IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Elvitegravir fixed combination – Benefit assessment according to § 35a Social Code Book V[1]

Extract

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[2] Due to legal data protection regulations, employees have the right not to be named.

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AIDS	acquired immunodeficiency syndrome
CD4	cluster of differentiation 4
CDC	Centers for Disease Control and Prevention
COBI	cobicistat
eGFR	estimated glomerular filtration rate
EFV	efavirenz
EVG	elvitegravir
FTC	emtricitabine
G-BA	*Gemeinsamer Bundesausschuss* (Federal Joint Committee)
IQWiG	*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* (Institute for Quality and Efficiency in Health Care)
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
PT	MedDRA Preferred Term
RCT	randomized controlled trial
RNA	ribonucleic acid
SAE	serious adverse event
SGB	*Sozialgesetzbuch* (Social Code Book)
SOC	MedDRA System Organ Class
TDF	tenofovir disoproxil fumarate
TLOVR	time to loss of virologic response

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 combination elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil (EVG/COBI/FTC/TDF). The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter abbreviated to "the company"). The dossier was sent to IQWiG on 14 June 2013.

Research question

The aim of this report is to assess the added benefit of EVG/COBI/FTC/TDF compared with the appropriate comparator therapy (ACT) in adults infected with human immunodeficiency virus type 1 (HIV-1).

In compliance with the approval, the G-BA specified separate appropriate comparator information for treatment-naive and pretreated patients (see Table 2).

Table 2: Subindications and ACT for EVG/COBI/FTC/TDF

Research question	Subindication	ACT specified by the G-BA
A	Treatment-naive patients	Efavirenz in combination with 2 nucleoside/nucleotide analogues (tenofovir plus emtricitabine or abacavir plus lamivudine)
B	Pretreated patients[a]	Individual therapy based on prior treatment(s) and under consideration of the reason for the switch of treatment, particularly treatment failure due to virologic failure and possible accompanying development of resistance, or due to AEs. The approval of the drugs is to be considered.
a: Patients who are infected with HIV-1 without known mutations associated with resistance to any of the 3 antiretroviral drugs of EVG/COBI/FTC/TDF. ACT: appropriate comparator therapy; AE: adverse event; EVG/COBI/FTC/TDF: elvitegravir/cobicistat/ emtricitabine/tenofovir disoproxil; G-BA: Federal Joint Committee; HIV-1: human immunodeficiency virus type 1		

Research question A: treatment-naive patients

The ACT specified by the G-BA was used for treatment-naive patients. The company claimed to concur with this ACT, but additionally referred to results on deviating comparator therapies (boosted protease inhibitors or raltegravir, each in combination with emtricitabine and tenofovir) because it considered these to be not inferior to the G-BA's ACT. This expansion was not accepted in the benefit assessment.

Research question B: pretreated patients

Contrary to the inclusion criteria originally formulated by the company, the company also included treatment-naive patients in the benefit assessment because it had not identified any study with pretreated patients suitable for the benefit assessment. This approach was not accepted because the company did not prove with adequate scientific research that the data from clinical studies with treatment-naive patients could be transferred to pretreated patients. Outcome-specific effect variations are conceivable in both treatment directions (larger or smaller effect differences versus the ACT). The results of studies can be regarded as "transferable" when it is proven with sufficient certainty and plausibility that the effect estimates of all patient-relevant outcomes investigated are not substantially influenced by the characteristic in question (here: prior treatment).

The ACT specified by the G-BA was used for pretreated patients (see Table 4). Although the company claimed to follow the G-BA's ACT, it limited the ACT to few treatment regimens (EFV/FTC/TDF or ATV/r+FTC/TDF or RAL+FTC/TDF), which, from its point of view, were representative. This limitation was not accepted in the benefit assessment. The ACT was a therapy tailored to the individual patient. In this context, limitation to a small number of drugs is not advisable because individual criteria (e.g. AEs or resistance) may make it necessary to use a treatment that deviates from the company's prespecification.

Summary

The assessment of EVG/COBI/FTC/TDF was conducted versus the ACT specified by the G-BA for treatment-naive patients (research question A) and for pretreated patients (research question B). The assessment was conducted based on patient-relevant outcomes and on randomized controlled trials (RCTs) with a minimum duration of 48 weeks. Only direct comparative studies were included in the assessment.

Results for treatment-naive patients (research question A)

Two RCTs were included in the assessment (GS-US-236-0102 and GS-US-236-0104). The phase III study GS-US-236-0102 included 707 randomized patients and was thus considerably larger than the phase II study GS-US-236-0104 with 71 randomized patients. In both studies, EVG/COBI/FTC/TDF was directly compared with the G-BA's ACT (efavirenz in combination with emtricitabine plus tenofovir [EFV/FTC/TDF]).

The risk of bias of both studies at study level was rated as low. Several times of analysis were available for both studies. The results at the time of analysis "96 weeks" was primarily used in the benefit assessment because the longer time of analysis is preferred in the therapeutic indication. However, only data from the study GS-US-236-0102 were available for this point of time. If there was a statistically significant difference after 96 weeks, the results of the meta-analysis from the studies GS-US-236-0102 and GS-US-236-0104 at the earlier time of analysis (48/60 weeks) were additionally used. If the pooled data confirmed the results after 96 weeks, the certainty of results was upgraded (e.g. from "indication" to "proof").

The study GS-US-236-0102 is an ongoing study with a planned treatment duration of 192 weeks. There were no results yet on this time of analysis when the dossier was submitted, but these would make sense in this therapeutic indication because the treatment is designed for long-term use.

Mortality

The result for the outcome "all-cause mortality" was not statistically significant after 96 weeks or after 48/60 weeks. An added benefit of EVG/COBI/FTC/TDF or greater harm from it compared with EFV/FTC/TDF is not proven for this outcome.

Morbidity

AIDS-defining events (CDC class C events)

At the time of analysis "96 weeks", statistically significantly more patients had an AIDS-defining event under treatment with EVG/COBI/FTC/TDF than under treatment with EFV/FTC/TDF (8 patients versus 1 patient). The pooled result after 48/60 weeks showed the same direction of effect, but the group difference was not statistically significant at this time. Overall, there was therefore an indication of lesser benefit of EVG/COBI/FTC/TDF for this outcome.

Virologic response (TLOVR) and CD4 cell count as sufficiently valid surrogates for the patient-relevant outcome "AIDS-defining illnesses/death"

Both measurements were used as sufficiently valid surrogate outcomes for the combined outcome "AIDS-defining illnesses/death" in the benefit assessment. Since the outcome that in fact is patient-relevant (AIDS-defining events [CDC class C events]) was recorded in the studies, the 2 surrogate outcomes were only provided as additional information in the benefit assessment, but were not included in the final balancing on the added benefit.

For virologic response, there was no statistically significant difference between the 2 treatment arms after 96 weeks or after 48 weeks.

A statistically significant difference in the increase in cell count was shown after 96 weeks for the cluster of differentiation 4 (CD4) cell count. This positive effect in favour of EVG/COBI/FTC/TDF was also shown in the result of the meta-analysis after 60 weeks. This effect was not very pronounced, however.

Overall, both surrogate outcomes did not provide any clear results and no clear advantage or disadvantage of EVG/COBI/FTC/TDF could be derived from them.

Health-related quality of life

No data on health-related quality of life were recorded in the studies. Hence an added benefit of EVG/COBI/FTC/TDF is not proven for this outcome.

Adverse events

Serious AEs (SAEs) occurred statistically significantly more frequently after 96 weeks under treatment with EVG/COBI/FTC/TDF. The pooled data after 48/60 weeks confirmed this result. Under consideration of the low risk of bias for this outcome, there was proof of greater harm from EVG/COBI/FTC/TDF compared with the ACT EFV/FTC/TDF.

Renal events occurred statistically significantly more frequently after 96 weeks under treatment with EVG/COBI/FTC/TDF. This result was not confirmed by the pooled data after 48/60 weeks. Overall, there was an indication of greater harm from EVG/COBI/FTC/TDF versus the ACT EFV/FTC/TDF.

For the outcomes "nervous system disorders" and "skin rash", there was a statistically significant advantage of EVG/COBI/FTC/TDF regarding the prevention of these events both after 96 and after 48/60 weeks. In both cases, there was proof of lesser harm from EVG/COBI/FTC/TDF versus the ACT EFV/FTC/TDF.

For the outcomes "AEs Grade 3-4", "treatment discontinuation due to AEs" and "gastrointestinal disorders", there was no statistically significant difference between the treatment groups in the total population after 96 or after 48/60 weeks. For the outcome "psychiatric disorders", there was a statistically significant difference regarding the prevention of these events in favour of EVG/COBI/FTC/TDF at both times of analysis, but the measured effect was only marginal. Greater/lesser harm from EVG/COBI/FTC/TDF versus the ACT EFV/FTC/TDF is therefore not proven for these outcomes.

Effect modification by the subgroup characteristic "ethnicity (white/non-white)"

There were indications or proof of an effect modification by the characteristic "ethnicity (white/non-white)" for several outcomes concerning AEs (SAEs, treatment discontinuation due to AEs, skin rash). The respective subgroup results were therefore used for the overall conclusion on the extent of added benefit.

Results for pretreated patients (research question B)

There were no relevant data for pretreated patients for a comparison of EVG/COBI/FTC/TDF versus the ACT (individual therapy). Hence an added benefit of EVG/COBI/FTC/TDF for pretreated patients is not proven.

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 combination EVG/COBI/FTC/TDF compared with the ACT separated for the 2 relevant populations is assessed as follows (see Table 3).

For **treatment-naive patients** (research question A), positive and negative effects remained – both for white and for non-white patients. On the negative side, there was an indication of lesser benefit regarding AIDS-defining events (CDC class C event) with the extent "considerable". For the outcome "SAEs", there was proof (whites) and indication (non-whites) of greater harm (extent [not more than] "considerable"). Regarding renal events, there was an indication of greater harm with the extent "minor" in both cases.

There were positive effects of EVG/COBI/FTC/TDF with regards to the prevention of non-serious/severe AEs (nervous system disorders and skin rash). The extent of added benefit in both cases was "minor". In addition, there was proof of lesser harm regarding the prevention of treatment discontinuations due to AEs (extent: "minor") for the group of non-whites.

Although the results on the level of the individual outcomes diverge slightly for both relevant patient groups (whites/non-whites), the negative treatment effects outweigh the positive ones in both groups. In summary, there is an indication of lesser benefit of EVG/COBI/FTC/TDF in comparison with the ACT EFV/FTC/TDF for treatment-naive patients as a whole.

For **pretreated patients** (research question B), there was no relevant study for the assessment of the added benefit versus the ACT. An added benefit of EVG/COBI/FTC/TDF versus the ACT (individual therapy) is not proven for this population.

[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 1-3 cannot be drawn from the available data), see [1]. 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), see [2].

Table 3: Summary – EVG/COBI/FTC/TDF: extent and probability of added benefit

Research question	**Sub-indication**	**ACT**	**Extent and probability of added benefit**
A	Treatment-naive patients	Efavirenz in combination with 2 nucleoside/nucleotide analogues (tenofovir plus emtricitabine or abacavir plus lamivudine)	Indication of a lesser benefit
B	Pretreated patients[a]	Individual therapy based on prior treatment(s) and under consideration of the reason for the switch of treatment, particularly treatment failure due to virologic failure and possible accompanying development of resistance, or due to AEs. The approval of the drugs is to be considered.	Added benefit not proven
a: Patients who are infected with HIV-1 without known mutations associated with resistance to any of the 3 antiretroviral drugs of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil. ACT: appropriate comparator therapy; AE: adverse event; HIV-1: human immunodeficiency virus type 1			

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

2.2 Research questions

The benefit assessment of EVG/COBI/FTC/TDF was conducted according to the Summary of Product Characteristics (SPC) [3] for the treatment of HIV-1 infection in adults in the following subindications:

- In patients who have not received antiretroviral treatment (hereinafter referred to as "**treatment-naive patients**")
- In patients who are infected with HIV-1 without known mutations associated with resistance to any of the 3 antiretroviral drugs of EVG/COBI/FTC/TDF (hereinafter referred to as "**pretreated patients**")

The G-BA specified an ACT for each of the different research questions. These are shown in Table 4.

Table 4: Subindications and ACT for EVG/COBI/FTC/TDF

Research question[a]	Subindication	ACT specified by the G-BA
A	Treatment-naive patients	Efavirenz in combination with 2 nucleoside/nucleotide analogues (tenofovir plus emtricitabine or abacavir plus lamivudine)
B	Pretreated patients[b]	Individual therapy based on prior treatment(s) and under consideration of the reason for the switch of treatment, particularly treatment failure due to virologic failure and possible accompanying development of resistance, or due to AEs. The approval of the drugs is to be considered.
a: Designation corresponds to the coding in the company's dossier. b: Patients who are infected with HIV-1 without known mutations associated with resistance to any of the 3 antiretroviral drugs of EVG/COB/FTC/TDF. ACT: appropriate comparator therapy; AE: adverse event; EVG/COBI/FTC/TDF: elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil; G-BA: Federal Joint Committee; HIV-1: human immunodeficiency virus type 1		

Research question A: treatment-naive patients

The ACT specified by the G-BA was used for treatment-naive patients (efavirenz in combination with 2 nucleoside/nucleotide analogues [tenofovir plus emtricitabine or abacavir plus lamivudine]).

The company claimed to concur with this ACT, but additionally referred to results on deviating comparator therapies (boosted protease inhibitors or raltegravir, each in combination with emtricitabine and tenofovir) because it considered these to be not inferior to the G-BA's ACT. This expansion was not accepted in the benefit assessment because the company primarily decided to use the G-BA's ACT. Hence the supplementary analyses on additional comparator therapies presented by the company in Module 5 of the dossier were not considered.

Research question B: pretreated patients

Contrary to the inclusion criteria originally formulated by the company, the company also included treatment-naive patients in the benefit assessment because it had not identified any study with pretreated patients suitable for the benefit assessment. This approach was not accepted because the company did not prove with adequate scientific research that the data from clinical studies with treatment-naive patients could be transferred to pretreated patients. Outcome-specific effect variations are conceivable in both treatment directions (larger or smaller effect differences versus the ACT). The results of studies can be regarded as "transferable" when it is proven with sufficient certainty and plausibility that the effect estimates of all patient-relevant outcomes investigated are not substantially influenced by the characteristic in question (here: prior treatment) (see Section 2.6.3.2 of the full dossier assessment).

The ACT specified by the G-BA was used for pretreated patients (see Table 4). Although the company claimed to follow the G-BA's ACT, it limited the ACT to few treatment regimens (EFV/FTC/TDF or ATV/r+FTC/TDF or RAL+FTC/TDF), which, from its point of view, were representative. This limitation was not accepted in the benefit assessment. The ACT was a therapy tailored to the individual patient. In this context, limitation to a small number of drugs is not advisable because individual criteria (e.g. AEs or resistance) may make it necessary to use a treatment that deviates from the company's prespecification.

Summary

The assessment of EVG/COBI/FTC/TDF was conducted versus the ACT specified by the G-BA for treatment-naive patients (research question A) and for pretreated patients (research question B). The assessment was conducted based on patient-relevant outcomes and on RCTs with a minimum duration of 48 weeks. Only direct comparative studies were included in the assessment.

Further information about the research question can be found in Module 3A, Section 3.1 and Module 4A, Section 4.2.1 of the dossier, and in Sections 2.6.2.1, 2.6.2.2, 2.6.3.1 and 2.6.3.2 of the full dossier assessment.

2.3 Research question A: elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil for treatment-naive patients

2.3.1 Information retrieval and study pool (research question A)

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 EVG/COBI/FTC/TDF (studies completed up to 30 April 2013)
- Search in trial registries for studies on EVG/COBI/FTC/TDF (last search on 9 April 2013)

The Institute's own search to check the search results of the company:

- Search in trial registries for studies on EVG/COBI/FTC/TDF (last search on 2 July 2013)

This check produced no deviations from the study pool presented in the dossier.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4A, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.6.2.2 and 2.6.2.4 of the full dossier assessment.

2.3.1.1 Studies included

The studies GS-US-236-0102 and GS-US-236-0104 listed in the following tables were included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: EVG/COBI/FTC/TDF vs. EFV/FTC/TDF

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
GS-US-236-0102	yes	yes	no
GS-US-236-0104	yes	yes	no

a: Study for which the company was sponsor, or in which the company was otherwise financially involved.
COBI: cobicistat; EFV: efavirenz; EVG: elvitegravir; FTC: emtricitabine; RCT: randomized controlled trial; TDF: tenofovir disoproxil fumarate; vs.: versus

The study pool for the benefit assessment of EVG/COBI/FTC/TDF concurred with the one of the company. In both studies, EVG/COBI/FTC/TDF was directly compared with the G-BA's ACT (efavirenz in combination with 2 nucleoside/nucleotide analogues).

Section 2.3.4 contains a reference list for the studies included.

Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4A, Section 4.3.1.1 of the dossier and in Sections 2.6.2.4.1 and 2.6.2.4.2 of the full dossier assessment.

2.3.1.2 Study characteristics

Table 6 and Table 7 describe the studies used for the benefit assessment (GS-US-236-0102 and GS-US-236-0104).

Table 6: Characteristics of the studies included – RCT, direct comparison: EVG/COBI/FTC/TDF vs. EFV/FTC/TDF

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
GS-US-236-0102	RCT, double-blind, double-dummy, parallel, multicentre	HIV-1-infected adults without previous antiretroviral treatment; adequate renal function (eGFR ≥ 70 ml/min)	EVG/COBI/FTC/TDF: N = 353 EFV/FTC/TDF: N = 354	Screening: 5 weeks Treatment: 96 weeks[b] + time until unblinding Then **either**: open-label treatment: until the product is commercially available or Gilead stops the research programme **or** follow-up: 30 days	USA (97 centres) and Puerto Rico (5 centres) Data cut-off at week 48: 3/2010 – 8/2011 Data cut-off at week 96: 3/2010 – 7/2012	Primary outcome: virologic response at week 48 Secondary outcomes: virologic response at week 96, change in CD4 cell count, mortality, AEs
GS-US-236-0104	RCT, double-blind, double-dummy, parallel, multicentre	HIV-1-infected adults without previous antiretroviral treatment; adequate renal function (eGFR ≥ 80 ml/min)	EVG/COBI/FTC/TDF: N = 48 EFV/FTC/TDF: N = 23	Screening: 4 weeks Randomized treatment: 60 weeks[c] Then **either**: open-label treatment: until the product is commercially available or Gilead stops the research programme **or** follow-up: 30 days	USA (30 centres) 3/2009 – 5/2011	Primary outcome: virologic response at week 24 Secondary outcomes: virologic response at week 48, change in CD4 cell count, mortality, AEs

a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes contain exclusively information on relevant available outcomes for the present benefit assessment.
b: According to Amendment 2 (19 January 2012), the blinded phase was extended from 96 to 192 weeks. The study is still ongoing. The results presented in this dossier assessment are from 2 interim analyses (48 and 96 weeks).
c: The randomized treatment phase contained 48 weeks (time of the second interim analysis) + time until unblinding (week 60)

AE: adverse event; EFV/FTC/TDF: efavirenz/emtricitabine/tenofovir disoproxil; eGFR: estimated glomerular filtration rate; EVG/COBI/FTC/TDF: elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil; HIV-1: human immunodeficiency virus type 1; N: number of randomized patients; n: relevant subpopulation; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the interventions – RCT, direct comparison: EVG/COBI/FTC/TDF vs. EFV/FTC/TDF

Study	Intervention	Comparison	Concomitant medication
GS-US-236-0102	150 mg elvitegravir, 150 mg cobicistat, 200 mg emtricitabine, 245 mg tenofovir disoproxil[a] (EVG/COBI/FTC/TDF) once daily with food + placebo for EFV/FTC/TDF once a day on an empty stomach prior to bedtime	600 mg efavirenz, 200 mg emtricitabine, 245 mg tenofovir disoproxil[a] (EFV/FTC/TDF) once a day on an empty stomach prior to bedtime + placebo for EVG/COBI/FTC/TDF once daily with food	No other antiretroviral treatment allowed Other medication that was not allowed: drugs with high interaction potential (e.g. carbamazepine, HMG-CoA reductase inhibitors, St. John's Wort)
GS-US-236-0104	150 mg elvitegravir, 150 mg cobicistat, 200 mg emtricitabine, 245 mg tenofovir disoproxil[a] (EVG/COBI/FTC/TDF) once daily with food + placebo for EFV/FTC/TDF once a day on an empty stomach prior to bedtime	600 mg efavirenz, 200 mg emtricitabine, 245 mg tenofovir disoproxil[a] (EFV/FTC/TDF) once a day on an empty stomach prior to bedtime + placebo for EVG/COBI/FTC/TDF once daily with food	Medication that was not allowed: drugs with high interaction potential (e.g. carbamazepine, HMG-CoA reductase inhibitors, St. John's Wort)
a: Equivalent to 300 mg tenofovir disoproxil fumarate or 136 mg tenofovir. EFV/FTC/TDF: efavirenz/emtricitabine/tenofovir disoproxil; EVG/COBI/FTC/TDF: elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil; RCT: randomized controlled trial; vs.: versus			

The study GS-US-236-0102 is an ongoing, double-blind phase III approval study with a planned study duration of 192 weeks. The results of the interim analysis after 48 or after 96 weeks were included in the assessment. There were no data yet on the time of analysis 192 for the present benefit assessment. The study GS-US-236-0104 was a completed, double-blind, phase II approval study with a study duration of 96 weeks. Only the first 60 weeks of treatment were double-blind and conducted under randomized and controlled conditions and were included in the assessment. The studies were conducted in the USA (GS-US-236-0102 and GS-US-236-0104) and Puerto Rico (GS-US-236-0102). EVG/COBI/FTC/TDF was compared with the fixed combination of EFV/FTC/TDF in both studies so that a direct comparison versus the G-BA's ACT was possible. HIV-1 infected adults without previous antiretroviral treatment were included in the studies. The patients were stratified in the studies according to the HIV-1 RNA (≤ 100,000 copies/ml or > 100,000 copies/ml) at screening. In the study GS-US-236-0102, 707 patients in total were randomized to the 2 study arms (EVG/COBI/FTC/TDF: 353 patients, EFV/FTC/TDF: 354 patients). The study GS-US-236-0104 included 71 randomized patients and was therefore considerably smaller (EVG/COBI/FTC/TDF: 48 patients, EFV/FTC/TDF: 23 patients). The patients included had to have adequate renal function in both studies (GS-US-236-0102: creatinine clearance

≥ 70 ml/min; GS-US-236-0104: creatinine clearance ≥ 80 ml/min). According to the SPC of EVG/COBI/FTC/TDF, this drug should only be used in patients with creatinine clearance ≥ 70 ml/min, and treatment with EVG/COBI/FTC/TDF should not be initiated in patients with creatinine clearance < 90 ml/min unless, after review of the available treatment options, it is considered that EVG/COBI/FTC/TDF is the preferred treatment for the individual patient [3]. According to the inclusion criterion chosen, both studies therefore possibly included patients who only should have been allowed to receive EVG/COBI/FTC/TDF under this condition. It could not be assessed on the basis of the available documents whether EVG/COBI/FTC/TDF was the preferred treatment for these patients (after review of the available treatment options). Based on the distribution of the creatinine clearance values, this problem could only have been the case in a negligible proportion of the study population (< 20%)[5], so that this did not substantially influence the result, and, in each case, the total study population could be used for the assessment.

In the studies, both EVG/COBI/FTC/TDF and EFV/FTC/TDF were administered in compliance with their approval orally once a day [3,4]. The preferred administration of EVG/COBI/FTC/TDF once daily with food versus the preferred administration of EFV/FTC/TDF on an empty stomach before going to bed required the additional administration of a placebo (double-dummy) in the studies to maintain blinding. The fact that the fixed drug combination EFV/FTC/TDF is only approved for pretreated patients was not a problem because each individual substance also has approval for treatment-naive patients [5,6].

Table 8 and Table 9 show the characteristics of the patients in the studies included.

[5] Study GS-US-236-0102 (total population): first quartile (98.4 ml/min); study GS-US-236-0104 (total population): first quartile (110.28 ml/min). Creatinine clearance was recorded as estimated glomerular filtration rate (eGFR, calculated using the Cockcroft-Gault equation).

Table 8: Characteristics of the study population (demography) – RCT, direct comparison: EVG/COBI/FTC/TDF vs. EFV/FTC/TDF

Study Group	N[a]	Age [years] mean (SD)	Sex [f/m] %	Ethnicity %		Treatment discon-tinuations week 48/60[c] n (%)	Treatment discon-tinuations week 96 n (%)
				Whites	Non-whites[b]		
GS-US-236-0102							
EVG/COBI/FTC/ TDF	348[d]	38 (10)	11.8/88.2	61.5	38.5[e]	37 (10.6)	53 (15.2)
EFV/FTC/TDF	352[d]	38 (11)	10.2/89.9	64.5	35.5[e]	46 (13.1)	61 (17.3)
GS-US-236-0104							
EVG/COBI/FTC/ TDF	48	36 (9)	8.3/91.7	68.8	31.2[e]	3 (6.3)	–
EFV/FTC/TDF	23	35 (10)	8.7/91.3	78.3	21.7[e]	3 (13.0)	–

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding column if the deviation is relevant.
b: This group includes Asians, blacks/patients of African heritage, native Americans/native Alaskans, Hawaiians/Pacific Islanders, and others.
c: Treatment discontinuations at week 48 for the study GS-US-236-0102, and treatment discontinuations at the end of the blinded phase (week 60) for the study GS-US-236-0104.
d: Number of patients in the safety population.
e: Institute's calculation of percentages.
EFV/FTC/TDF: efavirenz/emtricitabine/tenofovir disoproxil; EVG/COBI/FTC/TDF: elvitegravir/ cobicistat/emtricitabine/tenofovir disoproxil; f: female; m: male; N: number of randomized patients; n: number of patients with characteristic; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Table 9: Characteristics of the study populations (severity of disease at the start of the study) – RCT, direct comparison: EVG/COBI/FTC/TDF vs. EFV/FTC/TDF

Study Group	N[a]	Baseline viral load n (%)		CD4 cell count at start of study n (%)		HIV disease stage n (%)		
		≤ 100,000 HIV-1 RNA copies/ml	> 100,000 HIV-1 RNA copies/ml	≤ 350/µl	> 350/µl	asymptomatic	symptomatic	AIDS
GS-US-236-0102								
EVG/COBI/FTC/TDF	348[b]	230 (66.1)	118 (33.9)	155 (44.5)[c]	193 (55.5)[c]	290 (83.3)	30 (8.6)	28 (8.0)
EFV/FTC/TDF	352[b]	236 (67.0)	116 (33.0)	147 (41.8)[c]	205 (58.2)[c]	295 (83.8)	33 (9.4)	24 (6.8)
GS-US-236-0104								
EVG/COBI/FTC/TDF	48	37 (77.1)	11 (22.9)	24 (50.0)[c]	24 (50.0)[c]	40 (83.3)	5 (10.4)	3 (6.3)
EFV/FTC/TDF	23	18 (78.3)	5 (21.7)	8 (34.8)[c]	15 (65.2)[c]	22 (95.7)	0 (0)	1 (4.3)

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding column if the deviation is relevant.
b: Number of patients in the safety population.
e: Institute's calculation of number and percentages.

AIDS: acquired immunodeficiency syndrome; CD4: cluster of differentiation 4; EFV/FTC/TDF: efavirenz/emtricitabine/tenofovir disoproxil; EVG/COBI/FTC/TDF: elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil; f: female; HIV-1: human immunodeficiency virus type 1; m: male; N: number of randomized patients; n: number of patients with characteristic; RCT: randomized controlled trial; RNA: ribonucleic acid; SD: standard deviation; vs.: versus

There were no important differences between the treatment groups with regards to age, sex and ethnicity. The mean age of the patients was between 35 and 38 years, and substantially more men than women were included in both studies (about 10% women, about 90% men), reflecting the higher prevalence of HIV-1 infection [7]. Regarding ethnicity, there were also only minor differences between the treatment groups. In respect of disease severity – assessed using the characteristics "baseline viral load", "CD4 cell count" and "HIV disease stage" – the patients in the study GS-US-236-0102 were distributed about equally to both treatment arms. Exclusively treatment-naive patients were included in both studies. There was a minor difference regarding CD4 cell count, HIV disease stage and treatment discontinuations after 48 weeks in the study GS-US-236-0104. Since this study was comparably small, this imbalance did not raise doubts about the adequate randomization, however.

Table 10 shows the risk of bias at study level.

Table 10: Risk of bias at study level – RCT, direct comparison: EVG/COBI/FTC/TDF vs. EFV/FTC/TDF

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			
GS-US-236-0102	yes	yes	yes	yes	yes	yes	low
GS-US-236-0104	yes	yes	yes	yes	yes	yes	low
RCT: randomized controlled trial; vs.: versus							

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

Further information about the study design, study populations and risk of bias at the study level can be found in Module 4A, Sections 4.3.1.2.1 and 4.3.1.2.2, and Appendix 4-G of the dossier and in Sections 2.6.2.5.1 and 2.6.2.5.2 of the full dossier assessment.

2.3.2 Results on added benefit

The following patient-relevant outcomes were considered in this assessment for the assessment of research question A (treatment-naive patients) (for reasons, see Section 2.6.2.5.3 of the full dossier assessment):

- Mortality
  - All-cause mortality
- Morbidity
  - AIDS-defining events (CDC class C events)
  - Presented as additional information: virologic response (time to loss of virologic response [TLOVR]) and CD4 cell count as sufficiently valid surrogates for the patient-relevant outcome "AIDS-defining illnesses/death"
- Health-related quality of life
- Adverse events
  - Overall rate of SAEs
  - Treatment discontinuation due to AEs
  - AEs Grade 3-4 (GSI Grading Scale)
  - Psychiatric disorders (System Organ Class [SOC])
  - Nervous system disorders (SOC)
  - Skin rash (prespecified choice of Preferred Term [PT])
  - Gastrointestinal disorders (SOC)
  - Renal events (prespecified choice of PT)

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4). In addition to the dossier, the outcome "AIDS-defining events (CDC class C events)" was rated as patient-relevant in the benefit assessment because this outcome directly represents the AIDS-defining illnesses important in the indication. For this reason, the surrogate parameters rated as sufficiently valid for the outcome "AIDS-defining illnesses/death" were only considered as additional information in the benefit assessment. Reasons for the choice of outcomes are given in Section 2.6.2.5.3 of the full dossier assessment.

Table 11 shows for which outcomes and at which times of analysis data were available in the studies included.

Table 11: Matrix of outcomes – RCT, direct comparison: EVG/COBI/FTC/TDF vs. EFV/FTC/TDF

Study	Outcomes												
	All-cause mortality	AIDS-defining events (CDC class C events)	Virologic response (TLOVR)[a]	CD4 cell count[a]	Health-related quality of life	SAEs	Treatment discontinuation due to AEs	AEs Grade 3-4[b]	Psychiatric disorders (SOC)	Nervous system disorders (SOC)	Skin rash[c]	Gastrointestinal disorders (SOC)	Renal events[c]
GS-US-236-0102													
48 weeks	y	y	y	y	-[d]	y	y	y	y	y	y	y	y
60 weeks	no	no	no	y	-[d]	no	no	no	no	no	no	no	no
96 weeks	y	y	y	y	-[d]	y	y	y	y	y	y	y	y
GS-US-236-0104													
48 weeks	y	y	y	y	-[d]	y	y	y	y	y	y	y	y
60 weeks	y	y	no	y	-[d]	y	y	y	y	y	y	y	y

a: Virologic response and CD4 cell count as sufficiently valid surrogates for the combined outcome "AIDS-defining illnesses/death" are presented as additional information in the benefit assessment .
b: Classification based on the "Gilead Sciences Grading Scale for Severity of Adverse Events and Laboratory Abnormalities“.
c: Represented using a choice of PTs prespecified by the company in the statistical analysis plan of the study GS-US-236-0102.
d: Outcome was not recorded.
AIDS: acquired immunodeficiency syndrome; CD4: cluster of differentiation 4; CDC: Centers for Disease Control and Prevention; LOCF: last observation carried forward; PT: MedDRA Preferred Term; RCT: randomized controlled trial; SOC: MedDRA System Organ Class; TLOVR: time to loss of virologic response; vs.: versus; y: yes

Overall, good data availability could be assumed for the relevant studies. The only problem was the lack of recording data on health-related quality of life. For the study GS-US-236-102, data for the times of analysis at week 48 and 96 were available for all relevant outcomes (for the CD4 cell count, results after 60 weeks were additionally available). The study GS-US-236-104 provided results on nearly all relevant outcomes after 48 and 60 weeks. Mainly the 60 week data were included in the benefit assessment (exception: for the virologic response, only the results after 48 weeks were available).

Table 12 shows the risk of bias for these outcomes.

Table 12: Risk of bias at study and outcome level – RCT, direct comparison: EVG/COBI/FTC/TDF vs. EFV/FTC/TDF

Study		Outcomes												
	Study level	All-cause mortality	AIDS-defining events (CDC class C event)	Virologic response (TLOVR)	CD4 cell count	Health-related quality of life	SAEs	Treatment discontinuation due to AEs	AEs Grade 3-4[a]	Psychiatric disorders (SOC)	Nervous system disorders (SOC)	Skin rash[b]	Gastrointestinal disorders (SOC)	Renal events[b]
GS-US-236-0102	l	l	l	l	l/h[c]	-[d]	l	l	l	l	l	l	l	l
GS-US-236-0104	l	l	l	l	l	-[d]	l	l	l	l	l	l	l	l

a: Classification based on the "Gilead Sciences Grading Scale for Severity of Adverse Events and Laboratory Abnormalities".
b: Represented using a choice of PTs prespecified by the company in the statistical analysis plan of the study GS-US-236-0102.
c: 48 weeks/96 weeks (LOCF analysis in week 96 highly biased because proportion of replaced values > 10%).
d: Outcome was not recorded.

AIDS: acquired immunodeficiency syndrome; CD4: cluster of differentiation 4; CDC: Centers for Disease Control and Prevention; h: high; l: low; LOCF: last observation carried forward; PT: MedDRA Preferred Term; RCT: randomized controlled trial; SOC: MedDRA System Organ Class; TLOVR: time to loss of virologic response; vs.: versus

The company's assessment of the risk of bias was mainly followed. There were deviations regarding the following outcomes, however: Missing values were replaced for > 10% of the patients for the outcome "CD4 cell count (LOCF analysis)" at 96 weeks for the study GS-US-236-0102. Hence an unbiased result could no longer be assumed and the risk of bias for this time of analysis was therefore rated as high. It was not possible to estimate the direction of a possible bias. Contrary to the company's assessment, skin rash and renal events in the study GS-US-236-0104 were rated as having a low risk of bias. The reason for this was that the PT terms chosen post-hoc in this study were based on the choice prespecified in the study GS-US-236-0102. Selective reporting was therefore unlikely.

The risk of bias for the outcome "AIDS-defining events (CDC class C events) additionally included in the benefit assessment was rated as low because the events included (e.g. Kaposi sarcoma, Burkitt lymphoma) were specified a priori in the study protocol.

Further information on the choice of outcomes and risk of bias at outcome level can be found in Module 4A, Sections 4.3.1.2.2 and 4.3.1.3 of the dossier and in Sections 2.6.2.5.2 and 2.6.2.5.3 of the full dossier assessment.

2.3.2.1 Results

The results on the comparison of EVG/COBI/FTC/TDF with EFV/FTC/TDF in treatment-naive patients with HIV-1 infection are summarized in Table 13. The data from the company's dossier were supplemented, where necessary, by the Institute's own calculations. For outcomes for which relevant subgroup effects were identified in the further course of the assessment, these are already presented in Table 13. The results at the time of analysis "96 weeks" was primarily used for the benefit assessment because the longer time of analysis is preferred in the therapeutic indication (for detailed reasons see Sections 2.6.2.2 and 2.6.2.5.3 of the full dossier assessment). Only data from the phase III approval study GS-US-236-0102 were available for this outcome, however, so that, primarily, not more than "indications" of an added benefit could be derived. However, if there was a statistically significant difference after 96 weeks, the results of the meta-analysis from the studies GS-US-236-0102 and GS-US-236-0104 at the earlier time of analysis (48/60 weeks) were additionally used, which are presented as additional information in Appendix A of the full dossier assessment. If the pooled data confirmed the results after 96 weeks, the certainty of results could be upgraded (e.g. from "indication" to "proof").

Table 13: Results – RCT, direct comparison: EVG/COBI/FTC/TDF vs. EFV/FTC/TDF (week 96)

Study Outcome category Outcome	EVG/COBI/FTC/TDF		EFV/FTC/TDF		EVG/COBI/FTC/TDF vs. EFV/FTC/TDF
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI]; p-value[a]
GS-US-236-0102					
Mortality					
All-cause mortality	348	1 (0.3)	352	2 (0.6)	0.52 [0.05; 5.00][b]; 0.597
Morbidity					
AIDS-defining events (CDC class C events)	348	8 (2.3)[c]	352	1 (0.3)[c]	4.88 [1.31; 18.16][b]; 0.018
Virologic response (TLOVR)	348	276 (79.3)	352	272 (77.3)	1.03 [0.95; 1.11]; 0.538
CD4 cell count (number/µl)	348[d]	391 (188.6)[e] 278 (212.4)[f]	352[d]	382 (170.2)[e] 247 (188.3)[f]	30 [1; 60][g]; 0.046
AEs					
AEs	348	337 (96.8)	352	342 (97.2)	
SAEs	348	56 (16.1)[h]	352	33 (9.4)[h]	1.72 [1.15; 2.57]; 0.008
Subgroups according to ethnicity					*Interaction: p = 0.132[i]*
Whites	*214*	*34 (15.9)*	*227*	*16 (7.0)*	*2.25 [1.28; 3.96]; 0.004*
Non-whites[j]	*134*	*22 (16.4)*	*125*	*17 (13.6)*	*1.21 [0.67; 2.16]; 0.597*
Treatment discontinuation due to AEs	348	17 (4.9)	352	24 (6.8)	0.72 [0.39; 1.31]; 0.290
Subgroups according to ethnicity					*Interaction: p = 0.04[i]*
Whites	*214*	*14 (6.5)*	*227*	*13 (5.7)*	*1.14 [0.55; 2.37]; 0.775*
Non-whites[j]	*134*	*3 (2.2)*	*125*	*11 (8.8)*	*0.25 [0.07; 0.89]; 0.021*
AEs severity grades 3 and 4[k]	348	61 (17.5)	352	51 (14.5)	1.21 [0.86; 1.70]; 0.290
Psychiatric disorders (SOC)	348	138 (39.7)	352	179 (50.9)	0.78 [0.66; 0.92]; 0.003
Nervous system disorders (SOC)	348	112 (32.2)	352	159 (45.2)	0.71 [0.59; 0.86]; < 0.001
Skin rash[l]	348	74 (21.3)	352	108 (30.7)	0.69 [0.54; 0.895]; 0.005
Subgroups according to ethnicity					*Interaction: p = 0.149[i]*
Whites	*214*	*47 (22.0)*	*227*	*81 (35.7)*	*0.62 [0.45; 0.84]; 0.002*
Non-whites[j]	*134*	*27 (20.1)*	*125*	*27 (21.6)*	*0.93 [0.58; 1.50]; 0.806*
Gastrointestinal disorders (SOC)	348	211 (60.6)	352	188 (53.4)	1.14 [0.998; 1.29]; 0.055
Renal events[l]	348	7 (2.0)	352	1 (0.3)	4.60 [1.14; 18.54][b]; 0.032

(continued)

Table 13: Results – RCT, direct comparison: EVG/COBI/FTC/TDF vs. EFV/FTC/TDF (week 96) (continuation)

Italic type: Effects for subgroups in which relevant indications or proof of an effect modification were present.
a: Institute's calculation of estimate, corresponding CI and p-value (unconditional exact test (CSZ method according to [8]).
b: Peto odds ratio because the rates were below 1% in at least one cell.
e: Institute's calculation of percentage.
d: Number of patients analysed at 96 weeks. The values at the start of the study can be based on other patient numbers.
e: Values at the start of the study (mean [SD]).
f: Change at the end of the study (mean [SD]). LOCF analysis of the ITT population.
g: Difference of the least square means from an ANOVA (analysis of variance) adjusted for the baseline HIV-1 RNA level (≤ 100,000 and > 100,000 copies/ml); [95% CI]; p-value.
h: The group difference in this outcome is particularly attributable to events of the SOC "infections and infestations" (EVG/COBI/FTC/TDF: 26 patients [7.5%]; EFV/FTC/TDF: 10 patients [2.8%].
i: Institute's calculation, test for heterogeneity (Q statistics).
j: This group includes Asians, blacks/patients of African heritage, native Americans/native Alaskans, Hawaiians/Pacific Islanders, and others.
k: Classification based on the "Gilead Sciences Grading Scale for Severity of Adverse Events and Laboratory Abnormalities".
l: Represented using a choice of PTs prespecified by the company in the statistical analysis plan of the study GS-US-236-0102.
AE: adverse event; AIDS: acquired immunodeficiency syndrome; ANOVA: analysis of variance; CD4: cluster of differentiation 4; CDC: Centers for Disease Control and Prevention; CI: confidence interval; EFV/FTC/TDF: efavirenz/emtricitabine/tenofovir disoproxil; EVG/COBI/FTC/TDF: elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil; ITT: intention to treat; LOCF: last observation carried forward; N: number of analysed patients; n: number of patients with event; PT: MedDRA Preferred Term; RCT: randomized controlled trial; RNA: ribonucleic acid; RR: relative risk; SAE: serious adverse event; SD: standard deviation; SOC: MedDRA System Organ Class; TLOVR: time to loss of virologic response; vs.: versus

Mortality

The result for the outcome "all-cause mortality" was not statistically significant after 96 weeks (GS-US-236-0102) or after 48/60 weeks (GS-US-236-0102/GS-US-236-0104; see Appendix A of the full dossier assessment). An added benefit of EVG/COBI/FTC/TDF or greater harm from it compared with EFV/FTC/TDF is not proven for this outcome. This concurs with the company's assessment.

It is to be considered, however, that, due to the study duration and the number of patients included, the studies were not designed to prove differences between the treatments in the outcome "all-cause mortality".

Morbidity

AIDS-defining events (CDC class C events)

At the time of analysis "96 weeks", statistically significantly more patients had an AIDS-defining event under treatment with EVG/COBI/FTC/TDF than under treatment with EFV/FTC/TDF (8 patients versus 1 patient). The pooled result after 48/60 weeks showed the same direction of effect, but the group difference was not statistically significant at this time

(see Appendix A of the full dossier assessment). Overall, there was therefore an indication of lesser benefit of EVG/COBI/FTC/TDF for this outcome.

It was not clear from the documents presented whether events of patients who were already diagnosed with AIDS at the start of the study, were counted again in the course of the study. This affected 28 (8%; EVG/COBI/FTC/TDF) and 24 (6.8%; EFV/FTC/TDF) patients (see Table 9). However, sensitivity analyses under exclusion of these patients showed that the effect to the disadvantage of EVG/COBI/FTC/TDF became even marginally larger and therefore was rather underestimated by including these patients in the analysis.

Virologic response (TLOVR) and CD4 cell count as sufficiently valid surrogates for the patient-relevant outcome "AIDS-defining illnesses/death"

Virologic response and CD4 cell count per se are no patient-relevant outcomes. This concurs with the company's assessment.

Both measurements were used as sufficiently valid surrogate outcomes for the combined outcome "AIDS-defining illnesses/death" in the benefit assessment (see Section 2.6.2.10.4 of the full dossier assessment and the benefit assessment of rilpivirine [9]). Since the outcome that in fact was patient-relevant (AIDS-defining events [CDC class C event]) was recorded in the studies presented, the 2 surrogate outcomes were only provided as additional information in the benefit assessment, but were not included in the final balancing on the added benefit. Since both surrogate outcomes should replace the same patient-relevant outcome [10,11], there is also a joint consideration and interpretation of the results on both surrogate outcomes.

There was no statistically significant difference between the 2 treatment arms after 96 weeks (GS-US-236-0102) or after 48 weeks (GS-US-236-0102/GS-US-236-0104) for the **virologic response**.

A statistically significant increase in cell count was shown after 96 weeks for the **CD4 cell count**. This positive effect in favour of EVG/COBI/FTC/TDF was also shown in the result of the meta-analysis after 60 weeks (see Appendix A of the full dossier assessment).

Overall, the 2 surrogate outcomes did not show any clear results. Whereas there was no difference in virologic response between the 2 treatment arms, there was an advantage of EVG/COBI/FTC/TDF for CD4 cell count, but with high risk of bias and minor effect size. Overall, no advantage or disadvantage of EVG/COBI/FTC/TDF could be derived from these data. Since there were also results available for the truly patient-relevant outcomes – AIDS-defining events (CDC class C event) and death – no further conclusions were drawn from the results on surrogate outcomes. This contradicts the company's assessment, which derived proof of added benefit of EVG/COBI/FTC/TDF from the CD4 cell count.

Health-related quality of life

No data on health-related quality of life were recorded in the studies. Hence an added benefit of EVG/COBI/FTC/TDF is not proven for this outcome.

Adverse events

Overall rate of adverse effects

The outcome "overall rate of adverse effects" is presented in Table 13 only as additional information. Almost all patients in both groups had at least 1 adverse event (AE). The result of this outcome was not interpretable.

Serious adverse events

SAEs occurred statistically significantly more frequently after 96 weeks (study GS-US-236-0102) under treatment with EVG/COBI/FTC/TDF. The pooled data after 48/60 weeks (GS-US-236-0102/GS-US-236-0104) confirmed this result (see Appendix A of the full dossier assessment). Under consideration of the low risk of bias for this outcome, there was therefore proof of greater harm from EVG/COBI/FTC/TDF compared with the ACT EFV/FTC/TDF for the total population. This concurs with the company's assessment. The difference was caused to a considerable proportion by the difference of SAEs in the SOC "infections and infestations": Whereas under EVG/COBI/FTC/TDF, 7.5% of the patients had SAEs in this SOC, the percentage was only 2.8 in the EFV/FTC/TDF groups. The company explained that the unusually high frequency of severe infections in the study GS-US-236-102 could not be medically connected to the drug to be assessed, and that, accordingly, these infections were rated as unconnected to the study medication by the investigator (Module 4A, p. 265). Since it was an RCT, however, it could be assumed that there were no systematic differences between the groups and that resulting treatment effects could be causally attributed to the intervention.

It should also be pointed out that this outcome may at least partially overlap with the results from other outcomes or outcome categories. Particularly, AIDS-defining events (CDC class C events), which usually include serious symptoms, were possibly also recorded as SAEs. Since only a small proportion of patients in both groups was affected in the outcome "CDC class C events" (2.3% versus 0.3%), the results were presumably not substantially changed by the potential double counting.

The assessment of subgroup characteristics resulted in an indication of an effect modification by the characteristic "ethnicity" (whites/non-whites). As a result, conclusions on added benefit regarding this outcome were based on the subgroups. Under consideration of the subgroup data, there was proof of greater harm in whites and an indication of greater harm in non-whites for the outcome "SAEs". The subgroup analyses, the corresponding interpretation of results and overview of the evidence can be found in Section 2.3.2.2.

Treatment discontinuation due to adverse events

There was no statistically significant difference between the treatment groups in the outcome "treatment discontinuation due to AEs" for the total population – neither after 96 nor after 48/60 weeks. Greater/lesser harm from EVG/COBI/FTC/TDF compared with EFV/FTC/TDF is therefore not proven for this outcome. This concurs with the company's assessment.

However, the assessment of subgroup characteristics resulted in proof of an effect modification by the characteristic "ethnicity". As a result, conclusions on added benefit regarding this outcome were based on the subgroups. Under consideration of the subgroup data, there was proof of lesser harm in non-whites for the outcome "treatment discontinuation due to AEs", whereas the treatment effect in whites continued to be not statistically significant. The subgroup analyses, the corresponding interpretation of results and overview of the evidence can be found in Section 2.3.2.2.

Adverse events Grade 3-4 (GSI Grading Scale)

There was no statistically significant difference between the treatment groups in AEs Grade 3-4 – neither after 96 nor after 48/60 weeks. Greater/lesser harm from EVG/COBI/FTC/TDF compared with EFV/FTC/TDF is therefore not proven for this outcome. This concurs with the company's assessment.

Psychiatric disorders (SOC)

There was a statistically significant difference in favour of EVG/COBI/FTC/TDF compared with EFV/FTC/TDF for the outcome "psychiatric disorders (SOC)" at the time of analysis "96 weeks". Since there was only an effect of marginal effect size (the upper confidence interval [CI_o] was above the threshold of 0.9; outcome category: non-severe/non-serious AEs [12]), an added benefit of EVG/COBI/FTC/TDF versus EFV/FTC/TDF was not proven (see Table 15 in Section 2.3.3.1). The pooled data at the time of analysis "48/60 weeks" showed a statistically significant result, which, moreover, was more than marginal ($CI_o < 0.9$). However, since the longer time of analysis was preferred in connection with a lifelong treatment and the positive effect after 96 weeks was only marginal, this did not result in an advantage in favour of EVG/COBI/FTC/TDF. This contradicts the company's assessment, which derived proof of considerable added benefit of EVG/COBI/FTC/TDF versus the ACT EFV/FTC/TDF.

Nervous system disorders (SOC)

There was a statistically significant advantage in favour of EVG/COBI/FTC/TDF compared with EFV/FTC/TDF for the outcome "nervous system disorders (SOC)" at the time of analysis "96 weeks". Since the pooled data after 48/60 weeks confirmed this result, proof of lesser harm from EVG/COBI/FTC/TDF compared with the ACT EFV/FTC/TDF could be derived overall. This concurs with the company's assessment.

Skin rash (prespecified choice of PT)

Skin rash occurred statistically significantly more frequently after 96 weeks (study GS-US-236-0102) under treatment with EFV/FTC/TDF. The pooled data after 48/60 weeks (GS-US-236-0102/GS-US-236-0104) confirmed this result (see Appendix A of the full dossier assessment). Under consideration of the low risk of bias for this outcome, there was therefore proof of lesser harm from EVG/COBI/FTC/TDF compared with the ACT EFV/FTC/TDF for the total population. This concurs with the company's assessment.

The assessment of subgroup characteristics resulted in an indication of an effect modification by the characteristic "ethnicity". As a result, conclusions on added benefit regarding this outcome were based on the subgroups. Under consideration of the subgroup data, there was proof of lesser harm in whites and an indication of lesser harm in non-whites for skin rash. The subgroup analyses, the corresponding interpretation of results and overview of the evidence can be found in Section 2.3.2.2.

Gastrointestinal disorders (SOC)

There was no statistically significant difference between the treatment groups in gastrointestinal disorders – neither after 96 nor after 48/60 weeks. Greater/lesser harm from EVG/COBI/FTC/TDF compared with EFV/FTC/TDF is therefore not proven for this outcome. This contradicts the company's assessment, which derived an indication of greater harm from EVG/COBI/FTC/TDF versus the ACT EFV/FTC/TDF on the basis of a meta-analysis of the relevant studies after 48 weeks.

Renal events (prespecified choice of PT)

Renal events occurred statistically significantly more frequently after 96 weeks (study GS-US-236-0102) under treatment with EVG/COBI/FTC/TDF. This result was not confirmed by the pooled data after 48/60 weeks. More renal events had also already occurred under EVG/COBI/FTC/TDF than under EFV/FTC/TDF at this time (see Table 25 in Appendix A of the full dossier assessment), but the result was not statistically significant. This might be due to the low event rate. Overall, there was an indication of greater harm from EVG/COBI/FTC/TDF versus the ACT EFV/FTC/TDF. This concurs with the assessment by the company.

2.3.2.2 Subgroup analyses

Selected subgroups were investigated for the presence of heterogeneous treatment effects in order to identify possible effect modification. The company presented the corresponding analyses for the outcomes it rated as relevant. Hence there were no subgroup analyses on the outcome "AIDS-defining events (CDC class C events)", which was additionally rated as relevant. They could also not be calculated subsequently from the available documents.

Subgroup analyses for the following characteristics were considered for the benefit assessment:

- Age (< 40/≥ 40 years)
- Sex
- Baseline viral load (≤ 100,000/> 100,000 HIV-1-RNA copies/ml)
- CD4 cell count at the start of the study (≤ 350/> 350 cells/µl)
- Ethnicity (whites/non-whites)

The subgroup characteristic "adherence to treatment" (< 95%/≥ 95%) additionally considered by the company, was rated as not relevant for the benefit assessment and therefore not considered (for reasons, see Section 2.6.2.3 of the full dossier assessment).

Only the results on subgroups and outcomes with at least indications of an interaction between treatment effect and subgroup characteristic and with statistically significant results in at least one of the subgroups are presented. The prerequisite for proof of different subgroup effects was a statistically significant interaction ($p < 0.05$). A p-value of ≥ 0.05 and < 0.2 provided an indication of an effect modification.

Table 14: Subgroups with at least indications of interaction – RCT, direct comparison: EVG/COBI/FTC/TDF vs. EFV/FTC/TDF (96 weeks)

Study Outcome Characteristic Subgroup	EVG/COBI/FTC/TDF N	EVG/COBI/FTC/TDF Patients with events n (%)	EFV/FTC/TDF N	EFV/FTC/TDF Patients with events n (%)	EVG/COBI/FTC/TDF vs. EFV/FTC/TDF RR [95% CI][a]	 p-value[a]
GS-US-236-0102						
SAEs						
Ethnicity					Interaction:	p = 0.132[b]
Whites	214	34 (15.9)	227	16 (7.0)	2.25 [1.28; 3.96]	0.004
Non-whites[c]	134	22 (16.4)	125	17 (13.6)	1.21 [0.67; 2.16]	0.597
Treatment discontinuation due to AEs						
Ethnicity					Interaction:	p = 0.042[b]
Whites	214	14 (6.5)	227	13 (5.7)	1.14 [0.55; 2.37]	0.775
Non-whites[c]	134	3 (2.2)	125	11 (8.8)	0.25 [0.07; 0.89]	0.021
Gastrointestinal disorders (SOC)						
Baseline viral load (copies/ml)					Interaction:	p = 0.030[b]
≤ 100,000	230	134 (58.3)	236	134 (56.8)	1.03 [0.88; 1.20]	0.801
> 100,000	118	77 (65.3)	116	54 (46.6)	1.40 [1.11; 1.77][d]	0.004
CD4 cell count at start of study (cells/µl)					Interaction:	p = 0.116[b]
≤ 350	155	93 (60.0)	147	68 (46.3)	1.30 [1.04; 1.61][e]	0.018
> 350	193	118 (61.1)	205	120 (58.5)	1.04 [0.89, 1.23]	0.629
Nervous system disorders (SOC)						
Sex					Interaction:	p = 0.158[b]
Men	307	93 (30.3)	316	142 (44.9)	0.67 [0.55; 0.83]	< 0.001
Women	41	19 (46.3)	36	17 (47.2)	0.98 [0.61; 1.58]	0.997
Skin rash						
Ethnicity					Interaction:	p = 0.149[b]
Whites	214	47 (22.0)	227	81 (35.7)	0.62 [0.45; 0.84]	0.002
Non-whites[c]	134	27 (20.1)	125	27 (21.6)	0.93 [0.58; 1.50]	0.806

a: Institute's calculation of estimate, corresponding CI and p-value (unconditional exact test (CSZ method according to [8]).
b: Institute's calculation, test for heterogeneity (Q statistics).
c: This group includes Asians, blacks/patients of African heritage, native Americans/native Alaskans, Hawaiians/Pacific Islanders, and others.
d: Inverse estimate 0.71 [0.56, 0.903]; Institute's calculation with reversed direction of effect (EFV/FTC/TDF vs. EVG/COBI/FTC/TDF) to derive extent of added benefit. Since the effect is only marginal ($CI_o > 0.9$; outcome category: non-severe/non-serious AEs), the result is not relevant for the further course of the benefit assessment.
e: Inverse estimate 0.77 [0.62, 0.96]; Institute's calculation with reversed direction of effect (EFV/FTC/TDF vs. EVG/COBI/FTC/TDF) to derive extent of added benefit. Since the effect is only marginal ($CI_o > 0.9$; outcome category: non-severe/non-serious AEs), the result is not relevant for the further course of the benefit assessment.

(continued)

Table 14: Subgroups with at least indications of interaction – RCT, direct comparison: EVG/COBI/FTC/TDF vs. EFV/FTC/TDF (96 weeks) (continuation)

AE: adverse event; CD4: cluster of differentiation 4; CDC: Centers for Disease Control and Prevention; CI: confidence interval; EFV/FTC/TDF: efavirenz/emtricitabine/tenofovir disoproxil; EVG/COBI/FTC/TDF: elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil; N: number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: MedDRA System Organ Class; TLOVR: time to loss of virologic response; vs.: versus

Subgroup characteristic: ethnicity

For the characteristic "ethnicity", there was an indication of an effect modification regarding the outcomes "SAEs" ($p = 0.132$) and skin rash ($p = 0.149$) and proof of an effect modification ($p = 0.042$) regarding the outcome "treatment discontinuation due to AEs".

For the outcome "**SAEs**", the indication of effect modification manifested itself in the maintenance of the statistically significant effect in the total population (greater harm from EVG/COBI/FTC/TDF) in the subgroup of whites. In contrast, the effect in the group of non-whites was no longer statistically significant. The pooled data after 48/60 weeks did no longer show an indication of an interaction ($p = 0.293$, see Table 26 in Appendix A of the full dossier assessment), but there was also a difference of the same direction of effect and of similar magnitude between whites and non-whites, so that the results did not contradict the data after 96 weeks. Overall, in non-whites, a proof of greater harm could no longer be assumed, but only an indication. The extent of the greater harm for non-whites was "non-quantifiable", but it could not be larger than that of the total population ("considerable"). There continued to be a statistically significant effect in the subgroup of whites to the disadvantage of EVG/COBI/FTC/TDF so that proof of greater harm could still be assumed here.

There was a similar scenario for the outcome "**skin rash**": the statistically significant effect (lesser harm from EVG/COBI/FTC/TDF) was maintained in the group of whites, whereas it was no longer maintained in non-whites. As already explained in the case of SAEs, this resulted in a downgrading of the certainty of results in non-whites, for whom, overall, there was only an indication of lesser harm from EVG/COBI/FTC/TDF. The extent of the lesser harm for non-whites was "non-quantifiable", but it could not be larger than that of the total population ("minor") and was therefore rated as "minor". For the group of whites, proof of lesser harm from EVG/COBI/FTC/TDF could still be assumed.

The proof of an interaction for the outcome "**treatment discontinuation due to AEs**" manifested itself insofar as no statistically significant difference between the treatment arms could be observed in the group of whites – as in the total population. Hence, greater/lesser harm is not proven for the group of whites. However, in the group of non-whites, there was a statistically significant effect in favour of EVG/COBI/FTC/TDF: Non-whites discontinued treatment less frequently due to AEs under treatment with EVG/COBI/FTC/TDF than they did under treatment with EFV/FTC/TDF. This effect modification also already occurred in the pooled data after 48/60 weeks in a similar magnitude (see Table 26 in Appendix A of the full

dossier assessment). Overall, proof of lesser harm in the outcome "treatment discontinuation due to AEs" from EVG/COBI/FTC/TDF in the group of non-whites can therefore be assumed.

Overall, there was an indication or proof of an effect modification by the characteristic "ethnicity" for several outcomes concerning AEs. These results concurred with the ones of the company, which also considered there to be indications or proof of an effect modification by the characteristic "ethnicity" for the outcomes mentioned. The respective subgroup results were used for the overall conclusion on the extent of added benefit.

Further subgroup characteristics

In the following subgroups, there were statistically significant differences between the treatments in at least one subgroup, but the resulting treatment effects in the subgroups were only marginal or did not show consistent results across several outcomes.

Disease severity (CD4 cell count and baseline viral load)

There was an indication of an effect modification by the subgroup characteristic "CD4 cell count at the start of the study" and proof of an effect modification by the characteristic "baseline viral load" for the outcome "**gastrointestinal disorders**". This result was also statistically significant in patients with a higher baseline viral load (> 100,000 copies/ml) and lower CD4 cell count at the start of the study (≤ 350 cells/µl), but the effects were only marginal ($CI_o > 0.9$) and therefore did not exceed the necessary relevance threshold for outcomes of the category "non-severe/non-serious AEs". The subgroup results were therefore not considered any further.

Sex

In the outcome "**nervous system disorders (SOC)**", there was an indication of an effect modification by the characteristic “sex”. Whereas the statistically significant difference in favour of EVG/COBI/FTC/TDF was maintained in men (30.3% versus 44.9%), this advantage did not occur in women (46.2% versus 47.2%). The indication of this effect modification also occurred in the pooled data after 48/60 weeks (see Table 26 in Appendix A of the full dossier assessment). Hence only an indication of lesser harm from EVG/COBI/FTC/TDF can be assumed in women. Since there were no further interactions for the characteristic "sex", and there are also potential dependencies between the characteristics "sex" and "ethnicity", this subgroup result was not considered any further.

2.3.3 Extent and probability of added benefit

The derivation of extent and probability of the added benefit of EVG/COBI/FTC/TDF versus the ACT specified by the G-BA (efavirenz in combination with 2 nucleoside/nucleotide analogues [tenofovir plus emtricitabine or abacavir plus lamivudine] is presented below at outcome level (Section 2.3.3.1), taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in Appendix A of Benefit Assessment A11-02 [2].

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 (Section 2.3.3.2). The G-BA decides on the added benefit.

2.3.3.1 Assessment of added benefit at outcome level

The available data presented in Section 2.3.2 resulted in the following assessment for EVG/COBI/FTC/TDF in comparison with the ACT (efavirenz in combination with 2 nucleoside/nucleotide analogues [tenofovir plus emtricitabine or abacavir plus lamivudine]) for treatment-naive patients:

- Indication of a lesser benefit regarding the proportion of patients with AIDS-defining events (CDC class C events)
- Proof (whites) or indication (non-whites) of greater harm regarding SAEs
- Proof of lesser harm for non-whites regarding the proportion of patients with treatment discontinuation due to AEs
- Proof of lesser harm regarding the proportion of patients with nervous system disorders
- Proof (whites) or indication (non-whites) of lesser harm regarding the proportion of patients with skin rash
- Indication of greater harm regarding the proportion of patients with renal events

The extent of the respective added benefit at outcome level was estimated from these results (see Table 15).

Table 15: Extent of added benefit at outcome level: EVG/COBI/FTC/TDF vs. EFV/FTC/TDF

Outcome category **Outcome**	**EVG/COBI/FTC/TDF vs. EFV/FTC/TDF** **Proportion of events** **Effect estimates [95% CI][a]; p-value** **Probability[b]**	**Derivation of extent[c]**
Mortality		
All-cause mortality	0.3% vs. 0.6% Peto OR 0.52 [0.05; 5.00]; p = 0.597	Added benefit not proven
Morbidity		
AIDS-defining events (CDC class C event)	2.3% vs. 0.3% Peto OR 4.88 [1.31; 18.16]; p = 0.018 Peto OR[d] 0.20 [0.06; 0.76] probability: "indication"	Outcome category: serious/severe symptoms/late complications *CI_o < 0.90* lesser benefit, extent: "considerable"
Health-related quality of life		
	No data available	
AEs		
SAEs	16.1% vs. 9.4% RR 1.72 [1.15; 2.57]; p = 0.008 probability: "proof"	
Whites	*15.9% vs. 7.0%* *RR 2.25 [1.28; 3.96]; p = 0.004* *RR[d] 0.44 [0.25; 0.78]* *probability: "proof"*	*Outcome category: serious/severe AEs* *0.75 < CI_o < 0.90* *greater harm,* *extent: "considerable"*
Non-whites[e]	*16.4% vs. 13.6%* *RR 1.21 [0.67; 2.16]; p = 0.597* *probability: "indication"*	*Outcome category: serious/severe AEs* *greater harm,* *extent: "non-quantifiable" (not more than "considerable")*
Treatment discontinuation due to AEs	4.9% vs. 6.8% RR 0.72 [0.39; 1.31]; p = 0.290	
Whites	*6.5% vs. 5.7%* *RR 1.14 [0.55; 2.37]; p = 0.775*	*Greater/lesser harm not proven*
Non-whites[e]	2.2% vs. 8.8% RR 0.25 [0.07; 0.897]; p = 0.021 *probability: "proof"*	*Outcome category: non-serious/severe AEs[f]* *0.8 < CI_o < 0.90* *lesser harm, extent: "minor"*
AEs Grade 3-4	17.5% vs. 14.5% RR 1.21 [0.86; 1.70]; p = 0.290	Greater/lesser harm not proven
Psychiatric disorders	39.7% vs. 50.9% RR 0.78 [0.66; 0.92]; p = 0.003	Outcome category: non-serious/severe AEs CI_o > 0.90 greater/lesser harm not proven[g]

(continued)

Table 15: Extent of added benefit at outcome level: EVG/COBI/FTC/TDF vs. EFV/FTC/TDF (continuation)

Outcome category **Outcome**	**EVG/COBI/FTC/TDF vs. EFV/FTC/TDF** **Proportion of events** **Effect estimates [95% CI][a]; p-value** **Probability[b]**	**Derivation of extent[c]**
Nervous system disorders	32.2% vs. 45.2% RR 0.71 [0.59; 0.86]; p < 0.001 probability: "proof"	Outcome category: non-serious/severe AEs $0.8 < CI_o < 0.90$ lesser harm, extent: "minor"
Skin rash	21.3% vs. 30.7% RR 0.69 [0.54; 0.895]; p = 0.005 probability: "proof"	
Whites	*22.0% vs. 35.7%* *RR 0.62 [0.45; 0.84]; p = 0.002* *probability: "proof"*	*Outcome category: non-serious/severe AEs* *$0.8 < CI_o < 0.90$* *lesser harm, extent: "minor"*
Non-whites[e]	*20.1% vs. 21.6%* *RR 0.93 [0.58; 1.50]; p = 0.806* *probability: "indication"*	*Outcome category: non-serious/severe AEs* *lesser harm, extent: "minor"*
Gastrointestinal disorders	60.6% vs. 53.4% RR 1.14 [0.998; 1.29]; p = 0.055	Greater/lesser harm not proven.
Renal events	2.0% vs. 0.3% Peto OR 4.60 [1.14; 18.54]; p = 0.032 Peto OR[d] 0.22 [0.05; 0.88] probability: "indication"	Outcome category: non-serious/severe AEs $0.8 < CI_o < 0.90$ greater harm, extent: "minor"

Italic type: Effects for subgroups in which relevant indications or proof of an effect modification were present.

a: 96-week data of the study GS-US-236-0102 provided.
b: Probability provided, if statistically significant differences were present.
c: Estimations of effect size are made depending on the outcome category with different limits based on the upper limit of the confidence interval (CI_o).
d: Institute's calculation: reversed direction of effect to enable direct use of limits to derive added benefit.
e: This group includes Asians, blacks/patients of African heritage, native Americans/native Alaskans, Hawaiians/Pacific Islanders, and others.
f: Overall, it was unclear from the available documents whether the treatment discontinuations due to AEs were SAEs. Since the direction of effect for this outcome is reversed in comparison with the outcome "SAEs", it was assumed that the greater proportion of events was non-serious.
g: The CI_o is above the named threshold of 0.90.

CI: confidence interval; CI_o: upper limit of CI; EFV/FTC/TDF: efavirenz/emtricitabine/tenofovir disoproxil; EVG/COBI/FTC/TDF: elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil; Peto OR: Peto odds ratio; RR: relative risk; SD: standard deviation; SOC: MedDRA System Organ Class; vs.: versus

2.3.3.2 Overall conclusion on added benefit

The summary of the results that were included in the overall conclusion on the extent of added benefit is presented in Table 16 and Table 17, separated according to the relevant subgroups (whites/non-whites).

Overall conclusion for whites

Table 16: Whites – positive and negative effects from the assessment of EVG/COBI/FTC/TDF compared with EFV/FTC/TDF

Positive effects	Negative effects
Proof of lesser harm – extent: "minor" (non-serious/severe AEs: nervous system disorders)	Indication of a lesser benefit – extent: "considerable" (serious/severe symptoms/late complications: AIDS-defining events [CDC class C events])
Proof of lesser harm – extent: "minor" (non-serious/severe AEs: skin rash)	Proof of greater harm – extent: "considerable" (serious/severe AEs: SAEs)
	Indication of greater harm – extent "minor" (non-serious/severe AEs: renal events)
AE: adverse event; CDC: Centers for Disease Control and Prevention; EFV/FTC/TDF: efavirenz/ emtricitabine/tenofovir disoproxil; EVG/COBI/FTC/TDF: elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil; SAE: serious adverse event	

Overall, positive and negative effects remain for white patients. On the negative side, there is an indication of lesser benefit regarding AIDS-defining events (CDC class C events) with the extent "considerable". For the outcome "SAEs", there is proof of greater harm (extent also "considerable"). Regarding renal events, there is an indication of greater harm with the extent "minor".

There are positive effects of EVG/COBI/FTC/TDF with regards to the prevention of non-severe/serious AEs (nervous system disorders and skin rash). The extent of added benefit in both cases is rated as "minor".

Overall, it cannot be assumed that the positive effects, which have an extent of not more than "minor" and both of which are classified to the outcome category "non-severe/serious AEs", outweigh the negative effects. It should be particularly highlighted that the negative effects of considerable extent are from the categories "serious/severe symptoms" and "serious/severe AEs".

In summary, there is an indication of lesser benefit of EVG/COBI/FTC/TDF versus the ACT EFV/FTC/TDF for the group of whites.

Overall conclusion for non-whites

Table 17: Non-whites – positive and negative effects from the assessment of EVG/COBI/FTC/TDF compared with EFV/FTC/TDF

Positive effects	Negative effects
Proof of lesser harm – extent: "minor" (non-serious/severe AEs: treatment discontinuation due to AEs)	Indication of a lesser benefit – extent: "considerable" (serious/severe symptoms/late complications: AIDS-defining events [CDC class C events])
Proof of lesser harm – extent: "minor" (non-serious/severe AEs: nervous system disorders)	Indication of greater harm – extent: "non-quantifiable", not more than "considerable" (serious/severe AEs: SAEs)
Indication of lesser harm – extent: "minor" (non-serious/severe AEs: skin rash)	Indication of greater harm – extent "minor" (non-serious/severe AEs: renal events)
AE: adverse event; CDC: Centers for Disease Control and Prevention; EFV/FTC/TDF: efavirenz/ emtricitabine/tenofovir disoproxil; EVG/COBI/FTC/TDF: elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil; SAE: serious adverse event	

Overall, positive and negative effects remain for the group of non-whites. On the negative side, there is an indication of lesser benefit regarding AIDS-defining events (CDC class C event) with the extent "considerable". For the outcome "SAEs", there is an indication of greater harm (extent also "considerable"). Regarding renal events, there is an indication of greater harm with the extent "minor".

There are positive effects of EVG/COBI/FTC/TDF with regards to the prevention of non-serious/severe AEs (proof of lesser harm [nervous system disorders] and indication of lesser harm [skin rash]). The extent of added benefit in both cases is rated as "minor". In addition, there was proof of lesser harm with the extent "minor" regarding the prevention of treatment discontinuations due to AEs for the group of non-whites.

Hence, a more favourable picture was shown for EVG/COBI/FTC/TDF in non-whites versus whites, but the extent of the positive effects here was also not more than "minor", whereas the extent of the negative effects regarding serious symptoms/late complications and serious/severe AEs was (not more than) "considerable". Hence it cannot be assumed for this subgroup, either, that the negative effects are completely outweighed.

In summary, there is an indication of lesser benefit of EVG/COBI/FTC/TDF versus the ACT EFV/FTC/TDF also for the group of non-whites.

Summary

Although the results on the level of the individual outcomes diverge slightly for both relevant patient groups (whites/non-whites), the negative treatment effects outweigh the positive ones in both groups. In summary, there is an indication of lesser benefit of EVG/COBI/FTC/TDF in comparison with the ACT EFV/FTC/TDF for treatment-naive patients as a whole.

This deviates from the company's assessment, which derived proof of minor added benefit of EVG/COBI/FTC/TDF compared with the ACT EFV/FTC/TDF for treatment-naive patients.

2.3.4 List of included studies

GS-US-236-0102

Gilead Sciences. Study GS-US-236-0102: week 48 analysis [unpublished].

Gilead Sciences. Study GS-US-236-0102: week 96 analysis [unpublished].

Gilead Sciences. A phase 3, randomized, double-blind study to evaluate the safety and efficacy of elvitegravir/emtricitabine/tenofovir disoproxil fumarate/GS-9350 versus efavirenz/emtricitabine/tenofovir disoproxil fumarate in HIV-1 infected, antiretroviral treatment-naive adults; study GS-US-236-0102; interim week 96 clinical study report [unpublished]. 2012.

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2.4 Research question B: elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil for pretreated patients

2.4.1 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 lists on EVG/COBI/FTC/TDF for direct and indirect comparisons (studies completed up to 30 April 2013)
- Bibliographical literature search for direct comparisons on EVG/COBI/FTC/TDF (last search on 8 April 2013)
- Search in trial registries for studies on EVG/COBI/FTC/TDF for direct comparisons (last search on 9 April 2013)
- Bibliographical literature search on raltegravir for indirect comparisons (last search on 8 April 2013)
- Search in trial registries for studies on efavirenz, atazanavir, raltegravir (last search on 11 April 2013)

The Institute dispensed with checking the completeness because the studies included did not represent the approval status and did not comply with the specifications on the ACT. Hence, the company presented no relevant study.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4B, Sections 4.2.2 and 4.2.3 of the dossier, and in Section 2.6.3.2 of the full dossier assessment.

2.4.2 Results on added benefit

No relevant data were available for assessing the added benefit of EVG/COBI/FTC/TDF in pretreated patients. Hence the added benefit of EVG/COBI/FTC/TDF versus the ACT specified by the G-BA is not proven in this research question.

2.4.3 Extent and probability of added benefit

On the basis of the available data, there is no proof of an added benefit of EVG/COBI/FTC/TDF versus the ACT specified by the G-BA. Hence there are also no patient groups for whom a therapeutically important added benefit could be derived.

This deviates from the company's assessment, which overall derived proof of a minor added benefit of EVG/COBI/FTC/TDF.

2.5 Extent and probability of added benefit – summary

Table 19 of the full dossier assessment shows the extent and probability of added benefit of EVG/COBI/FTC/TDF versus the ACTs for the subindications "treatment-naive patients" and "pretreated patients".

Table 18: EVG/COBI/FTC/TDF: extent and probability of added benefit

Research question	Subindication	ACT	Extent and probability of added benefit
A	Treatment-naive patients	Efavirenz in combination with 2 nucleoside/nucleotide analogues (tenofovir plus emtricitabine or abacavir plus lamivudine)	Indication of a lesser benefit
B	Pretreated patients[a]	Individual therapy based on prior treatment(s) and under consideration of the reason for the switch of treatment, particularly treatment failure due to virologic failure and possible accompanying development of resistance, or due to AEs. The approval of the drugs is to be considered.	Added benefit not proven
a: Patients who are infected with HIV-1 without known mutations associated with resistance to any of the 3 antiretroviral drugs of EVG/COBI/FTC/TDF. ACT: appropriate comparator therapy; AE: adverse event; EVG/COBI/FTC/TDF: elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil; HIV-1: human immunodeficiency virus type 1			

The G-BA decides on the added benefit.

Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier, and in Section 2.6.2.9 of the full dossier assessment.

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Please see full dossier assessment for full reference list.

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