCAE grade ≥ 3)

A statistically significant difference to the disadvantage of cobimetinib in combination with vemurafenib was shown for the outcome "severe AEs (CTCAE grade ≥ 3)" (time to first event), and additionally proof of an effect modification by the characteristic "metastasis stage". For this reason, the results were interpreted separately for patients with metastasis stage IIIc, M1a or M1b and patients with metastasis stage M1c (see Section 2.4.4).

There was a hint of greater harm of cobimetinib in combination with vemurafenib for patients with metastasis stage IIIc, M1a or M1b. There was no hint of greater or lesser harm of cobimetinib in combination with vemurafenib compared with the ACT for patients with metastasis stage M1c; greater or lesser harm is therefore not proven for this subgroup. This deviates from the company's assessment, which considered the effect modification by the characteristic "metastasis stage" as irrelevant and, also on the basis of the statistically significant disadvantage in the total population, derived no greater or lesser harm for the outcome.

Specific adverse events

A statistically significant difference to the disadvantage of cobimetinib in combination with vemurafenib was shown for the outcome **"photosensitivity reaction"** (time to first event), and additionally proof of an effect modification by the characteristic "metastasis stage". For this reason, the results were interpreted separately for patients with metastasis stage IIIc, M1a or M1b and patients with metastasis stage M1c (see Section 2.4.4).

There was a hint of greater harm of cobimetinib in combination with vemurafenib for patients with metastasis stage M1c. There was no hint of greater harm of cobimetinib in combination with vemurafenib compared with the ACT for patients with metastasis stage IIIc, M1a or M1b; greater or lesser harm is therefore not proven for this subgroup. This deviates from the company's assessment, which considered the effect modification by the characteristic

"metastasis stage" as irrelevant and, also on the basis of the statistically significant disadvantage in the total population, derived no greater or lesser harm for the outcome.

A statistically significant difference in favour of cobimetinib in combination with vemurafenib was shown for each of the outcomes **"alopecia"** and **"hyperkeratosis"** (time to first event). Despite the high risk of bias, there was an indication of lesser harm of cobimetinib in combination with vemurafenib for each of these outcomes. The certainty of results for these 2 outcomes was not downgraded because notably more events occurred in the vemurafenib arm, which had a shorter observation duration, and it was therefore not assumed that the observed direction of effect was caused by bias alone. The company derived no greater or lesser harm for these outcomes.

A statistically significant difference to the disadvantage of cobimetinib in combination with vemurafenib was shown for each of the following outcomes: **diarrhoea, nausea, vomiting** and **serous retinopathy/retinal detachment** (in each case time to first event). There was a hint of greater harm from cobimetinib for each of the outcomes "diarrhoea", "nausea" and "vomiting". There was an indication of greater harm of cobimetinib for the outcome "serous retinopathy/retinal detachment" despite the high risk of bias. Due to the effect size, which cannot be explained by the different observation periods and the potentially informative censorings alone, a high certainty of results could be assumed for this result. The company derived no greater or lesser harm for these outcomes.

Further specific adverse events (neoplasms benign, malignant and unspecified [incl cysts and polyps])

The overview of the most common AEs (see Table 26 in Appendix B of the full dossier assessment) showed a potentially important difference between the treatment arms for the outcome "neoplasms benign, malignant and unspecified (incl cysts and polyps)". Due to the different observation periods in the 2 study arms and the missing survival time analyses for this outcome, a qualitative interpretation was conducted on the basis of naive proportions (see Section 2.7.2.4.2 of the full dossier assessment). Overall, notably more events occurred in the vemurafenib arm, which had a shorter observation duration, so that it was not assumed that the observed direction of effect (in favour of cobimetinib in combination with vemurafenib) was caused by bias alone. An indication of lesser harm of cobimetinib in combination with vemurafenib was derived on the basis of this qualitative consideration. This deviates from the company's assessment, which derived no greater or lesser harm for this outcome.

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics, which were predefined in the coBRIM study, were considered relevant for the present benefit assessment:

- age (< 65 years/≥ 65 years)
- sex (men/women)

- metastasis stage (M1c/IIIc, M1a, M1b)
- geographical region (North America/Europe/Australia/New Zealand/other)

Suitable subgroup analyses were available or could be calculated by the Institute for all outcomes except for the outcome “neoplasms benign, malignant and unspecified (incl cysts and polyps)”. Only naive proportions were available for the outcome “neoplasms benign, malignant and unspecified (incl cysts and polyps)”, however. Interaction tests were not calculated for this outcome because, due to the possible bias caused by the differences in observation periods in the 2 treatment arms, interaction tests would have been at most suitable to draw qualitative conclusions.

The results on subgroups with at least an indication of an effect modification and, additionally, statistically significant results in at least one subgroup are presented below for the outcomes “overall survival”, “symptoms”, “health status” and “health-related quality of life”. In addition, for the outcomes on morbidity and health-related quality of life, the 95% CI of Hedges’ g had to be fully above the irrelevance threshold of 0.2 to interpret this effect as relevant. The subgroup results on these outcomes were assessed based on the data of the third data cut-off.

There was a high risk of bias of possibly different degrees in the subgroups for the outcomes on AEs because of the different observation periods and informative censoring (see Section 2.7.2.4.2 of the full dossier assessment). Deviating from the other outcomes, only subgroup analyses with proof of an interaction ($p < 0.05$) were used in the present benefit assessment due to this uncertainty. The subgroup results on AEs were assessed based on the data of the second data cut-off.

The prerequisite for proof of differing effects is a statistically significant homogeneity and/or interaction test ($p < 0.05$). An indication of differing effects results from a p-value between 0.05 and 0.2.

Table 18: Subgroups (morbidity) – RCT, direct comparison: cobimetinib + vemurafenib vs. vemurafenib

Study **Outcome category**	**Cobimetinib + vemurafenib**			**Vemurafenib**			**Cobimetinib + vemurafenib vs. vemurafenib**
Outcome/ subscale **Characteristic** **Subgroup**	**N[a]**	**Baseline values mean (SD)**	**Change until cycle 8 mean[b] (SE)**	**N[a]**	**Baseline values mean (SD)**	**Change until cycle 8 mean[b] (SE)**	**MD [95% CI]; p-value[b]**
coBRIM							
Morbidity							
EORTC QLQ-C30/pain[c]							
Age							
< 65 years	151	ND	–3.9 (1.3)	141	ND	3.4 (1.4)	–7.31 [–11.06; –3.57] < 0.001 Hedges' g: –0.45 [–0.68; –0.21][d]
≥ 65 years	51	ND	0.5 (2.6)	61	ND	–0.6 (2.4)	1.08 [–5.96; 8.11] 0.762
						Interaction:	p-value = 0.039[e]

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study (and at other data cut-offs) may be based on other patient numbers.
b: Results from unadjusted MMRM analysis.
c: Results of the third data cut-off on 16 January 2015.
d: Institute's calculation based on the mean difference and CI of the MMRM.
e: Institute's calculation.

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; MMRM: mixed-effects model repeated measures; N: number of analysed patients; ND: no data, QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; vs.: versus

Table 19: Subgroups (AEs) – RCT, direct comparison: cobimetinib + vemurafenib vs. vemurafenib

Study **Outcome category**	**Cobimetinib + vemurafenib**		**Vemurafenib**		**Cobimetinib + vemurafenib vs. vemurafenib**	
Outcome **Characteristic** **Subgroup**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR[a] [95% CI]**	**p-value[b]**
coBRIM						
Adverse events						
Severe AEs (CTCAE grade ≥ 3)[c]						
Metastasis stage[d]						
IIIc, M1a, M1b	101	ND [ND; ND] 74 (73)	95	ND [ND; ND] 49 (52)	1.76 [1.23; 2.53]	0.002
M1c	146	ND [ND; ND] 102 (70)	151	ND [ND; ND] 97 (64)	1.04 [0.78; 1.37]	0.807
					Interaction:	0.021[e]
Photosensitivity reaction[c]						
Metastasis stage[d]						
IIIc, M1a, M1b	101	ND 32 (32)	95	ND 26 (27)	1.18 [0.71; 1.99]	0.521
M1c	146	ND 50 (34)	151	ND 19 (13)	2.81 [1.65; 4.76]	< 0.001
					Interaction:	0.026[e]

a: Results based on a Cox proportional hazards model.
b: Log-rank test.
c: Results of the second data cut-off on 19 September 2014.
d: According to AJCC classification [4].
e: Calculated using the likelihood ratio test.
AE: adverse event; AJCC: American Joint Committee on Cancer; 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; ND: no data; RCT: randomized controlled trial; vs.: versus

Morbidity

Symptom scales of the EORTC QLQ-C30

There was proof of an effect modification by the characteristic "age" for the outcome "pain" (interaction test p = 0.039; Table 18).

A statistically significant difference in favour of cobimetinib in combination with vemurafenib was shown for patients < 65 years. The 95% CI of Hedges' g was completely below the irrelevance threshold of –0.2. This was interpreted to be a relevant effect. There

was no statistically significant difference between the 2 treatment groups in the group of patients ≥ 65 years.

This resulted in a hint of an added benefit of cobimetinib in combination with vemurafenib compared with the ACT for patients under the age of 65 years. For patients ≥ 65 years of age, however, there was no hint of an added benefit of cobimetinib in combination with vemurafenib in comparison with the ACT; an added benefit is therefore not proven.

The company used the data of the first data cut-off for the derivation of the added benefit and did not consider the proof of an effect modification. Based on the total population, it derived proof of an added benefit for this outcome.

Adverse events

Severe adverse events (CTCAE grade ≥ 3)

There was proof of an effect modification by the characteristic "metastasis stage" for the outcome "severe AEs (CTCAE grade ≥ 3)" (interaction test p = 0.021; Table 19).

A statistically significant difference to the disadvantage of treatment with cobimetinib in combination with vemurafenib was shown for patients with metastasis stage IIIc, M1a or M1b. There was no statistically significant difference between the 2 treatment groups in the group of patients with metastasis stage M1c.

This resulted in a hint of greater harm of cobimetinib in combination with vemurafenib compared with the ACT for patients with metastasis stage IIIc, M1a or M1b. There was no hint of greater or lesser harm of cobimetinib in combination with vemurafenib compared with the ACT for patients with metastasis stage M1c; an added benefit is therefore not proven for this subgroup.

The company derived no greater or lesser harm of treatment with cobimetinib in combination with vemurafenib in comparison with the ACT for the outcome "severe AEs (CTCAE grade ≥ 3)".

Photosensitivity reaction

There was proof of an effect modification by the characteristic "metastasis stage" for the outcome "photosensitivity reaction" (interaction test p = 0.026; Table 19).

A statistically significant difference to the disadvantage of treatment with cobimetinib in combination with vemurafenib was shown for patients with metastasis stage M1c. There was no statistically significant difference between the 2 treatment groups in the group of patients with metastasis stage IIIc, M1a or M1b.

This resulted in a hint of greater harm of cobimetinib in combination with vemurafenib compared with the ACT for patients with metastasis stage M1c. There was no hint of greater or lesser harm of cobimetinib in combination with vemurafenib compared with the ACT for

patients with metastasis stage IIIc, M1a or M1b; an added benefit is therefore not proven for this subgroup.

The company derived no greater or lesser harm of treatment with cobimetinib in combination with vemurafenib in comparison with the ACT for the outcome “photosensitivity reaction”.

2.5 Extent and probability of added benefit

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

The approach for deriving an overall conclusion on 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.

2.5.1 Assessment of added benefit at outcome level

The data presented in Section 2.4 resulted in indications of an added benefit or of lesser harm of cobimetinib in combination with vemurafenib in the total population for the following outcomes: overall survival, neoplasms benign, malignant and unspecified (incl cysts and polyps), alopecia and hyperkeratosis. For patients < 65 years, a hint of an added benefit of cobimetinib in combination with vemurafenib was shown for the outcome “pain”. An indication or hints of lesser benefit or greater harm were shown in the total population for the following outcomes: diarrhoea, nausea, vomiting and serous retinopathy/retinal detachment. Moreover, there were hints of greater harm for patients with metastasis stage IIIc, M1a and M1b for the outcome “severe AEs (AEs of CTCAE grade ≥ 3) and for patients with metastasis stage M1c for the outcome “photosensitivity reaction”. The extent of the respective added benefit at outcome level was estimated from these results (see Table 20).

The outcomes “pain” and “diarrhoea” (EORTC symptom scales) were allocated to the outcome category “non-serious/non-severe symptoms/late complications” because a comparison with the data on AEs showed that the majority of the Preferred Terms (PTs) referring to pain and occurred cases of diarrhoea corresponded to a CTCAE grade < 3.

The outcomes “alopecia”, “hyperkeratosis”, “photosensitivity reaction”, “diarrhoea”, “nausea”, “vomiting” and “serous retinopathy/retinal detachment” operationalized as AEs were allocated to the outcome category “non-serious/non-severe AEs” because the majority of the AEs had a CTCAE grade < 3 in the analysis.

Most PTs that occurred in the coBRIM study and were allocated to the System Organ Class (SOC) “neoplasms benign, malignant and unspecified (incl cysts and polyps)” were of CTCAE grade ≥ 3, however, so that this outcome was allocated to the category “serious/ severe AEs”.

Table 20: Extent of added benefit at outcome level: cobimetinib + vemurafenib vs. vemurafenib

Outcome category **Outcome** **Effect modifier/subscale** **Subgroup**	**Cobimetinib + vemurafenib vs. vemurafenib** **Median time to event [months] or mean change** **Effect estimates [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	Third data cut-off Median: NA vs. 17.0 HR: 0.65 [0.49; 0.87]; p = 0.003 probability: "indication"	Outcome category: mortality $0.85 \leq CI_u < 0.95$ added benefit, extent "considerable"
Morbidity		
EORTC QLQ-C30 symptom scales		
Dyspnoea	Mean change: 1.0 vs. 0.3 MD: 0.78 [–2.44; 3.99]; p = 0.636	Lesser benefit/added benefit not proven
Fatigue	Mean change: 5.9 vs. 7.9 MD: –2.08 [–5.34; 1.17]; p = 0.209	Lesser benefit/added benefit not proven
Insomnia	Mean change: –6.4 vs. 0.3 MD: –6.74 [–10.35; –3.12]; p < 0.001 Hedges' g –0.36 [–0.56; –0.17][c]	Lesser benefit/added benefit not proven
Pain		
Age		
< 65 years	Mean change: –3.9 vs. 3.4 MD: –7.31 [–11.06; –3.57]; p < 0.001 Hedges' g –0.45 [–0.68; –0.21][c] probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "non-quantifiable"
≥ 65 years	Mean change: 0.5 vs. –0.6 MD: 1.08 [–5.96; 8.11]; p = 0.762	Lesser benefit/added benefit not proven
Appetite loss	Mean change: 1.8 vs. 4.6 MD: –2.83 [–6.61; 0.95]; p = 0.142	Lesser benefit/added benefit not proven
Diarrhoea	Mean change: 12.4 vs. 6.2 MD: 6.2 [3.34; 9.07]; p < 0.001 Hedges' g 0.42 [0.22; 0.62][c] probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications Lesser benefit, extent: "non-quantifiable"
Nausea and vomiting	Mean change: 3.7 vs. 1.4 MD: 2.25 [0.29; 4.2]; p = 0.024 Hedges' g 0.22 [0.03; 0.42][c]	Lesser benefit/added benefit not proven
Constipation	Mean change: –2.0 vs. –1.1 MD: –0.85 [–3.3; 1.59]; p = 0.494	Lesser benefit/added benefit not proven

(continued)

Table 20: Extent of added benefit at outcome level: cobimetinib + vemurafenib vs. vemurafenib (continued)

Outcome category **Outcome** **Effect modifier/subscale** **Subgroup**	**Cobimetinib + vemurafenib vs. vemurafenib** **Median time to event [months] or mean change** **Effect estimates [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Health status		
EQ-5D VAS	Mean change: –0.5 vs. –3.6 MD: 3.14 [0.34; 5.94]; p = 0.028 Hedges' g 0.22 [0.02; 0.41][c]	Lesser benefit/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 functional scales		
Global health status	Mean change: –4.2 vs. –5.2 MD: 1.04 [–1.9; 3.97]; p = 0.489	Lesser benefit/added benefit not proven
Physical functioning	Mean change: –2.2 vs. –4.5 MD: 2.28 [–0.28; 4.85]; p = 0.080	Lesser benefit/added benefit not proven
Role functioning	Mean change: –6.6 vs. –9.1 MD: 2.59 [–1.18; 6.36]; p = 0.177	Lesser benefit/added benefit not proven
Emotional functioning	Mean change: 3.6 vs. 2.6 MD: 1.06 [–1.67; 3.78]; p = 0.446	Lesser benefit/added benefit not proven
Cognitive functioning	Mean change: –3.4 vs. –3.0 MD: –0.32 [–2.85; 2.2]; p = 0.801	Lesser benefit/added benefit not proven
Social functioning	Mean change: –2.3 vs. –4.9 MD: 2.61 [–0.9; 6.12]; p = 0.144	Lesser benefit/added benefit not proven
Adverse events		
SAEs	Median: ND vs. ND HR: 1.27 [0.91; 1.75]; p = 0.154	Greater/lesser harm not proven
Discontinuation due to AEs	Median: ND vs. ND HR: 1.71 [0.99; 2.94]; p = 0.052	Greater/lesser harm not proven
AEs CTCAE grade ≥ 3		
Metastasis stage[d]		
IIIc, M1a, M1b	Median: ND vs. ND HR: 1.76 [1.23; 2.53] HR: 0.57 [0.40; 0.81][e] p = 0.002 probability: "hint"	Outcome category: serious/severe AEs $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"
M1c	Median: ND vs. ND HR: 1.04 [0.78; 1.37]; p = 0.807	Greater/lesser harm not proven

(continued)

Table 20: Extent of added benefit at outcome level: cobimetinib + vemurafenib vs. vemurafenib (continued)

Outcome category **Outcome** **Effect modifier/subscale** **Subgroup**	**Cobimetinib + vemurafenib vs. vemurafenib** **Median time to event [months] or mean change** **Effect estimates [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Alopecia	Median: ND vs. ND HR: 0.41 [0.28; 0.61]; p < 0.001 probability: "indication"[f]	Outcome category: non-serious/non-severe AEs CI_u < 0.80 lesser harm, extent: "considerable"
Hyperkeratosis	Median: ND vs. ND HR: 0.28 [0.18; 0.44]; p < 0.001 probability: "indication"[f]	Outcome category: non-serious/non-severe AEs CI_u < 0.80 lesser harm, extent: "considerable"
Photosensitivity reaction		
Metastasis stage[d]		
IIIc, M1a, M1b	Median: ND vs. ND HR: 1.18 [0.71; 1.99]; p = 0.521	Greater/lesser harm not proven
M1c	Median: ND vs. ND HR: 2.81 [1.65; 4.76] HR: 0.36 [0.21; 0.61][e] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe AEs CI_u < 0.80 greater harm, extent: "considerable"
Diarrhoea	Median: ND vs. ND HR: 2.60 [1.97; 3.44] HR: 0.38 [0.29; 0.51][e] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe AEs CI_u < 0.80 greater harm, extent: "considerable"
Nausea	Median: ND vs. ND HR: 1.80 [1.31; 2.47] HR: 0.56 [0.40; 0.76][e] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe AEs CI_u < 0.80 greater harm, extent: "considerable"

(continued)

Table 20: Extent of added benefit at outcome level: cobimetinib + vemurafenib vs. vemurafenib (continued)

Outcome category **Outcome** **Effect modifier/subscale** **Subgroup**	**Cobimetinib + vemurafenib vs. vemurafenib** **Median time to event [months] or mean change** **Effect estimates [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Vomiting	Median: ND vs. ND HR: 2.03 [1.32; 3.13] HR: 0.49 [0.32; 0.76][e] p = 0.001 probability: "hint"	Outcome category: non-serious/non-severe AEs CI_u < 0.80 greater harm, extent: "considerable"
Serous retinopathy/retinal detachment	Median: ND vs. ND HR: 9.72 [4.45; 21.23] HR: 0.10 [0.05; 0.22][e] p < 0.001 probability: "hint"[g]	Outcome category: non-serious/non-severe AEs CI_u < 0.80 greater harm, extent: "considerable"
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Qualitative consideration[h] probability: "indication"[f]	Outcome category: serious/severe AEs lesser harm, extent: "non-quantifiable"

a: Probability provided if statistically significant differences are present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Added benefit assumed with upper and lower CI limits < –0.2 or > 0.2.
d: According to AJCC classification [4].
e: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
f: The event was less frequent in the cobimetinib + vemurafenib arm than in the vemurafenib arm despite the longer observation period.
g: Due to the effect size, which cannot be explained by the different observation periods and the potentially informative censorings alone, a high certainty of results could be assumed for this result.
h: The AEs presented can only be interpreted in qualitative terms because of the differences in the median treatment duration in the 2 study arms.

AE: adverse event; AJCC: American Joint Committee on Cancer; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; MD: mean difference; NA: not achieved; ND: no data; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 21 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 21: Positive and negative effects from the assessment of cobimetinib in combination with vemurafenib compared with vemurafenib

Positive effects	**Negative effects**
Mortality ▪ overall survival: indication of an added benefit – extent: “considerable”	
Non-serious/non-severe symptoms/late complications ▪ EORTC QLQ-C30 symptom scales: pain ▫ < 65 years: hint of an added benefit, extent: “non-quantifiable”	Non-serious/non-severe symptoms/late complications ▪ EORTC QLQ-C30 symptom scales: diarrhoea: hint of lesser benefit, extent: “non-quantifiable”
Serious/severe AEs ▪ neoplasms benign, malignant and unspecified (incl cysts and polyps): indication of lesser harm, extent: “non-quantifiable”	Serious/severe AEs ▪ severe AEs (CTCAE grade ≥ 3) ▫ metastasis stage[a] (IIIc, M1a, M1b): hint of greater harm, extent: “considerable”
Non-serious/non-severe AEs ▪ alopecia: indication of lesser harm, extent: “considerable” ▪ hyperkeratosis: indication of lesser harm, extent: “considerable”	Non-serious/non-severe AEs ▪ photosensitivity reaction ▫ metastasis stage[a] (M1c): hint of greater harm, extent: “considerable” ▪ diarrhoea: hint of greater harm, extent: “considerable” ▪ nausea: hint of greater harm, extent: “considerable” ▪ vomiting: hint of greater harm, extent: “considerable” ▪ serous retinopathy/retinal detachment: indication of greater harm, extent: “considerable”
a: According to AJCC classification [4]. AE: adverse event; AJCC: American Joint Committee on Cancer; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; QLQ-C30: Quality of Life Questionnaire-Core 30	

Overall, considerable positive and considerable negative effects remain. The certainty of results of the positive effects is higher than the one of the negative effects. Balancing these effects, the considerable positive effects were not outweighed by the negative effects, but downgraded in their extent.

In summary, there is an indication of a minor added benefit of cobimetinib in combination with vemurafenib compared with the ACT vemurafenib for patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

The result of the assessment of the added benefit of cobimetinib in comparison with the ACT is summarized in Table 22.

Table 22: Cobimetinib – extent and probability of added benefit

Therapeutic indication	ACT[a]	Extent and probability of added benefit
Adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation[b]	Vemurafenib	Indication of minor added benefit
a: Presentation of the ACT specified by the G-BA. b: According to the SPC, the administration of cobimetinib in combination with vemurafenib is approved for patients with unresectable or metastatic melanoma with a BRAF V600 mutation – without restriction of pretreatment [3]. The study population of the included study for the assessment of the added benefit (only treatment-naive patients) therefore does not completely cover the therapeutic indication. It remains unclear whether the observed effects can be transferred to patients who have already had treatment for their advanced melanoma. ACT: appropriate comparator therapy; BRAF: rapidly accelerated fibrosarcoma – isoform B; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics		

This deviates from the company's approach, which derived proof of a considerable added benefit.

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

2.6 List of included studies

coBRIM

F. Hoffmann-La Roche. A phase III, double-blind, placebo-controlled study of vemurafenib versus vemurafenib plus GDC-0973 in previously untreated BRAFV600-mutation positive patients with unresectable locally advanced or metastatic melanoma [online]. In: EU-Clinical Trials Register. [Accessed: 5 January 2016]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-003008-11.

F. Hoffmann-La Roche. A Phase III double-blind, placebo-controlled study of vemurafenib versus vemurafenib plus GDC-0973 in previously untreated BRAF600-mutation positive patients with unresectable locally advanced or metastatic melanoma: report no. 1060643; study GO28141; primary clinical study report [unpublished]. 2014.

F. Hoffmann-La Roche. A Phase III double-blind, placebocontrolled study of vemurafenib versus vemurafenib plus GDC-0973 in previously untreated BRAF600-mutation positive patients with unresectable locally advanced or metastatic melanoma; study GO28141; Zusatzanalysen [unpublished]. 2014.

F. Hoffmann-La Roche. A Phase III double-blind, placebocontrolled study of vemurafenib versus vemurafenib plus GDC-0973 in previously untreated BRAF600-mutation positive patients with unresectable locally advanced or metastatic melanoma; study GO28141; Zusatzanalysen [unpublished]. 2015.

F. Hoffmann-La Roche. Safety update report for cobimetinib [unpublished]. 2015.

F. Hoffmann-La Roche. Efficacy update report for study GO28141 [unpublished]. 2015.

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F. Hoffmann-La Roche. A phase III, double-blind, placebo-controlled study of vemurafenib versus vemurafenib plus GDC-0973 in previously untreated BRAFV600-mutation positive patients with unresectable locally advanced or metastatic melanoma: study GO28141; statistical analysis plan version 3 [unpublished]. 2015.

F. Hoffmann-La Roche. A phase III, double-blind, placebo-controlled study of vemurafenib versus vemurafenib plus GDC-0973 in previously untreated BRAFV600-mutation positive patients with unresectable locally advanced or metastatic melanoma: study GO28141; statistical analysis plan version 1 [unpublished]. 2015.

F.Hoffmann-La Roche. A phase III, double-blind, placebo-controlled study of vemurafenib versus vemurafenib plus GDC-0973 in previously untreatedBRAFV600-mutation positive patients with unresectable locally advanced or metastatic melanoma [online]. In: PharmNet.Bund Klinische Prüfungen. [Accessed: 10 September 2015]. URL: https://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.html.

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Hoffmann-La Roche. A Phase III study comparing vemurafenib vs vemurafenib plus cobimetinib (GDC-0973) in patients with metastatic melanoma: study results [online]. In: ClinicalTrials.gov. 1 October 2015 [accessed: 5 January 2016]. URL: https://clinicaltrials.gov/ct2/show/results/NCT01689519.

Hoffmann-La Roche. coBRIM: A phase 3 study comparing GDC-0973 (cobimetinib), a MEK inhibitor, in combination with vemurafenib vs vemurafenib alone in patients with metastatic melanoma [online]. In: Roche Clinical Trial Registry. 8 May 2015 [accessed: 22 October 2015]. URL: http://www.roche-trials.com/trialDetailsGet.action?studyNumber=GO28141.

Larkin J, Ascierto PA, Dreno B, Atkinson V, Liszkay G, Maio M et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med 2014; 371(20): 1867-1876.

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Please see full dossier assessment for full reference list.

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The full report (German version) is published under https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/a15-52-cobimetinib-nutzenbewertung-gemaess-35a-sgb-v.7152.html.