

IQWiG Reports – Commission No. A15-61

**Elvitegravir/cobicistat/  
emtricitabine/  
tenofovir alafenamide –  
Benefit assessment according to  
§35a Social Code Book V<sup>1</sup>**

**Extract**

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# Table of contents

	Page
<b>List of tables .....</b>	<b>v</b>
<b>List of figures .....</b>	<b>vii</b>
<b>List of abbreviations.....</b>	<b>viii</b>
<b>2 Benefit assessment .....</b>	<b>1</b>
<b>2.1 Executive summary of the benefit assessment.....</b>	<b>1</b>
<b>2.2 Research questions.....</b>	<b>12</b>
<b>2.3 Research question 1: treatment-naïve adults .....</b>	<b>14</b>
2.3.1 Information retrieval and study pool .....	14
2.3.1.1 Studies included.....	14
2.3.1.2 Study characteristics .....	15
2.3.2 Results on added benefit.....	28
2.3.2.1 Outcomes included .....	28
2.3.2.2 Results.....	31
2.3.2.3 Subgroups and other effect modifiers .....	42
2.3.3 Extent and probability of added benefit .....	52
2.3.3.1 Assessment of added benefit at outcome level .....	52
2.3.3.2 Overall conclusion on added benefit .....	55
2.3.4 List of included studies.....	56
<b>2.4 Research question 2: treatment-naïve adolescents 12 years of age and older ....</b>	<b>61</b>
2.4.1 Information retrieval and study pool .....	61
2.4.2 Results on added benefit.....	61
2.4.3 Extent and probability of added benefit .....	61
<b>2.5 Research question 3: pretreated adults.....</b>	<b>62</b>
2.5.1 Information retrieval and study pool .....	62
2.5.1.1 Studies included.....	62
2.5.1.2 Study characteristics .....	63
2.5.2 Results on added benefit.....	69
2.5.2.1 Outcomes included .....	69
2.5.2.2 Risk of bias .....	70
2.5.2.3 Results.....	72
2.5.2.4 Subgroups and other effect modifiers .....	80
2.5.3 Extent and probability of added benefit .....	82

2.5.3.1	Assessment of added benefit at outcome level .....	82
2.5.3.2	Overall conclusion on added benefit .....	85
2.5.4	List of included studies.....	86
<b>2.6</b>	<b>Research question 4: pretreated adolescents 12 years of age and older .....</b>	<b>88</b>
2.6.1	Information retrieval and study pool .....	88
2.6.2	Results on added benefit.....	88
2.6.3	Extent and probability of added benefit .....	88
<b>2.7</b>	<b>Extent and probability of added benefit – summary .....</b>	<b>89</b>
<b>References for English extract .....</b>		<b>91</b>

**List of tables<sup>3</sup>**

	<b>Page</b>
Table 2: ACT for the benefit assessment of EVG/COBI/FTC/TAF .....	1
Table 3: EVG/COBI/FTC/TAF: extent and probability of added benefit .....	11
Table 4: ACT for the benefit assessment of EVG/COBI/FTC/TAF .....	12
Table 5: Study pool – RCT, indirect comparison: treatment-naïve adults, EVG/COBI/FTC/TAF vs. EFV/FTC/TDF .....	15
Table 6: Characteristics of the studies included – RCT, indirect comparison: treatment- naïve adults, EVG/COBI/FTC/TAF vs. EFV/FTC/TDF .....	16
Table 7: Characteristics of the interventions – RCT, indirect comparison: treatment-naïve adults, EVG/COBI/FTC/TAF vs. EFV/FTC/TDF .....	20
Table 8: Characteristics of the study populations (demography and renal function) – RCT, indirect comparison: treatment-naïve adults, EVG/COBI/FTC/TAF vs. EFV/FTC/TDF .....	24
Table 9: Characteristics of the study populations (severity of disease at the start of the study) – RCT, indirect comparison: treatment-naïve adults, EVG/COBI/FTC/TAF vs. EFV/FTC/TDF .....	25
Table 10: Risk of bias at study level – RCT, indirect comparison: treatment-naïve adults, EVG/COBI/FTC/TAF vs. EFV/FTC/TDF .....	28
Table 11: Matrix of outcomes – RCT, indirect comparison: treatment-naïve adults, EVG/COBI/FTC/TAF vs. EFV/FTC/TDF .....	30
Table 12: Results (mortality and morbidity) – RCT, indirect comparison: treatment-naïve, EVG/COBI/FTC/TAF vs. EFV/FTC/TDF (96 weeks) .....	32
Table 13: Results (side effects) – RCT, indirect comparison: treatment-naïve adults, EVG/COBI/FTC/TAF vs. EFV/FTC/TDF (96 weeks) .....	35
Table 14: Subgroups (surrogate outcome CD4 cell count) – RCT, indirect comparison: treatment-naïve adults, EVG/COBI/FTC/TAF vs. EFV/FTC/TDF (96 weeks) .....	44
Table 15: Subgroups (SAEs) – RCT, indirect comparison: treatment-naïve adults, EVG/COBI/FTC/TAF vs. EFV/FTC/TDF (96 weeks) .....	45
Table 16: Subgroups (specific AEs) – RCT, indirect comparison: treatment-naïve adults, EVG/COBI/FTC/TAF vs. EFV/FTC/TDF (96 weeks) .....	46
Table 17: Extent of added benefit at outcome level: treatment-naïve adults, EVG/COBI/FTC/TAF vs. EFV/FTC/TDF .....	53
Table 18: Positive and negative effects from the assessment of EVG/COBI/FTC/TAF compared with EFV/FTC/TDF .....	55
Table 19: Study pool – RCT, direct comparison: pretreated adults, EVG/COBI/FTC/TAF vs. continuation of ongoing treatment (FTC/TDF + third agent <sup>a</sup> ) .....	62
Table 20: Characteristics of the study included – RCT, direct comparison: pretreated adults, EVG/COBI/FTC/TAF vs. continuation of ongoing treatment (FTC/TDF + third agent <sup>a</sup> ) .....	64

<sup>3</sup> Table numbers start with “2” as numbering follows that of the full dossier assessment.

Table 21: Characteristics of the intervention – RCT, direct comparison: pretreated adults, EVG/COBI/FTC/TAF vs. continuation of ongoing treatment (FTC/TDF + third agent <sup>a</sup> ) .....	65
Table 22: Characteristics of the study population – RCT, direct comparison: pretreated adults, EVG/COBI/FTC/TAF vs. continuation of ongoing treatment (FTC/TDF + third agent <sup>a</sup> ).....	67
Table 23: Risk of bias at study level – RCT, direct comparison: pretreated adults, EVG/COBI/FTC/TAF vs. continuation of ongoing treatment (FTC/TDF + third agent <sup>a</sup> ) .....	68
Table 24: Matrix of outcomes – RCT, direct comparison: pretreated adults, EVG/COBI/FTC/TAF vs. continuation of ongoing treatment (FTC/TDF + third agent <sup>a</sup> ) .....	70
Table 25: Risk of bias at study and outcome level – RCT, direct comparison: pretreated adults, EVG/COBI/FTC/TAF vs. continuation of ongoing treatment (FTC/TDF + third agent <sup>a</sup> ).....	71
Table 26: Results (mortality, morbidity and quality of life) – RCT, direct comparison: pretreated adults, EVG/COBI/FTC/TAF vs. continuation of ongoing treatment (FTC/TDF + third agent <sup>a</sup> ).....	73
Table 27: Results (side effects) – RCT, direct comparison: pretreated adults, EVG/COBI/FTC/TAF vs. continuation of ongoing treatment (FTC/TDF + third agent <sup>a</sup> ) .....	75
Table 28: Subgroups (side effects) – RCT, direct comparison: pretreated adults, EVG/COBI/FTC/TAF vs. continuation of ongoing treatment (FTC/TDF + third agent <sup>a</sup> ) .....	81
Table 29: Extent of added benefit at outcome level: EVG/COBI/FTC/TAF vs. continuation of ongoing treatment (FTC/TDF + third agent <sup>a</sup> ) .....	83
Table 30: Positive and negative effects from the assessment of EVG/COBI/FTC/TAF compared with continuation of ongoing treatment (FTC/TDF + third agent <sup>a</sup> ).....	85
Table 31: EVG/COBI/FTC/TAF: extent and probability of added benefit .....	89

**List of figures****Page**

Figure 1: Data availability for the benefit assessment (treatment-naïve adults) .....	15
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**List of abbreviations**

<b>Abbreviation</b>	<b>Meaning</b>
ACT	appropriate comparator therapy
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ATV	atazanavir
ATV/co	cobicistat-boosted atazanavir
ATV/r	ritonavir-boosted atazanavir
CD4	cluster of differentiation 4
CDC	Centers for Disease Control and Prevention
CI	confidence interval
COBI	cobicistat
CSR	clinical study report
eGFR	estimated glomerular filtration rate
EFV	efavirenz
EQ-5D	European Quality of Life-5 Dimensions
EVG	elvitegravir
FTC	emtricitabine
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HIV-1	human immunodeficiency virus type 1
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
POR	Peto odds ratio
RCT	randomized controlled trial
RNA	ribonucleic acid
RR	relative risk
SAE	serious adverse event
SF-36	Short Form 36
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
SPC	Summary of Product Characteristics
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil (fumarate)
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 combination elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (EVG/COBI/FTC/TAF). 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 30 December 2015.

#### Research question

The aim of this report was to assess the added benefit of EVG/COBI/FTC/TAF compared with the appropriate comparator therapy (ACT) in adults and adolescents (12 years of age and older and with a body weight of at least 35 kg) infected with human immunodeficiency virus type 1 (HIV-1).

The G-BA's specification of the ACT for different patient groups resulted in 4 research questions, which are presented in the following Table 2.

Table 2: ACT for the benefit assessment of EVG/COBI/FTC/TAF

Research question	Therapeutic indication	Appropriate comparator therapy specified by the G-BA <sup>a</sup>
1	Treatment-naïve adults	<b>Efavirenz</b> in combination with 2 nucleoside/nucleotide analogues ( <b>tenofovir disoproxil plus emtricitabine</b> or abacavir plus lamivudine)
2	Treatment-naïve adolescents <sup>b</sup>	Efavirenz in combination with abacavir and lamivudine
3	Pretreated adults	Individual antiretroviral 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 side effects.
4	Pretreated adolescents <sup>b</sup>	

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.

b: 12 years of age and older and with a body weight of at least 35 kg.

ACT: appropriate comparator therapy; COBI: cobicistat; EVG: elvitegravir; FTC: emtricitabine; G-BA: Federal Joint Committee; TAF: tenofovir alafenamide

Within the pretreated patients (research questions 3 and 4), the company distinguished between the following patient groups:

- For patients with indication for a treatment switch (e.g. in the presence of treatment failure or side effects), the company specified switching to individual antiretroviral therapy in

dependence on the pretreatment(s) and under consideration of the reason for the treatment switch as operationalization of the ACT.

- For patients without indication for a treatment switch, the company operationalized the ACT as continuing the ongoing treatment.

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

## Results

### Research question 1 (treatment-naïve adults)

#### *Study pool and study characteristics*

No studies of direct comparison were identified for research question 1.

The added benefit of EVG/COBI/FTC/TAF in comparison with the ACT efavirenz/emtricitabine/tenofovir disoproxil (EFV/FTC/TDF) was assessed on the basis of an adjusted indirect comparison. Five potentially relevant studies were identified (3 studies on EVG/COBI/FTC/TAF [292-0102, 292-0104, 292-0111] and 2 studies on EVF/FTC/TDF [236-0102 and 236-0104], each in comparison with the common comparator elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil [EVG/COBI/FTC/TDF]).

#### *Studies with the intervention*

The studies 292-0102, 292-0104 and 292-0111 were randomized, active-controlled, multicentre, double-blind studies on the comparison of EVG/COBI/FTC/TAF with EVG/COBI/FTC/TDF. Treatment-naïve adults with HIV-1 infection were enrolled in each of the studies. All 3 studies have not yet been completed. Data from the analysis date of 48 weeks (studies 292-0102, 292-0104 and 292-0111) and 96 weeks (studies 292-0104 and 292-0111) were available for the assessment. In compliance with the approval, the investigational intervention EVG/COBI/FTC/TAF was administered once daily orally with food in the studies. The common comparator EVG/COBI/FTC/TDF was also administered once daily orally with food in all studies.

#### *Studies with the appropriate comparator therapy*

The studies 236-0102 and 236-0104 were randomized, active-controlled, multicentre, double-blind studies on the comparison of EFV/FTC/TDF with EVG/COBI/FTC/TDF. Treatment-naïve adults with HIV-1 infection were enrolled in each of the studies. Data from the analysis date of 48 weeks (studies 236-0104, 236-0102) and 96 weeks (study 236-0102) were available for the assessment. In the studies, the comparator therapy EFV/FTC/TDF and the common comparator EVG/COBI/FTC/TDF were administered once daily orally as fixed-dose combination.

*Similarity of the studies on EVG/COBI/FTC/TAF and EFV/FTC/TDF in the indirect comparison*

The available data on the study and intervention characteristics of the 5 studies showed that the studies were sufficiently similar regarding design and patient characteristics.

*Dates of analysis*

The results of the analysis date of 96 weeks were primarily used in the benefit assessment because the primary consideration of longer observation durations was considered meaningful for the present chronic therapeutic indication. As a result, the results of 2 of the 5 relevant studies (292-0102 and 236-0104; 242 patients of 2693 patients in total), for which only 48-week data were available, were not used for the adjusted indirect comparison. The proportion of patients not considered in the indirect comparison was comparatively small (about 10%), however. Hence 2 studies on the side of EVG/COBI/FTC/TAF and one study on the side of EFV/FTC/TDF were available for the adjusted indirect comparison.

***Risk of bias***

The risk of bias at study level was rated as low for all studies. The risk of bias at outcome level was not evaluated because the consistency could not be assessed for the present adjusted indirect comparison and therefore there was generally low certainty of results.

***Results****Mortality*

- All-cause mortality

The adjusted indirect comparison showed no statistically significant difference between EVG/COBI/FTC/TAF and EFV/FTC/TDF for the outcome “all-cause mortality”. This resulted in no hint of an added benefit of EVG/COBI/FTC/TAF in comparison with EFV/FTC/TDF; an added benefit for the outcome “all-cause mortality” is therefore not proven.

*Morbidity*

- AIDS-defining events (CDC class C events); supplementary consideration of the surrogate outcomes “virologic response” and “CD4 cell count”

The adjusted indirect comparison showed a statistically significant difference to the disadvantage of EVG/COBI/FTC/TAF for the outcome “acquired immunodeficiency syndrome (AIDS)-defining events”. The adjusted indirect comparison showed no statistically significant difference between EVG/COBI/FTC/TAF and EFV/FTC/TDF for virologic response (snapshot algorithm, missing = failure, missing = excluded). The adjusted indirect comparison showed a statistically significant difference in favour of EVG/COBI/FTC/TAF for the outcome “cluster of differentiation 4 (CD4) cell count”. The clinical relevance of this improvement was unclear, however.

In the overall consideration of the results, a hint of lesser benefit of EVG/COBI/FTC/TAF compared with the ACT was derived for the outcome “AIDS-defining events (Centers for Disease Control and Prevention [CDC] class C events) because the effect in the outcome of interest “AIDS-defining events (CDC class C events)” was decisive.

- Health status

No data were available for conducting an adjusted indirect comparison for the outcome “health status”.

*Health-related quality of life*

Health-related quality of life was not recorded in the studies included.

*Side effects*

- Serious adverse events

The adjusted indirect comparison showed a statistically significant difference to the disadvantage of EVG/COBI/FTC/TAF for the outcome “serious adverse events (SAEs)”.

In addition, there was an indication of an effect modification by the characteristic “ethnicity” for this outcome. There was a hint of greater harm from EVG/COBI/FTC/TAF in comparison with EFV/FTC/TDF for Caucasians. For non-Caucasians, there was no hint of greater or lesser harm of EVG/COBI/FTC/TAF in comparison with EFV/FTC/TDF; greater or lesser harm for this patient group is therefore not proven.

- Severe adverse events (grade 3-4)

The meta-analysis of the studies with the intervention showed unexplained heterogeneity without effects in the same direction for the outcome “severe adverse events (AEs) grade 3-4”. Hence no common estimate was calculated. Consequently, an indirect comparison based on the overall study pool could not be meaningfully calculated and interpreted. The adjusted indirect comparisons that only considered one of the studies 292-0104 and 292-0111 showed no statistically significant results. Based on the data, there was no hint of greater or lesser harm of EVG/COBI/FTC/TAF in comparison with EFV/FTC/TDF; greater or lesser harm is therefore not proven.

- Discontinuation due to adverse events; nervous system disorders, skin and subcutaneous tissue disorders

The adjusted indirect comparison showed a statistically significant difference in favour of EVG/COB/FTC/TAF for each of the outcomes “discontinuation due to AEs”, “nervous system disorders” and “skin and subcutaneous tissue disorders”. The extent of the effects in these outcomes of the category non-serious/non-severe side effects was no more than marginal, however; greater or lesser harm for these outcomes is therefore not proven.

- Psychiatric disorders

The adjusted indirect comparison showed a statistically significant difference in favour of EVG/COBI/FTC/TAF for the outcome “psychiatric disorders”.

In addition, there was an indication of an effect modification by the characteristic “age” for this outcome. There was a hint of lesser harm from EVG/COBI/FTC/TAF in comparison with EFV/FTC/TDF for patients  $\geq 40$  years of age. For patients  $< 40$  years of age, there was no hint of greater or lesser harm of EVG/COBI/FTC/TAF in comparison with EFV/FTC/TDF; greater or lesser harm for this patient group is therefore not proven.

- Gastrointestinal disorders, renal and urinary disorders

The adjusted indirect comparison showed no statistically significant difference between EVG/COBI/FTC/TAF and EFV/FTC/TDF for the outcomes “gastrointestinal disorders” and “renal and urinary disorders”. This resulted in no hint of greater or lesser harm of EVG/COBI/FTC/TAF in comparison with EFV/FTC/TDF; greater or lesser harm for these outcomes is therefore not proven.

- Infections and infestations

The adjusted indirect comparison showed a statistically significant difference to the disadvantage of EVG/COBI/FTC/TAF for the outcome “infections and infestations”. This resulted in a hint of greater harm from EVG/COBI/FTC/TAF in comparison with EFV/FTC/TDF.

### **Extent and probability of added benefit, patient groups with therapeutically important added benefit<sup>4</sup>**

On the basis of the results presented, the extent and probability of the added benefit of the drug EVG/COBI/FTC/TAF compared with the ACT in treatment-naïve adults is assessed as follows:

Overall, one positive effect and several negative effects with the same probability (“hint”) remain.

The positive effect in the outcome category “non-serious/non-severe side effects” for the outcome “psychiatric disorders” was only shown in the subgroup of patients 40 years of age or older (extent: “minor”).

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<sup>4</sup> 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].

On the negative side, lesser benefit was shown for the outcome “AIDS-defining events” (extent: “considerable”) and greater harm for the outcomes “SAEs” (extent: “major”) and “infections and infestations” (extent: “considerable”).

Balancing these effects, the positive effect of minor extent, which, in addition, only existed in the subgroup of patients  $\geq 40$  years of age, did not outweigh the negative effects. It should be particularly highlighted that the negative effects were from the categories “serious/severe symptoms/late complications” or “side effects”.

In summary, there is a hint of lesser benefit of EVG/COBI/FTC/TAF in comparison with the ACT for treatment-naïve adults with HIV-1 infection.

### **Research question 3 (pretreated adults)**

#### ***Study pool and study characteristics***

The study 292-0109 was included in the benefit assessment.

The 292-0109 study was an open-label, active-controlled randomized trial with patients with prior antiretroviral therapy. Virologically suppressed adults who had participated in different clinical studies conducted by the company with a treatment regimen consisting of the fixed FTC/TDF backbone therapy and a third antiretroviral agent were enrolled in the study. Efavirenz, cobicistat-boosted elvitegravir or cobicistat-boosted or ritonavir-boosted atazanavir were possible third agents. A total of 1443 patients were randomized, 963 patients to the EVG/COBI/FTC/TAF arm, and 480 patients to the comparator arm (continuation of ongoing treatment). The planned treatment duration in the study is 96 weeks; at the time point of the benefit assessment, however, only results for the period of analysis of 48 weeks were available. The antiretroviral agents used in the studies were administered in compliance with their approval.

An evaluation regarding content of the investigated patient population showed that mostly patients without medically required indication for a treatment switch (e.g. due to virologic failure or side effects) were enrolled in study 292-0109. Hence on the basis of the total population, study 292-0109 could be used for the assessment of the added benefit in treatment-naïve adults without indication for a treatment switch. Some uncertainty remained, however, whether a small proportion of patients with necessary treatment switch due to side effects were also included in the study.

It was not possible to assess the added benefit of EVG/COBI/FTC/TAF for pretreated adults with indication for a treatment switch on the basis of study 292-0109.

#### ***Risk of bias***

The risk of bias at the study level was rated as low for the study. The risk of bias for all outcomes except all-cause mortality, SAEs and severe AEs (grade 3-4) was rated as high.

## **Results**

### *Mortality*

- All-cause mortality

There was no statistically significant difference between the treatment groups for the outcome “all-cause mortality”. This resulted in no hint of an added benefit of EVG/COBI/FTC/TAF in comparison with continuation of ongoing treatment; an added benefit for the outcome “all-cause mortality” is therefore not proven.

### *Morbidity*

- AIDS-defining events (CDC class C events); supplementary consideration of the surrogate outcomes “virologic response” and “CD4 cell count”

There was no statistically significant difference between the treatment groups for the outcome “AIDS-defining events”.

A statistically significant difference in favour of EVG/COBI/FTC/TAF was shown for virologic response (snapshot algorithm). It is possible, however, that this result was influenced by the algorithm used for the analysis of virologic response. For this reason, results of the sensitivity analyses presented in the clinical study report (CSR) were additionally considered using other algorithms (missing = failure and missing = excluded). These analyses resulted in discrepant results regarding statistical significance; these analyses did therefore not support the statistically significant effect presented by the company.

However, all 3 analyses (snapshot, missing = failure and missing = excluded) may be biased if the proportions of patients without virologic data in the analysis time window who had discontinued treatment and whose last measurement was < 50 HIV-1 ribonucleic acid (RNA) copies/mL differed between the study arms. In the analyses, these patients were not rated as patients with virologic response (snapshot, missing = failure) or excluded from the analyses (missing = excluded). The bias can be caused by not rating these patients as responders although they had responded to treatment at the last time point of measurement.

The proportion of patients without virologic data in the period of analysis whose last measurement was < 50 HIV-1 RNA copies/mL and who discontinued treatment for reasons other than AEs or death differed notably between the treatment arms in the snapshot algorithm (7/959 [0.7%] in the intervention arm, 20/477 [4.2%] in the comparator arm). Hence an imputation strategy was used for the outcome “virologic response” to check the robustness of the effect. For this purpose, the values for patients without virologic data in the period of analysis was imputed as follows: for patients whose last measurement before the 48-week period of analysis was < 50 HIV-1 RNA copies/mL and who discontinued treatment for reasons other than AEs or death, it was assumed that the response rates corresponded to the response rates observed in the treatment arms. The result of the imputation strategy showed no statistically significant difference between the treatment arms. Hence the result on virologic response with the snapshot algorithm was not robust and was biased by events such



as treatment discontinuation of patients with a last measurement of < 50 HIV-1 RNA copies/mL.

No statistically significant difference between the treatment arms was shown for change in CD4 cell count.

In the overall consideration of the results, there was therefore no hint of an added benefit of EVG/COBI/FTC/TAF in comparison with continuation of ongoing treatment for the outcome “AIDS-defining events”; an added benefit is therefore not proven.

- Health status (EQ-5D VAS)

No statistically significant difference between the treatment groups was shown for the outcome “health status measured with the European Quality of Life-5 Dimensions (EQ-5D) visual analogue scale (VAS)”. This resulted in no hint of an added benefit of EVG/COBI/FTC/TAF in comparison with continuation of ongoing treatment; an added benefit is therefore not proven.

*Health-related quality of life*

- SF-36 – physical sum score

No statistically significant difference between the treatment groups was shown for the outcome “physical sum score of the Short Form 36 (SF-36)”. This resulted in no hint of an added benefit of EVG/COBI/FTC/TAF in comparison with continuation of ongoing treatment; an added benefit is therefore not proven.

- SF-36 – mental sum score

A statistically significant difference in favour of EVG/COBI/FTC/TAF was shown for the mental sum score of the SF-36. The standardized mean difference SMD in the form of Hedges’ g was considered to check the relevance of the result. The 95% confidence interval (CI) was not completely above the irrelevance threshold of 0.2. It can therefore not be inferred that the effect is relevant. This resulted in no hint of an added benefit of EVG/COBI/FTC/TAF in comparison with continuation of ongoing treatment; an added benefit is therefore not proven.

*Side effects*

- Serious adverse events, psychiatric disorders, skin and subcutaneous tissue disorders, gastrointestinal disorders, renal and urinary disorders

No statistically significant difference between the treatment groups was shown for any of the following outcomes: SAEs, psychiatric disorders, skin and subcutaneous tissue disorders, gastrointestinal disorders and renal and urinary disorders. This resulted in no hint of greater or lesser harm of EVG/COBI/FTC/TAF in comparison with continuation of ongoing treatment for these outcomes; greater or lesser harm for these outcomes is therefore not proven.

- Severe adverse events (grade 3-4)

No statistically significant difference between the treatment groups was shown for the outcome “severe AEs (grade 3-4)”.

However, there was an indication of an effect modification by the characteristic “ethnicity” (Caucasian/non-Caucasian) for this outcome. For Caucasian patients, there was a hint of a lesser harm of EVG/COBI/FTC/TAF for the outcome “severe AEs (grade 3-4)”. For non-Caucasian patients, there was no hint of greater or lesser harm of EVG/COBI/FTC/TAF in comparison with continuation of ongoing treatment; greater or lesser harm for this patient group is therefore not proven.

- Discontinuation due to adverse events

A statistically significant difference in favour of EVG/COBI/FTC/TAF was shown for the outcome “discontinuation due to AEs”. There was an uncertainty for this outcome, however, because patients with indication for a treatment switch might have been included in the study.

Considering the rate of patients with treatment discontinuation (of any cause), it was shown in study 292-0109 already after 4 weeks of treatment that fewer patients in the intervention arm than in the comparator arm tended to discontinue treatment (0.1% vs. 1.0%). In comparison, the difference for the outcome “discontinuation due to AEs” between the treatment arms was only 1.6%. It is therefore not excluded that the statistically significant effect in discontinuation due to AEs was due to patients who had experienced burdensome side effects under their prior therapy already before the start of the study. The result for the outcome “discontinuation due to AEs” was therefore overall considered to be not interpretable with certainty. Hence greater or lesser harm for this outcome is not proven.

- Nervous system disorders

A statistically significant difference to the disadvantage of EVG/COBI/FTC/TAF was shown for the outcome “nervous system disorders”.

However, there was proof of an effect modification by the characteristic “sex” for this outcome. For men, there was a hint of greater harm from EVG/COBI/FTC/TAF in comparison with continuation of ongoing treatment for the outcome “nervous system disorders”. For women, there was no hint of greater or lesser harm of EVG/COBI/FTC/TAF in comparison with continuation of ongoing treatment; greater or lesser harm in this patient group is therefore not proven.

### **Extent and probability of added benefit, patient groups with therapeutically important added benefit**

On the basis of the results presented, the extent and probability of the added benefit of the drug EVG/COBI/FTC/TAF compared with the ACT in pretreated adults is assessed as follows:

Overall, one positive effect and one negative effect remain.

For severe AEs, there was a hint of lesser harm (extent: “minor”) in Caucasians. However, since patients of Caucasian origin represent the main ethnicity for the health care area of the present benefit assessment, no separate balancing for Caucasians and non-Caucasians was conducted. There was a hint of greater harm (extent: “considerable”) for the outcome “nervous system disorders”, which only applied to men. This led to a separate balancing of the added benefit in men and women.

For women, only a positive effect in the category “severe/serious side effects” remained so that a hint of a minor added benefit was derived for women.

For men, a positive effect in the category “severe/serious side effects” and a negative effect in the category “non-serious/non-severe side effects”, each with the same certainty of results (“hint”), remain. The extent of the positive effect for the outcome “severe AEs (grade 3-4)” was only minor and was therefore outweighed by considerable greater harm for the outcome of “(non-serious) nervous system disorders”. Overall, there was therefore no hint of an added benefit for men; an added benefit is not proven.

No data were available for pretreated HIV-infected patients with indication for a treatment switch. There was no hint of an added benefit of EVG/COBI/FTC/TAF in comparison with the ACT for this patient population; an added benefit for these patients is not proven.

#### **Research question 2 and 4 (treatment-naïve and pretreated adolescents)**

The company presented no data for the assessment of the added benefit of EVG/COBI/FTC/TAF in comparison with the ACT (efavirenz in combination with abacavir and lamivudine or individual antiretroviral therapy) for treatment-naïve and pretreated adolescents. Hence there was no hint of an added benefit of EVG/COBI/FTC/TAF in comparison with the ACT. An added benefit for treatment-naïve and pretreated adolescents is therefore not proven.

#### **Extent and probability of added benefit – summary**

Table 3 presents a summary of the extent and probability of the added benefit of EVG/COBI/FTC/TAF.

Table 3: EVG/COBI/FTC/TAF: extent and probability of added benefit

Research question	Therapeutic indication	ACT <sup>a</sup>	Sub-group	Extent and probability of added benefit
1	Treatment-naïve adults	<b>Efavirenz</b> in combination with 2 nucleoside/nucleotide analogues ( <b>tenofovir disoproxil plus emtricitabine</b> or abacavir plus lamivudine)		Hint of lesser benefit
2	Treatment-naïve adolescents <sup>b</sup>	Efavirenz in combination with abacavir and lamivudine		Added benefit not proven
3	Pretreated adults (without indication for a treatment switch)	Individual antiretroviral 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 side effects.	Men	Added benefit not proven
			Women	Hint of minor added benefit
	Pretreated adults (with indication for a treatment switch)			Added benefit not proven
4	Pretreated adolescents <sup>b</sup>			Added benefit not proven
<p>a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.</p> <p>b: 12 years of age and older and with a body weight of at least 35 kg.</p> <p>ACT: appropriate comparator therapy; COBI: cobicistat; EVG: elvitegravir; FTC: emtricitabine; G-BA: Federal Joint Committee; TAF: tenofovir alafenamide</p>				

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 aim of this report was to assess the added benefit of EVG/COBI/FTC/TAF compared with the ACT in adults and adolescents (12 years of age and older and with a body weight of at least 35 kg) infected with HIV-1.

The G-BA's specification of the ACT for different patient groups resulted in 4 research questions, which are presented in the following Table 4.

Table 4: ACT for the benefit assessment of EVG/COBI/FTC/TAF

Research question	Therapeutic indication	Appropriate comparator therapy specified by the G-BA <sup>a</sup>
1	Treatment-naïve adults	<b>Efavirenz</b> in combination with 2 nucleoside/nucleotide analogues ( <b>tenofovir disoproxil plus emtricitabine</b> or abacavir plus lamivudine)
2	Treatment-naïve adolescents <sup>b</sup>	Efavirenz in combination with abacavir and lamivudine
3	Pretreated adults	Individual antiretroviral 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 side effects.
4	Pretreated adolescents <sup>b</sup>	
<p>a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.</p> <p>b: 12 years of age and older and with a body weight of at least 35 kg.</p> <p>ACT: appropriate comparator therapy; COBI: cobicistat; EVG: elvitegravir; FTC: emtricitabine; G-BA: Federal Joint Committee; TAF: tenofovir alafenamide</p>		

The company followed the specification of the G-BA's ACT for all research questions. Within the pretreated patients (research questions 3 and 4), it distinguished between the following patient groups:

- For patients with indication for a treatment switch (e.g. in the presence of treatment failure or side effects), the company specified switching to individual antiretroviral therapy in dependence on the pretreatment(s) and under consideration of the reason for the treatment switch as operationalization of the ACT.
- For patients without indication for a treatment switch (e.g. due to virologic failure, development of resistances, or side effects), the company operationalized the ACT as continuing the ongoing therapy.

The company's approach to distinguish between different operationalizations of the ACT in patients with and without indication for a treatment switch was followed in the present benefit assessment. The implementation of the individually optimized treatment and its suitability for the population included was investigated in the studies (see also Section 2.8.1 of the full dossier assessment).

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 48 weeks were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

## **2.3 Research question 1: treatment-naïve adults**

### **2.3.1 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 list on EVG/COBI/FTC/TAF (status: 15 October 2015)
- bibliographical literature search on EVG/COBI/FTC/TAF (last search on 19 October 2015)
- search in trial registries for studies on EVG/COBI/FTC/TAF (last search on 20 October 2015)
- bibliographical literature search on the ACT (last search on 19 October 2015)
- search in trial registries for studies on the ACT (last search on 21 October 2015)

To check the completeness of the study pool:

- search in trial registries for studies on EVG/COBI/FTC/TAF (last search on 13 January 2016)
- search in trial registries for studies on the ACT (last search on 15 January 2016)

No additional relevant study was identified from the check.

#### **2.3.1.1 Studies included**

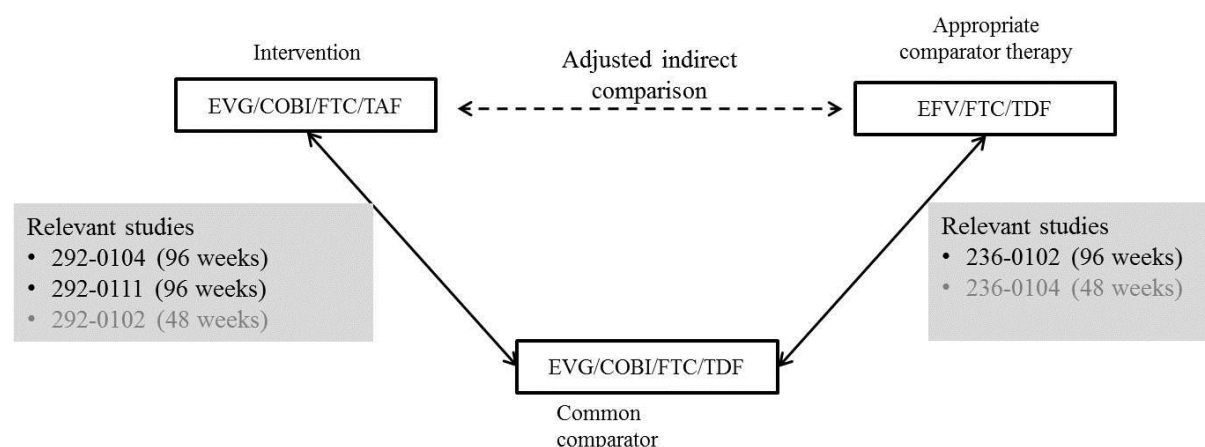
The company identified no studies that directly compared EVG/COBI/FTC/TAF with efavirenz in combination with tenofovir disoproxil and emtricitabine (EFV/FTC/TDF). Instead, the company presented an adjusted indirect comparison using the common comparator EVG/COBI/FTC/TDF in Module 4 A of the dossier to assess EVG/COBI/FTC/TAF in comparison with EFV/FTC/TDF.

The studies listed in Table 5 were included in the benefit assessment.

Table 5: Study pool – RCT, indirect comparison: treatment-naïve adults, EVG/COBI/FTC/TAF vs. EFV/FTC/TDF

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study <sup>a</sup> (yes/no)	Third-party study (yes/no)
<b>Studies with intervention</b>			
GS-US-292-0102 (292-0102) <sup>b</sup>	Yes	Yes	No
GS-US-292-0104 (292-0104) <sup>b</sup>	Yes	Yes	No
GS-US-292-0111 (292-0111) <sup>b</sup>	Yes	Yes	No
<b>Studies with ACT</b>			
GS-US-236-0102 (236-0102) <sup>b</sup>	No	Yes	No
GS-US-236-0104 (236-0104) <sup>b</sup>	No	Yes	No
a: Study for which the company was sponsor. b: Hereinafter, the study is referred to with its abbreviated form. ACT: appropriate comparator therapy; COBI: cobicistat; EFV: efavirenz; EVG: elvitegravir; FTC: emtricitabine; RCT: randomized controlled trial; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; vs.: versus			

The study pool for the benefit assessment is presented in Figure 1 and corresponds to that of the company.



COBI: cobicistat; EFV: efavirenz; EVG: elvitegravir; FTC: emtricitabine; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil

Figure 1: Data availability for the benefit assessment (treatment-naïve adults)

Section 2.3.4 contains a reference list for the studies included.

### 2.3.1.2 Study characteristics

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



Table 6: Characteristics of the studies included – RCT, indirect comparison: treatment-naïve adults, EVG/COBI/FTC/TAF vs. EFV/FTC/TDF

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes <sup>a</sup>
<b>Studies with intervention</b>						
292-0102	RCT, double-blind, parallel <sup>b</sup>	Antiretroviral treatment-naïve HIV-1 infected adults with plasma HIV-1 RNA viral load $\geq 5000$ copies/mL and eGFR $\geq 70$ mL/min	EVG/COBI/FTC/TAF (N = 113) EVG/COBI/FTC/TDF (N = 58)	Screening: 35 days prior to the start of treatment  Randomized treatment: 48 weeks + time to unblinding, then all study participants have the option to receive unblinded EVG/COBI/FTC/TAF treatment  Follow-up: 30 days	37 centres in America (Puerto Rico, USA) 12/2011–ongoing Data cut-off at week 96: 3/2014 <sup>c</sup>	Primary: virologic response at week 24 Secondary: AIDS-defining events (CDC class C events), virologic response at week 48, change in CD4 cell count, mortality, AEs
292-0104	RCT, double-blind, parallel <sup>d</sup>	Antiretroviral treatment-naïve HIV-1 infected adults with plasma HIV-1 RNA viral load $\geq 1000$ copies/mL and eGFR $\geq 50$ mL/min	EVG/COBI/FTC/TAF (N = 438) EVG/COBI/FTC/TDF (N = 434)	Screening: 30 days prior to the start of treatment  Treatment: 96 weeks <sup>e</sup> + time to unblinding  Follow-up: 30 days	120 centres in Australia, Austria, Belgium, Canada, Italy, Japan, Spain, Switzerland, Thailand, USA, United Kingdom 12/2012–ongoing Data cut-offs: week 48: 8/2014 week 96: 7/2015	Primary: virologic response at week 48 Secondary: AIDS-defining events (CDC class C events), virologic response at week 96, change in CD4 cell count, health status, quality of life, mortality, AEs

(continued)

Table 6: Characteristics of the studies included – RCT, indirect comparison: treatment-naïve adults, EVG/COBI/FTC/TAF vs. EFV/FTC/TDF (continued)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes <sup>a</sup>
<b>Studies with intervention</b>						
292-0111	RCT, double-blind, parallel <sup>d</sup>	Antiretroviral treatment-naïve HIV-1 infected adults with plasma HIV-1 RNA viral load $\geq 1000$ copies/mL and eGFR $\geq 50$ mL/min	EVG/COBI/FTC/TAF (N = 435) EVG/COBI/FTC/TDF (N = 437)	Screening: 30 days prior to the start of treatment  Treatment: 96 weeks <sup>f</sup> + time to unblinding  Follow-up: 30 days	121 centres in Canada, Dominican Republic, France, Italy, Mexico, Netherlands, Portugal, Sweden, USA, United Kingdom 3/2013–ongoing Data cut-offs: week 48: 9/2014 week 96: 8/2015	Primary: virologic response at week 48 Secondary: AIDS-defining events (CDC class C events), virologic response at week 96, change in CD4 cell count, health status, quality of life, mortality, AEs
<b>Studies with ACT</b>						
236-0102	RCT, double-blind, parallel <sup>b</sup>	Antiretroviral treatment-naïve HIV-1 infected adults with HIV-1 RNA viral load level $\geq 5000$ copies/mL and eGFR $\geq 70$ mL/min	EVG/COBI/FTC/TDF (N = 353) EFV/FTC/TDF (N = 354)	Screening: 35 days prior to the start of treatment  Treatment: 96 weeks <sup>g</sup> + time to unblinding  Follow-up: 30 days	102 centres in America (Puerto Rico, USA) 3/2010–9/2014 <sup>h</sup> Data cut-offs: week 48: 8/2011 week 96: 7/2012	Primary: virologic response at week 48 Secondary: AIDS-defining events (CDC class C events), virologic response at week 96, change in CD4 cell count, mortality, AEs

(continued)

Table 6: Characteristics of the studies included – RCT, indirect comparison: treatment-naïve adults, EVG/COBI/FTC/TAF vs. EFV/FTC/TDF (continued)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes <sup>a</sup>
236-0104	RCT, double-blind, parallel <sup>b</sup>	Antiretroviral treatment-naïve HIV-1 infected adults with plasma HIV-1 RNA viral load $\geq 5000$ copies/mL and eGFR $\geq 80$ mL/min	EVG/COBI/FTC/TDF (N = 48) EFV/FTC/TDF (N = 23)	Screening: 28 days prior to the start of treatment  Treatment: 48 weeks + time to unblinding (week 60), then all study participants could receive unblinded EVG/COBI/FTC/TDF treatment  Follow-up: 30 days	30 centres in USA 3/2009–9/2013 Data cut-off at week 96: 8/2011 <sup>c</sup>	Primary: virologic response at week 24 Secondary: AIDS-defining events (CDC class C events), virologic response at week 48, change in CD4 cell count, mortality, AEs

(continued)

Table 6: Characteristics of the studies included – RCT, indirect comparison: treatment-naïve adults, EVG/COBI/FTC/TAF vs. EFV/FTC/TDF (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: Stratified by HIV-1 RNA ( $\leq 100\,000$  copies/mL,  $> 100\,000$  copies/mL) at screening.

c: The results of the randomized treatment phase from the 96-week CSR refer to week 48 (+ time to unblinding).

d: Stratified by HIV-1 RNA ( $\leq 100\,000$  copies/mL,  $> 100\,000$  copies/mL to  $\leq 400\,000$  copies/mL or  $> 400\,000$  copies/mL), CD4 cell count ( $< 50$  cells/ $\mu$ L, 50–199 cells/ $\mu$ L or  $\geq 200$  cells/ $\mu$ L and region (USA, non-USA) at screening.

e: According to Amendment 3 to the study protocol (18 December 2014), the blinded phase was prolonged from 96 weeks to 144 weeks (+ time to unblinding). After unblinding, all study participants, except the ones in the United Kingdom, have the possibility to receive unblinded EVG/COBI/FTC/TAF treatment until the product is commercially available or until Gilead stops the study in the corresponding countries.

f: According to Amendment 2 to the study protocol (18 December 2014), the blinded phase was prolonged from 96 weeks to 144 weeks (+ time to unblinding). After unblinding, all study participants, except the ones in the United Kingdom, have the possibility to receive unblinded EVG/COBI/FTC/TAF treatment until the product is commercially available or until Gilead stops the study in the corresponding countries.

g: According to Amendment 2 to the study protocol (19 January 2012), the blinded phase was prolonged from 96 weeks to 192 weeks (+ time until blinding). After unblinding, all study participants have the possibility to receive unblinded EVG/COBI/FTC/TDF treatment until the product is commercially available or until Gilead stops the corresponding research programme.

h: Only data on week 48 and week 96 were available in this dossier assessment.

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; CSR: clinical study report; EFV: efavirenz; eGFR: estimated glomerular filtration rate (according to Cockcroft-Gault equation); EVG: elvitegravir; FTC: emtricitabine; HIV-1: human immunodeficiency virus type 1; N: number of randomized patients; RCT: randomized controlled trial; RNA: ribonucleic acid; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; vs: versus

Table 7: Characteristics of the interventions – RCT, indirect comparison: treatment-naïve adults, EVG/COBI/FTC/TAF vs. EFV/FTC/TDF

Study	Intervention/ comparator therapy	Common comparator	Prior and concomitant medication
<b>Studies with intervention</b>			
292-0102	EVG 150 mg/COBI 150 mg/ FTC 200 mg/TAF 10 mg (fixed-dose combination) once daily orally with food + placebo for EVG/COBI/FTC/TDF once daily orally with food	EVG 150 mg/COBI 150 mg/ FTC 200 mg/TDF 300 mg <sup>a</sup> (fixed-dose combination) once daily orally with food + placebo for EVG/COBI/FTC/TAF once daily orally with food	<b>Pretreatment:</b> no pretreatment with antiretroviral therapies <sup>b</sup> <b>Non-permitted concomitant treatment:</b> drugs with high interaction potential (e.g. carbamazepine, HMG- CoA reductase inhibitors, St. John's Wort)
292-0104	EVG 150 mg/COBI 150 mg/ FTC 200 mg/TAF 10 mg (fixed-dose combination) once daily orally with food + placebo for EVG/COBI/FTC/TDF once daily orally with food	EVG 150 mg/COBI 150 mg/ FTC 200 mg/TDF 300 mg <sup>a</sup> (fixed-dose combination) once daily orally with food + placebo for EVG/COBI/FTC/TAF once daily orally with food	<b>Pretreatment:</b> no pretreatment with antiretroviral therapies <sup>c</sup> <b>Non-permitted concomitant treatment:</b> drugs with high interaction potential (e.g. carbamazepine, HMG- CoA reductase inhibitors, St. John's Wort)
292-0111	EVG 150 mg/COBI 150 mg/ FTC 200 mg/TAF 10 mg (fixed-dose combination) once daily orally with food + placebo for EVG/COBI/FTC/TDF once daily orally with food	EVG 150 mg/COBI 150 mg/ FTC 200 mg/TDF 300 mg <sup>a</sup> (fixed-dose combination) once daily orally with food + placebo for EVG/COBI/FTC/TAF once daily orally with food	<b>Pretreatment:</b> no pretreatment with antiretroviral therapies <sup>c</sup> <b>Non-permitted concomitant treatment:</b> drugs with high interaction potential (e.g. carbamazepine, HMG- CoA reductase inhibitors, St. John's Wort)

(continued)

Table 7: Characteristics of the interventions – RCT, indirect comparison: treatment-naïve adults, EVG/COBI/FTC/TAF vs. EFV/FTC/TDF (continued)

Study	Intervention/comparator therapy	Common comparator	Prior and concomitant medication
<b>Studies with ACT</b>			
236-0102	EFV 600 mg/FTC 200 mg/TDF 300 mg (fixed-dose combination) once daily orally on an empty stomach prior to bedtime + placebo for EVG/COBI/FTC/TDF once daily orally with food	EVG 150 mg/COBI 150 mg/FTC 200 mg/TDF 300 mg <sup>a</sup> (fixed-dose combination) once daily orally with food + placebo for EFV/FTC/TDF once daily orally on an empty stomach prior to bedtime	<b>Pretreatment:</b> no pretreatment with antiretroviral therapies <b>Non-permitted concomitant treatment:</b> drugs with high interaction potential (e.g. carbamazepine, HMG-CoA reductase inhibitors, St. John's Wort)
236-0104	EFV 600 mg/FTC 200 mg/TDF 300 mg (fixed-dose combination) once daily orally on an empty stomach prior to bedtime + placebo for EVG/COBI/FTC/TDF once daily orally with food	EVG 150 mg/COBI 150 mg/FTC 200 mg/TDF 300 mg <sup>a</sup> (fixed-dose combination) once daily orally with food + placebo for EFV/FTC/TDF once daily orally on an empty stomach prior to bedtime	<b>Pretreatment:</b> no pretreatment with antiretroviral therapies <b>Non-permitted concomitant treatment:</b> drugs with high interaction potential (e.g. carbamazepine, HMG-CoA reductase inhibitors, St. John's Wort)
<p>a: Equivalent to 245 mg tenofovir disoproxil.</p> <p>b: In the extension phase (optional possibility to receive EVG/COBI/FTC/TAF after the randomized phase) of the study, patients from study GS-US-299-0102 who had been pretreated with darunavir + cobicistat could be additionally included.</p> <p>c. Antiretroviral therapies in the framework of a pre- or post-exposure prophylaxis up to 6 months before the start of the study were exempt.</p> <p>ACT: appropriate comparator therapy; COBI: cobicistat; EFV: efavirenz, EVG: elvitegravir; FTC: emtricitabine, HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme-A; RCT: randomized controlled trial; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate; vs.: versus</p>			

### Studies with the intervention

The studies 292-0102, 292-0104 and 292-0111 were randomized, active-controlled, multicentre, double-blind studies on the comparison of EVG/COBI/FTC/TAF (intervention) with EVG/COBI/FTC/TDF (common comparator in the indirect comparison). HIV-1 infected treatment-naïve adults were included who had to have a baseline viral load of  $\geq 5000$  HIV-1 RNA copies/mL (292-0102) or  $\geq 1000$  HIV-1 RNA copies/mL (292-0104 and 292-0111).

In each of the studies 292-0104 and 292-0111, 872 patients were randomly allocated in a ratio of 1:1 to the 2 study arms. In study 292-0102, which was notably smaller, 171 patients were randomized in a ratio of 2:1 to the 2 study arms (EVG/COBI/FTC/TAF: 113 patients; EVG/COBI/FTC/TDF: 58 patients). The patients in the studies were stratified by baseline viral load (292-0102, 292-0104 and 292-0111), CD4 cell count, and region (292-0104 and 292-0111).

The randomized treatment duration in study 292-0102 was 48 weeks (+ time to unblinding). Subsequently, all patients could receive unblinded EVG/COBI/FTC/TAF treatment. The originally planned blinded treatment duration of 96 weeks in the studies 292-0104 und 292-0111 was prolonged to 144 weeks with an amendment to the protocol. All 3 studies have not yet been completed. Data from the analysis date of 48 weeks (studies 292-0102, 292-0104 and 292-0111) and 96 weeks (studies 292-0104 and 292-0111) were available for the assessment. The results at the analysis date of 96 weeks were primarily used in the benefit assessment (see Section 2.8.2.5.3 of the full dossier assessment).

In compliance with the approval, the investigational intervention EVG/COBI/FTC/TAF was administered once daily orally with food in the studies [3]. Placebo was used in both treatment arms to maintain blinding. According to the Summary of Product Characteristics (SPC), EVG/COBI/FTC/TAF is only to be used if the HI viruses of the patients have no known mutations associated with resistance to the drugs FTC and TAF or the class of integrase inhibitors. Only patients with sensitivity to the agents EVG, FTC and TDF used in the study were included in the studies 292-0104 and 292-0111. In the 292-0102 study, only sensitivity to FTC and TDF was required. According to the inclusion criteria of this study, sensitivity to elvitegravir was not explicitly checked. Due to the low rate of primary resistances to integrase inhibitors [4], it can be assumed that the majority of the patients had sensitivity to this drug class. Furthermore, due to the same resistance profile of TAF versus TDF [5], it can be assumed that patients who are sensitive to TDF are also sensitive to TAF.

The common comparator EVG/COBI/FTC/TDF was also administered once daily orally with food in all studies. The approval status of the common comparator EVG/COBI/FTC/TDF was not investigated more closely because the assumption of similarity of the studies regarding the common comparator is decisive for conducting an adjusted indirect comparison (see section on the similarity of the studies below).

### **Studies with the appropriate comparator therapy**

The studies 236-0102 and 236-0104 were randomized, active-controlled, multicentre, double-blind studies on the comparison of EFV/FTC/TDF (ACT) with EVG/COBI/FTC/TDF (common comparator in the indirect comparison). Treatment-naïve adults with HIV-1 infection who had to have a baseline viral load of  $\geq 5000$  HIV-1 RNA copies/mL were enrolled.

In study 236-0102, a total of 707 patients were randomly allocated in a ratio of 1:1 to the 2 study arms. In study 236-0104, which was notably smaller, 71 patients were randomized in a ratio of 2:1 to the 2 study arms (EVG/COBI/FTC/TDF: 48 patients; EFV/FTC/TDF: 23 patients). Randomization was stratified by baseline viral load in both studies.

The randomized treatment duration in study 236-0104 was 48 weeks (+ time to unblinding in week 60). The originally planned blinded treatment duration of 96 weeks in study 236-0102 was prolonged to 192 weeks with an amendment to the protocol. Data from the analysis date

of 48 weeks (studies 236-0104, 236-0102) and 96 weeks (study 236-0102) were available for the assessment. The results at the analysis date of 96 weeks were primarily used in the benefit assessment (see Section 2.8.2.5.3 of the full dossier assessment).

In the studies, the comparator therapy EFV/FTC/TDF and the common comparator EVG/COBI/FTC/TDF were administered once daily orally as fixed-dose combination. The preferred administration of EVG/COBI/FTC/TDF once daily with food versus the preferred administration of EFV/FTC/TDF on an empty stomach prior to bedtime 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 [6] was not a problem insofar as each individual substance is also approved for treatment-naïve patients [7-9].

The approval status of the common comparator EVG/COBI/FTC/TDF was not investigated more closely because the assumption of similarity of the studies regarding the common comparator is decisive for conducting an adjusted indirect comparison (see section on the similarity of the studies below).

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



Table 8: Characteristics of the study populations (demography and renal function) – RCT, indirect comparison: treatment-naïve adults, EVG/COBI/FTC/TAF vs. EFV/FTC/TDF

Study Group	N <sup>a</sup>	Age [years] mean (SD)	Sex [F/M] %	Ethnicity Caucasian/Asian/other <sup>b</sup> %	eGFR (mL/min) median (Q1; Q3)	Treatment discontinuations week 96 n (%)	Study discontinuations week 96 n (%)
<b>Studies with intervention</b>							
292-0102							
EVG/COBI/FTC/TAF	112	35 (11)	3.6/96.4	66.1/2.7/31.3	115.2 (100.8; 131.7)	7 (6.3) <sup>d</sup>	5 (4.5) <sup>d</sup>
EVG/COBI/FTC/TDF	58	37 (11)	1.7/98.3	69.0/1.7/29.3 <sup>c</sup>	113.3 (97.7; 129.4)	5 (8.6) <sup>d</sup>	5 (8.6) <sup>d</sup>
292-0104							
EVG/COBI/FTC/TAF	435	35 (10)	16.3/83.7	57.5/17.5/25.0 <sup>c</sup>	118.5 (101.6; 135.7)	36 (8.3)	34 (7.8)
EVG/COBI/FTC/TDF	432	36 (11)	13.0/87.0	59.0/17.8/23.2 <sup>c</sup>	112.8 (97.8; 134.2)	50 (11.6)	44 (10.2)
292-0111							
EVG/COBI/FTC/TAF	431	35 (11)	14.4/85.6	54.5/3.5/41.9 <sup>c</sup>	115.9 (98.4; 135.6)	56 (13.0)	50 (11.6)
EVG/COBI/FTC/TDF	435	36 (11)	16.3/83.7	55.9/2.8/41.3 <sup>c</sup>	114.7 (99.6; 133.4)	67 (15.4)	52 (12.0)
<b>Studies with ACT</b>							
236-0102							
EFV/FTC/TDF	352	38 (11)	10.2/89.8	64.5/2.8/32.7 <sup>c</sup>	114.1 (98.2; 135.0)	61 (17.3)	53 (15.1)
EVG/COBI/FTC/TDF	348	38 (10)	11.8/88.2	61.5/1.7/36.8 <sup>c</sup>	114.6 (98.7; 137.5)	53 (15.2)	44 (12.6)
236-0104							
EFV/FTC/TDF	23	35 (10)	8.7/91.3	78.3/0/21.7 <sup>c</sup>	121.2 (110.3; 144.9)	3 (13.0) <sup>d</sup>	2 (8.7) <sup>d</sup>
EVG/COBI/FTC/TDF	48	36 (9)	8.3/91.7	68.8/2.1/29.2 <sup>c</sup>	120.7 (108.5; 155.9)	3 (6.3) <sup>d</sup>	3 (6.3) <sup>d</sup>
<p>a: Number of patients in the safety population, which includes all patients who were randomized and received at least one dose of the study treatment.</p> <p>b: This group includes blacks or patients of African or Afro-American origin, native Americans/native Alaskans, Hawaiians/Pacific Islanders, and others.</p> <p>c: Institute's calculation.</p> <p>d: Patients who discontinued the study or treatment up to week 48 (+ time to unblinding).</p> <p>ACT: appropriate comparator therapy; COBI: cobicistat; EFV: efavirenz; eGFR: estimated glomerular filtration rate (according to Cockcroft-Gault equation); EVG: elvitegravir; F: female; FTC: emtricitabine; M: male; n: number of patients with event; N: number of patients included; Q: quartile; RCT: randomized controlled trial; SD: standard deviation; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; vs.: versus</p>							

Table 9: Characteristics of the study populations (severity of disease at the start of the study) – RCT, indirect comparison: treatment-naïve adults, EVG/COBI/FTC/TAF vs. EFV/FTC/TDF

Study Group	N <sup>a</sup>	Viral load (log10 copies/ mL) median (Q1; Q3)	Baseline viral load HIV-1 RNA copies/mL n (%)		CD4 cell count/μL median (Q1; Q3)	CD4 cell count/μL n (%)		HIV disease stage n (%)		
			≤ 100 000	> 100 000		< 350	≥ 350	Asymp- tomatic	Symp- tomatic	AIDS
Studies with intervention										
292-0102										
EVG/COBI/FTC/TAF	112	4.55 (4.30; 4.89)	93 (83.0)	19 (17.0)	385 (283; 528)	46 (41.1) <sup>b</sup>	66 (58.9) <sup>b</sup>	99 (88.4)	9 (8.0)	4 (3.6)
EVG/COBI/FTC/TDF	58	4.58 (4.35; 5.08)	42 (72.4)	16 (27.6)	397 (232; 535)	25 (43.1) <sup>b</sup>	33 (56.9) <sup>b</sup>	52 (89.7)	5 (8.6)	1 (1.7)
292-0104										
EVG/COBI/FTC/TAF	435	4.59 (4.15; 4.98)	331 (76.1)	104 (23.9)	407 (280; 581)	161 (37.0) <sup>b</sup>	274 (63.0) <sup>b</sup>	402 (92.6)	23 (5.3)	9 (2.1)
EVG/COBI/FTC/TDF	432	4.62 (4.20; 4.96)	336 (77.8)	96 (22.2)	404 (296; 536)	164 (38.0) <sup>b</sup>	268 (62.0) <sup>b</sup>	406 (94.2)	15 (3.5)	10 (2.3)
292-0111										
EVG/COBI/FTC/TAF	431	4.55 (4.12; 4.94)	339 (78.7)	92 (21.3)	402 (283; 531)	169 (39.2) <sup>b</sup>	261 (60.6) <sup>b</sup>	378 (88.1)	30 (7.0)	21 (4.9)
EVG/COBI/FTC/TDF	435	4.54 (4.11; 4.96)	336 (77.2)	99 (22.8)	407 (288; 555)	153 (35.2) <sup>b</sup>	282 (64.8) <sup>b</sup>	396 (91.7)	20 (4.6)	16 (3.7)

(continued)

Table 9: Characteristics of the study populations (severity of disease at the start of the study) – RCT, indirect comparison: treatment-naïve adults, EVG/COBI/FTC/TAF vs. EFV/FTC/TDF (continued)

Study Group	N <sup>a</sup>	Viral load (log10 copies/ mL) median (Q1; Q3)	Baseline viral load HIV-1 RNA copies/mL n (%)		CD4 cell count/μL median (Q1; Q3)	CD4 cell count n (%)		HIV disease stage n (%)		
			≤ 100 000	> 100 000		< 350	≥ 350	Asymp- tomatic	Symp- tomatic	AIDS
Studies with ACT										
236-0102										
EFV/FTC/TDF	352	4.78 (4.37; 5.15)	236 (67.0)	116 (33.0)	383 (268; 479)	147 (41.8) <sup>b</sup>	205 (58.2) <sup>b</sup>	295 (83.8)	33 (9.4)	24 (6.8)
EVG/COBI/FTC/TDF	348	4.75 (4.32; 5.15)	230 (66.1)	118 (33.9)	376 (276; 487)	155 (44.5) <sup>b</sup>	193 (55.5) <sup>b</sup>	290 (83.3)	30 (8.6)	28 (8.0)
236-0104										
EFV/FTC/TDF	23	4.56 (4.19; 4.96)	18 (78.3)	5 (21.7)	436 (333; 543)	8 (34.8)	15 (65.2) <sup>b</sup>	22 (95.7)	0 (0)	1 (4.3)
EVG/COBI/FTC/TDF	48	4.58 (4.12; 4.96)	37 (77.1)	11 (22.9)	354 (265; 466)	24 (50.0) <sup>b</sup>	24 (50.0) <sup>b</sup>	40 (83.3)	5 (10.4)	3 (6.3)
a: Number of patients in the safety population, which includes all patients who were randomized and received at least one dose of the study treatment.										
b: Institute’s calculation.										
ACT: appropriate comparator therapy; AIDS: acquired immunodeficiency syndrome; CD4: cluster of differentiation 4; COBI: cobicistat; EFV: efavirenz; EVG: elvitegravir; FTC: emtricitabine; HIV-1: human immunodeficiency virus type 1; n: number of patients with event; N: number of patients included; Q: quartile; RCT: randomized controlled trial; RNA: ribonucleic acid; SD: standard deviation; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; vs.: versus										

**Studies with the intervention or with the appropriate comparator therapy**

Regarding their demographic characteristics, the patients in all 5 studies were largely comparable both between the treatment arms and between the studies. The mean age of the patients was between 35 and 38 years. Corresponding to the higher prevalence of HIV-1 infection in men [10], notably more men (83.7% to 98.3%) than women (1.7% to 16.3%) were included in all studies. The majority of the patients included in the studies were of Caucasian origin (54.5% to 78.3%). Regarding renal function, the patients in the studies included were comparable (median estimated glomerular filtration rate [eGFR] was between 112.8 mL/min and 121.2 mL/min) so that the different inclusion criterion regarding the eGFR (see Table 6) between the studies had no decisive influence on the study populations included.

Regarding the characteristics to estimate the severity of the disease, no important differences were detected in 4 of the 5 studies included in the indirect comparison – neither between the treatment arms nor between the studies (studies 292-0102, 292-0104, 292-0111 and 236-0104). The median viral load (log<sub>10</sub> copies/mL) in these studies was between 4.54 and 4.62. Hence the slightly different inclusion criterion in the studies regarding baseline viral load (see Table 6) did not lead to major deviations in baseline viral load between the patients included in the studies. Compared with the other studies, patients with slightly more severe disease (regarding the characteristics baseline viral load, CD4 cell count and HIV disease stage) were included in study 236-0102. The median and mean values of viral load, CD4 cell count and disease stage in study 236-0102 were considered sufficiently comparable with the other studies, however.

**Similarity of the studies on EVG/COBI/FTC/TAF and EFV/FTC/TDF in the adjusted indirect comparison**

The available data on the study and intervention characteristics of the 5 studies showed that the studies were sufficiently similar regarding design and common comparator. There were partly differences in geographical regions where the studies were conducted. This did not raise doubts about the suitability of the studies for an adjusted indirect comparison, however. There were also no decisive differences in the relevant patient characteristics. Overall, the studies 292-0102, 292-0104, 292-0111, 236-0102 and 236-0104 were considered to be sufficiently similar so that the assumption of similarity for an adjusted indirect comparison was not rejected.

Table 10 shows the risk of bias at study level.

Table 10: Risk of bias at study level – RCT, indirect comparison: treatment-naïve adults, EVG/COBI/FTC/TAF 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			
Studies with intervention							
292-0102	Yes	Yes	Yes	Yes	Yes	Yes	Low
292-0104	Yes	Yes	Yes	Yes	Yes	Yes	Low
292-0111	Yes	Yes	Yes	Yes	Yes	Yes	Low
Studies with ACT							
236-0102	Yes	Yes	Yes	Yes	Yes	Yes	Low
236-0104	Yes	Yes	Yes	Yes	Yes	Yes	Low
ACT: appropriate comparator therapy; COBI: cobicistat; EFV: efavirenz; EVG: elvitegravir; FTC: emtricitabine; RCT: randomized controlled trial; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; vs.: versus							

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

## 2.3.2 Results on added benefit

### 2.3.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.8.2.4.3 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity
  - AIDS-defining events (CDC class C events)
  - presented as additional information: virologic response and CD4 cell count as surrogate outcomes for the patient-relevant outcome “AIDS-defining illnesses/death”
  - health status measured with the EQ-5D VAS
- Health-related quality of life

- Side effects
  - SAEs
  - discontinuation due to AEs
  - severe AEs (grade 3-4)
  - 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) and presented the outcome “AIDS-defining events (CDC class C events)” only as additional information (see Section 2.8.2.4.3 of the full dossier assessment).

Table 11 shows for which outcomes data were available in the studies included.

Table 11: Matrix of outcomes – RCT, indirect comparison: treatment-naïve adults, EVG/COBI/FTC/TAF vs. EFV/FTC/TDF

Study	Outcomes									
	All-cause mortality	AIDS-defining events (CDC class C events)	Virologic response (snapshot) <sup>a</sup>	CD4 cell count <sup>a</sup>	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Discontinuation due to AEs	Severe AEs (grade 3-4) <sup>b</sup>	Further specific AEs <sup>c</sup>
<b>Studies with intervention</b>										
292-0102 <sup>d</sup>	Yes	Yes	Yes	Yes	- <sup>e</sup>	- <sup>e</sup>	Yes	Yes	Yes	Yes
292-0104 <sup>f</sup>	Yes	Yes	Yes	Yes	Yes	- <sup>e</sup>	Yes	Yes	Yes	Yes
292-0111 <sup>f</sup>	Yes	Yes	Yes	Yes	Yes	- <sup>e</sup>	Yes	Yes	Yes	Yes
<b>Studies with ACT</b>										
236-0102 <sup>f</sup>	Yes	Yes	Yes	Yes	- <sup>e</sup>	- <sup>e</sup>	Yes	Yes	Yes	Yes
236-0104 <sup>d</sup>	Yes	Yes	Yes	Yes	- <sup>e</sup>	- <sup>e</sup>	Yes	Yes	Yes	Yes
<p>a: Virologic response and CD4 cell count as surrogate outcomes for the patient-relevant outcome “AIDS-defining illnesses/death” are presented as additional information.</p> <p>b: Classification based on the “Gilead Sciences Grading Scale for Severity of Adverse Events and Laboratory Abnormalities”.</p> <p>c: The following events (MedDRA coding) are considered: nervous system disorders (SOC), psychiatric disorders (SOC), skin and subcutaneous tissue disorders (SOC), gastrointestinal disorders (SOC), renal and urinary disorders (SOC), and infections and infestations (SOC at SAE level).</p> <p>d: The information on data availability refers to the analysis date of 48 weeks.</p> <p>e: The outcome was not recorded in the study.</p> <p>f: The information on data availability refers to the analysis dates of 48 and 96 weeks.</p> <p>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; EFV: efavirenz; EQ-5D: European Quality of Life-5 Dimensions; EVG: elvitegravir; FTC: emtricitabine; MedDRA: Medical Dictionary for Regulatory Activities; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; VAS: visual analogue scale; vs.: versus</p>										

None of the studies recorded data on health-related quality of life. Health status could not be included in the indirect comparison because the outcome was not recorded on the side of the ACT.

The risk of bias at outcome level was not assessed in the present benefit assessment (see Section 2.8.2.5.2 of the full dossier assessment).

### 2.3.2.2 Results

The results on the comparison of EVG/COBI/FTC/TAF with EFV/FTC/TDF in treatment-naïve adults with HIV-1 infection are summarized in Table 12 and Table 13. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations.

The results at the later analysis date of 96 weeks were primarily used in the benefit assessment (for reasons, see Section 2.8.2.5.3 of the full dossier assessment). As a result, the results of 2 of the 5 relevant studies (292-0102 and 236-0104; 242 patients of 2693 patients in total), for which only 48-week data were available, were not used for the adjusted indirect comparison. Hence 2 studies on the side of EVG/COBI/FTC/TAF and one study on the side of EFV/FTC/TDF were available for the adjusted indirect comparison. This approach deviated from that of the company, which conducted the adjusted indirect comparison both on the basis of the data at 48 weeks (with 5 studies) and of the data at 96 weeks (with 3 studies).

In the presence of important heterogeneity of the study results on the EVG/COBI/FTC/TAF side, the studies were not pooled.

The Peto odds ratio (POR) offers a good approximation of the relative risk in certain situations (see Section 2.8.2.2 of the full dossier assessment). In these situations the POR was calculated as estimator for the relative risk and used for the assessment.

Forest plots showing the data availability are only presented if the choice of outcomes or the operationalization deviates from those of the company (see Appendix A and Appendix B of the full dossier assessment).



Table 12: Results (mortality and morbidity) – RCT, indirect comparison: treatment-naïve, EVG/COBI/FTC/TAF vs. EFV/FTC/TDF (96 weeks)

Outcome category	EVG/COBI/FTC/TAF or EFV/FTC/TDF		EVG/COBI/FTC/TDF		Group difference
Outcome	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Comparison Study					
<b>Mortality</b>					
<b>All-cause mortality</b>					
EVG/COBI/FTC/TAF vs. EVG/COBI/FTC/TDF					
292-0104	435	1 (0.2)	432	1 (0.2)	POR: 0.99 [0.06; 15.90]; 0.996
292-0111	431	1 (0.2)	435	2 (0.5)	POR: 0.52 [0.05; 4.99]; 0.569
Total					POR: 0.67 [0.12; 3.88]; 0.657
EFV/FTC/TDF vs. EVG/COBI/FTC/TDF					
236-0102	352	2 (0.6)	348	1 (0.3)	POR: 1.93 [0.20; 18.61]; 0.570
<b>Adjusted indirect comparison<sup>a</sup>:</b>					
<b>EVG/COBI/FTC/TAF vs. EFV/FTC/TDF</b>					POR: 0.35 [0.02; 6.12]; 0.471
<b>Morbidity</b>					
<b>AIDS-defining events (CDC class C)</b>					
EVG/COBI/FTC/TAF vs. EVG/COBI/FTC/TDF					
292-0104	435	8 (1.8)	432	3 (0.7)	2.65 [0.71; 9.92] <sup>b</sup> ; ND
292-0111	431	8 (1.9)	435	8 (1.8)	1.01 [0.38; 2.66] <sup>b</sup> ; ND
Total					1.47 [0.58; 3.70]; 0.415 <sup>c</sup>
EFV/FTC/TDF vs. EVG/COBI/FTC/TDF					
236-0102	352	1 (0.3)	348	8 (2.3)	0.12 [0.02; 0.98]; ND
<b>Adjusted indirect comparison<sup>d</sup>:</b>					
<b>EVG/COBI/FTC/TAF vs. EFV/FTC/TDF</b>					11.88 [1.23; 114.99]; 0.033

(continued)

Table 12: Results (mortality and morbidity) – RCT, indirect comparison: treatment-naïve, EVG/COBI/FTC/TAF vs. EFV/FTC/TDF (96 weeks) (continued)

Outcome category	EVG/COBI/FTC/TAF or EFV/FTC/TDF		EVG/COBI/FTC/TDF		Group difference
Outcome					
Comparison	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Study					
<b>Additional information: surrogate outcome “virologic response” snapshot (HIV-1 RNA &lt; 50 copies/mL)</b>					
<b>Snapshot<sup>e</sup></b>					
EVG/COBI/FTC/TAF vs. EVG/COBI/FTC/TDF					
292-0104	435	388 (89.2)	432	381 (88.2)	1.01 [0.96; 1.06]; 0.642
292-0111	431	362 (84.0)	435	358 (82.3)	1.02 [0.96; 1.08]; 0.506
Total					1.01 [0.98; 1.05]; 0.437
EFV/FTC/TDF vs. EVG/COBI/FTC/TDF					
236-0102	352	287 (81.5)	348	293 (84.2)	0.97 [0.91; 1.04]; 0.350
<b>Adjusted indirect comparison<sup>a</sup>:</b>					
<b>EVG/COBI/FTC/TAF vs. EFV/FTC/TDF</b>					1.05 [0.97; 1.13]; 0.233
<b>Sensitivity analysis: missing = failure<sup>f</sup></b>					
EVG/COBI/FTC/TAF vs. EVG/COBI/FTC/TDF					
292-0104	435	390 (89.7)	432	387 (89.6)	1.00 [0.96; 1.05] <sup>b</sup> ; ND
292-0111	431	368 (85.4)	435	372 (85.5)	1.00 [0.95; 1.04] <sup>b</sup> ; ND
Total					1.00 [0.97; 1.04]; 0.993 <sup>c</sup>
EFV/FTC/TDF vs. EVG/COBI/FTC/TDF					
236-0102	352	293 (83.2)	348	300 (86.2)	0.97 [0.91; 1.03] <sup>b</sup> ; ND
<b>Adjusted indirect comparison<sup>d</sup>:</b>					
<b>EVG/COBI/FTC/TAF vs. EFV/FTC/TDF</b>					1.04 [0.96; 1.11]; 0.342
<b>Sensitivity analysis: missing = excluded<sup>f</sup></b>					
EVG/COBI/FTC/TAF vs. EVG/COBI/FTC/TDF					
292-0104	398	390 (98.0)	392	387 (98.7)	0.99 [0.97; 1.01] <sup>b</sup> ; ND
292-0111	378	368 (97.4)	384	372 (96.9)	1.00 [0.98; 1.03] <sup>b</sup> ; ND
Total					1.00 [0.98; 1.01]; 0.675 <sup>c</sup>
EFV/FTC/TDF vs. EVG/COBI/FTC/TDF					
236-0102	301	293 (97.3)	307	300 (97.7)	1.00 [0.97; 1.02] <sup>b</sup> ; ND
<b>Adjusted indirect comparison<sup>d</sup>:</b>					
<b>EVG/COBI/FTC/TAF vs. EFV/FTC/TDF</b>					1.00 [0.97; 1.03]; 0.959

(continued)

Table 12: Results (mortality and morbidity) – RCT, indirect comparison: treatment-naïve, EVG/COBI/FTC/TAF vs. EFV/FTC/TDF (96 weeks) (continued)

Outcome category Outcome	EVG/COBI/FTC/TAF or EFV/FTC/TDF			EVG/COBI/FTC/TDF			Group difference
Comparison Study	N <sup>g</sup>	Baseline values mean (SD)	Change at end of study mean <sup>h</sup> (SD)	N <sup>g</sup>	Baseline values mean (SD)	Change at end of study mean <sup>h</sup> (SD)	MD [95% CI]; p-value
<b>Additional information: surrogate outcome “CD4 cell count/μL”</b>							
EVG/COBI/FTC/TAF vs. EVG/COBI/FTC/TDF							
292-0104	432	437 (223.7)	276 (202.7)	431	426 (212.3)	266 (208.8)	10.00 [–17.46; 37.46]; 0.475
292-0111	427	414 (206.8)	271 (187.0)	432	431 (226.8)	250 (183.7)	21.00 [–3.79; 45.79] 0.097
Total							16.06 [–2.34; 34.46]; 0.087
EFV/FTC/TDF vs. EVG/COBI/FTC/TDF							
236-0102	352	382 (170.2)	247 (188.3)	348	391 (188.6)	278 (212.4)	–31.00 [–60.75; –1.25]; 0.041
<b>Adjusted indirect comparison<sup>a</sup>:</b>							
<b>EVG/COBI/FTC/TAF vs. EFV/FTC/TDF</b>							47.06 [12.08; 82.04]; 0.008
<p>a: Adjusted indirect comparison according to Bucher [11].</p> <p>b: Institute’s calculation.</p> <p>c: Institute’s calculation, meta-analysis.</p> <p>d: Institute’s calculation, adjusted indirect comparison according to Bucher [11].</p> <p>e: Calculated with FDA snapshot algorithm, primary analysis of the company. Time window for the analysis: day 631 to 714 (study 236-0102) and day 630 to 713 (studies 292-0104 and 292-0111); if results from several samples are available within the time window, the last measurement is relevant [12].</p> <p>f: Time window for the analysis: week 96 ± 6 weeks (studies 292-0104 and 292-0111) and week 96 ± 6 days (study 236-0102). Based on other approval processes in the therapeutic indication [13], it is assumed that in the algorithms M = E and M = F, in contrast to the snapshot algorithm, the value that is closer to week 96 is relevant if several measurements are available within the analysis time window. There is no detailed description of the algorithms in the study documents.</p> <p>g: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.</p> <p>h: LOCF analysis.</p> <p>AIDS: acquired immunodeficiency syndrome; CDC: Centers for Disease Control and Prevention;  CI: confidence interval; COBI: cobicistat; EFV: efavirenz; EVG: elvitegravir; FDA: Food and Drug Administration; FTC: emtricitabine; HIV-1: human immunodeficiency virus type 1; ITT: intention to treat;  LOCF: last observation carried forward; M = E: missing = excluded; M = F: missing = failure; MD: mean difference; ND: no data; n: number of patients with (at least one) event; N: number of analysed patients;  POR: Peto odds ratio; RCT: randomized controlled trial; RNA: ribonucleic acid; RR: relative risk; SD: standard deviation; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; vs.: versus</p>							

Table 13: Results (side effects) – RCT, indirect comparison: treatment-naïve adults, EVG/COBI/FTC/TAF vs. EFV/FTC/TDF (96 weeks)

Outcome category	EVG/COBI/FTC/TAF or EFV/FTC/TDF		EVG/COBI/FTC/TDF		Group difference				
Outcome	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value				
Comparison									
Study									
<b>Side effects</b>									
<b>AEs (supplementary information)</b>									
EVG/COBI/FTC/TAF vs. EVG/COBI/FTC/TDF									
292-0104	435	410 (94.3)	432	410 (94.9)	–				
292-0111	431	397 (92.1)	435	413 (94.9)	–				
EFV/FTC/TDF vs. EVG/COBI/FTC/TDF									
236-0102	352	342 (97.2)	348	337 (96.8)	–				
<b>SAEs</b>									
EVG/COBI/FTC/TAF vs. EVG/COBI/FTC/TDF									
292-0104	435	54 (12.4)	432	47 (10.9)	1.14 [0.79; 1.65]; 0.482				
292-0111	431	43 (10.0)	435	40 (9.2)	1.08 [0.72; 1.63]; 0.696				
Total					1.12 [0.85; 1.47]; 0.433				
EFV/FTC/TDF vs. EVG/COBI/FTC/TDF									
236-0102	352	33 (9.4)	348	56 (16.1)	0.58 [0.39; 0.87]; 0.009				
<b>Adjusted indirect comparison<sup>a</sup>:</b>									
<b>EVG/COBI/FTC/TAF vs. EFV/FTC/TDF</b>					1.91 [1.18; 3.12]; 0.009				
<b>Severe AEs (grade 3-4)<sup>b</sup></b>									
EVG/COBI/FTC/TAF vs. EVG/COBI/FTC/TDF									
292-0104	435	55 (12.6)	432	41 (9.5)	1.33 [0.91; 1.95]; 0.141				
292-0111	431	51 (11.8)	435	60 (13.8)	0.86 [0.61; 1.22]; 0.389				
Total									
		Heterogeneity:		Q = ND; df = ND; p = 0.095; I <sup>2</sup> = 64.1%					
EFV/FTC/TDF vs. EVG/COBI/FTC/TDF									
236-0102	352	51 (14.5)	348	61 (17.5)	0.83 [0.59; 1.16]; 0.274				
<b>Adjusted indirect comparison<sup>a</sup>:</b>									
<b>EVG/COBI/FTC/TAF vs. EFV/FTC/TDF</b>					– <sup>c</sup>				
<b>Discontinuation due to AEs</b>									
EVG/COBI/FTC/TAF vs. EVG/COBI/FTC/TDF									
292-0104	435	5 (1.1)	432	11 (2.5)	0.45 [0.16; 1.29]; 0.137				
292-0111	431	5 (1.2)	435	9 (2.1)	0.56 [0.19; 1.66]; 0.296				
Total					0.50 [0.24; 1.07]; 0.073				
EFV/FTC/TDF vs. EVG/COBI/FTC/TDF									
236-0102	352	24 (6.8)	348	17 (4.9)	1.40 [0.76; 2.55]; 0.279				
<b>Adjusted indirect comparison<sup>a</sup>:</b>									
<b>EVG/COBI/FTC/TAF vs. EFV/FTC/TDF</b>					0.36 [0.14; 0.94]; 0.038				

(continued)

Table 13: Results (side effects) – RCT, indirect comparison: treatment-naïve adults, EVG/COBI/FTC/TAF vs. EFV/FTC/TDF (96 weeks) (continued)

Outcome category	EVG/COBI/FTC/TAF or EFV/FTC/TDF		EVG/COBI/FTC/TDF		Group difference				
Outcome	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value				
Comparison									
Study									
<b>Nervous system disorders</b>									
EVG/COBI/FTC/TAF vs. EVG/COBI/FTC/TDF									
292-0104	435	111 (25.5)	432	108 (25.0)	1.02 [0.81; 1.28]; 0.861				
292-0111	431	140 (32.5)	435	136 (31.3)	1.04 [0.86; 1.26]; 0.701				
Total					1.03 [0.89; 1.20]; 0.684				
EFV/FTC/TDF vs. EVG/COBI/FTC/TDF									
236-0102	352	159 (45.2)	348	112 (32.2)	1.40 [1.16; 1.70]; < 0.001				
<b>Adjusted indirect comparison<sup>a</sup>:</b>									
<b>EVG/COBI/FTC/TAF vs. EFV/FTC/TDF</b>									
					0.73 [0.58; 0.94]; 0.013				
<b>Psychiatric disorders</b>									
EVG/COBI/FTC/TAF vs. EVG/COBI/FTC/TDF									
292-0104	435	103 (23.7)	432	116 (26.9)	0.88 [0.70; 1.11]; 0.283				
292-0111	431	117 (27.1)	435	121 (27.8)	0.98 [0.79; 1.21]; 0.825				
Total					0.93 [0.79; 1.09]; 0.370				
EFV/FTC/TDF vs. EVG/COBI/FTC/TDF									
236-0102	352	179 (50.9)	348	138 (39.7)	1.28 [1.09; 1.51]; 0.003				
<b>Adjusted indirect comparison<sup>a</sup>:</b>									
<b>EVG/COBI/FTC/TAF vs. EFV/FTC/TDF</b>									
					0.73 [0.58; 0.91]; 0.006				
<b>Skin and subcutaneous tissue disorders</b>									
EVG/COBI/FTC/TAF vs. EVG/COBI/FTC/TDF									
292-0104	435	130 (29.9)	432	117 (27.1)	1.10 [0.89; 1.36]; 0.361				
292-0111	431	132 (30.6)	435	141 (32.4)	0.94 [0.78; 1.15]; 0.572				
Total					1.02 [0.87; 1.18]; 0.839				
EFV/FTC/TDF vs. EVG/COBI/FTC/TDF									
236-0102	352	147 (41.8)	348	111 (31.9)	1.31 [1.08; 1.59]; 0.007				
<b>Adjusted indirect comparison<sup>a</sup>:</b>									
<b>EVG/COBI/FTC/TAF vs. EFV/FTC/TDF</b>									
					0.78 [0.61; 0.99]; 0.046				

(continued)

Table 13: Results (side effects) – RCT, indirect comparison: treatment-naïve adults, EVG/COBI/FTC/TAF vs. EFV/FTC/TDF (96 weeks) (continued)

Outcome category	EVG/COBI/FTC/TAF or EFV/FTC/TDF		EVG/COBI/FTC/TDF		Group difference
Outcome					
Comparison	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Study					
<b>Gastrointestinal disorders</b>					
EVG/COBI/FTC/TAF vs. EVG/COBI/FTC/TDF					
292-0104	435	225 (51.7)	432	235 (54.4)	0.95 [0.84; 1.08]; 0.430
292-0111	431	238 (55.2)	435	238 (54.7)	1.01 [0.89; 1.14]; 0.881
Total					0.98 [0.90; 1.07]; 0.661
EFV/FTC/TDF vs. EVG/COBI/FTC/TDF					
236-0102	352	188 (53.4)	348	211 (60.6)	0.88 [0.77; 1.00]; 0.054
<b>Adjusted indirect comparison<sup>a</sup>:</b>					
<b>EVG/COBI/FTC/TAF vs. EFV/FTC/TDF</b>					1.11 [0.95; 1.30]; 0.176
<b>Renal and urinary disorders</b>					
EVG/COBI/FTC/TAF vs. EVG/COBI/FTC/TDF					
292-0104	435	30 (6.9)	432	36 (8.3)	0.83 [0.52; 1.32]; 0.426
292-0111	431	35 (8.1)	435	58 (13.3)	0.61 [0.41; 0.91]; 0.015
Total					0.69 [0.51; 0.94]; 0.018
EFV/FTC/TDF vs. EVG/COBI/FTC/TDF					
236-0102	352	34 (9.7)	348	42 (12.1)	0.80 [0.52; 1.23]; 0.307
<b>Adjusted indirect comparison<sup>a</sup>:</b>					
<b>EVG/COBI/FTC/TAF vs. EFV/FTC/TDF</b>					0.87 [0.51; 1.46]; 0.590
<b>Infections and infestations</b>					
EVG/COBI/FTC/TAF vs. EVG/COBI/FTC/TDF					
292-0104	435	25 (5.7)	432	17 (3.9)	1.46 [0.80; 2.67]
292-0111	431	18 (4.2)	435	12 (2.8)	1.51 [0.74; 3.10]
Total					1.48 [0.93; 2.35]; 0.094
EFV/FTC/TDF vs. EVG/COBI/FTC/TDF					
236-0102	352	10 (2.8)	348	26 (7.5)	0.38 [0.19; 0.78]
<b>Adjusted indirect comparison<sup>d</sup>:</b>					
<b>EVG/COBI/FTC/TAF vs. EFV/FTC/TDF</b>					3.90 [1.67; 9.12]; 0.002

(continued)

Table 13: Results (side effects) – RCT, indirect comparison: treatment-naïve adults, EVG/COBI/FTC/TAF vs. EFV/FTC/TDF (96 weeks) (continued)

a: Adjusted indirect comparison according to Bucher [11].
b: Classification based on the “Gilead Sciences Grading Scale for Severity of Adverse Events and Laboratory Abnormalities”.
c: Result of the adjusted indirect comparison not meaningfully interpretable due to heterogeneity in the comparison of EVG/COBI/FTC/TAF vs. EVG/COBI/FTC/TDF. The adjusted indirect comparisons that only considered one of the studies 292-0104 and 292-0111 produced no statistically significant results.
d: Institute’s calculation, adjusted indirect comparison according to Bucher [11].
AE: adverse event; CI: confidence interval; COBI: cobicistat; EFV: efavirenz; EVG: elvitegravir; FTC: emtricitabine; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; vs.: versus

The results of the indirect comparison per se had a low certainty of results. Only results from adjusted indirect comparisons of particularly high methodological quality that are based to an important degree on studies with a low risk of bias can be considered as having a moderate certainty of results. Based on the available data it was not possible to assess consistency, which is required for an upgrading, so that at most hints, e.g. of an added benefit, were derived. This deviates from the company’s assessment, which derived proof of an added benefit based on the adjusted indirect comparison presented.

## Mortality

### *All-cause mortality*

The adjusted indirect comparison showed no statistically significant difference between EVG/COBI/FTC/TAF and EFV/FTC/TDF for the outcome “all-cause mortality”. This resulted in no hint of an added benefit of EVG/COBI/FTC/TAF in comparison with EFV/FTC/TDF; an added benefit for the outcome “all-cause mortality” is therefore not proven.

This concurs with the company’s assessment.

## Morbidity

### *AIDS-defining events (CDC class C events); supplementary consideration of the surrogate outcomes “virologic response” and “CD4 cell count”*

The adjusted indirect comparison showed a statistically significant difference to the disadvantage of EVG/COBI/FTC/TAF for the outcome “AIDS-defining events”.

The adjusted indirect comparison showed no statistically significant difference between EVG/COBI/FTC/TAF and EFV/FTC/TDF for virologic response (snapshot algorithm). It is possible, however, that the result on virologic response was influenced by the algorithm used for the analysis of virologic response (see Section 2.8.2.2 of the full dossier assessment). For this reason, results of the sensitivity analyses were additionally considered using other

algorithms (missing = failure and missing = excluded). These also showed no statistically significant differences between the treatment options in the adjusted indirect comparison.

The adjusted indirect comparison showed a statistically significant difference in favour of EVG/COBI/FTC/TAF for the outcome “CD4 cell count”. The clinical relevance of this improvement was unclear, however.

In the overall consideration of the results, a hint of lesser benefit of EVG/COBI/FTC/TAF compared with the ACT was derived for the outcome “AIDS-defining events (CDC class C events)” because the effect in the outcome of interest “AIDS-defining events (CDC class C events)” was decisive.

This assessment deviates from that of the company in several aspects. The company considered the outcomes “virologic response” and “CD4 cell count” separately. Based on the data at 48 weeks (snapshot algorithm), the company derived an added benefit for the outcome “virologic response”. Since the statistically significant difference in this outcome no longer existed at week 96, however, the company assumed a hint of an added benefit.

The company conducted no sensitivity analyses, which are required for this outcome for the reasons stated above. A statistically significant difference in favour of EVG/COBI/FTC/TAF for virologic response based on the snapshot algorithm was presented after 48 weeks. The results of the sensitivity analyses on virologic response (missing = failure and missing = excluded) additionally used showed no statistically significant difference between the treatment options in the adjusted indirect comparison after 48 weeks, however (see Appendix A of the full dossier assessment). Hence the result on virologic response after 48 weeks is not robust.

Based on the total population, the company derived no hint of an added benefit for the outcome “CD4 cell count”.

The company presented the outcome “AIDS-defining events (CDC class C events)” only as additional information because, from the company’s point of view, the outcome is no informative parameter for the assessment of the efficacy and the treatment (see Section 2.8.2.4.3 of the full dossier assessment). Furthermore, the company discussed the results for the outcome “AIDS-defining events” on the basis of an operationalization that deviated from the CDC classification, which was not followed, however (see Section 2.8.2.4.3 of the full dossier assessment). In contrast to the present benefit assessment, the results of the company’s analysis showed no statistically significant difference between the treatment options.

### ***Health status***

For the studies with the ACT, no data were available for conducting an adjusted indirect comparison for the outcome “health status”.



**Health-related quality of life**

None of the studies included recorded health-related quality of life.

**Side effects*****SAEs***

The adjusted indirect comparison showed a statistically significant difference to the disadvantage of EVG/COBI/FTC/TAF for the outcome “SAEs”.

In addition, there was an indication of an effect modification by the characteristic “ethnicity” for this outcome (see Section 2.3.2.3). There was a hint of greater harm from EVG/COBI/FTC/TAF in comparison with EFV/FTC/TDF for Caucasians. For non-Caucasians, there was no hint of greater or lesser harm of EVG/COBI/FTC/TAF in comparison with EFV/FTC/TDF; greater or lesser harm for this patient group is therefore not proven.

This deviates from the company’s assessment, which derived no greater harm for this outcome. The company also described a statistically significant difference to the disadvantage of EVG/COBI/FTC/TAF, but saw no causal relationship of the occurred SAEs with EVG/COBI/FTC/TAF and assumed that this finding occurred due to statistical chance.

***Severe adverse events (grade 3-4)***

The meta-analysis of the studies with the intervention showed unexplained heterogeneity without effects in the same direction for the outcome “severe AEs grade 3-4”. Hence no common estimate was calculated. Consequently, an indirect comparison based on the overall study pool could not be meaningfully calculated and interpreted. The adjusted indirect comparisons that only considered one of the studies 292-0104 and 292-0111 showed no statistically significant results. Based on the data, there was no hint of greater or lesser harm of EVG/COBI/FTC/TAF in comparison with EFV/FTC/TDF; greater or lesser harm is therefore not proven.

This concurs with the company’s assessment.

***Discontinuation due to adverse events***

The adjusted indirect comparison showed a statistically significant difference in favour of EVG/COBI/FTC/TAF for the outcome “discontinuation due to AEs”. The extent of the effect in this outcome of the category non-serious/non-severe side effects was no more than marginal, however; greater or lesser harm for the outcome “discontinuation due to AEs” is therefore not proven.

The company also saw a statistically significant effect in favour of EVG/COBI/FTC/TAF. Based on an effect modification by the characteristic “CD4 cell count at the start of the study” and under consideration of the results at week 48, it derived proof of an added benefit only for patients with a CD4 cell count of > 350 cells/ $\mu$ L. The company claimed a hint of an added

benefit in patients with a CD4 cell count of  $\leq 350$  cells/ $\mu$ L. No relevant effects in the subgroups by CD4 cell count at the start of the study could be derived from the subgroup analyses at week 96.

### ***Nervous system disorders***

The adjusted indirect comparison showed a statistically significant difference in favour of EVG/COBI/FTC/TAF for the outcome “nervous system disorders”. The extent of the effect in this outcome of the category non-serious/non-severe side effects was no more than marginal, however; greater or lesser harm for the outcome “nervous system disorders” is therefore not proven.

This deviates from the company’s assessment, which derived proof of an added benefit of EVG/COBI/FTC/TAF.

### ***Psychiatric disorders***

The adjusted indirect comparison showed a statistically significant difference in favour of EVG/COBI/FTC/TAF for the outcome “psychiatric disorders”.

In addition, there was an indication of an effect modification by the characteristic “age” for this outcome (see Section 2.3.2.3). There was a hint of lesser harm from EVG/COBI/FTC/TAF in comparison with EFV/FTC/TDF for patients  $\geq 40$  years of age. For patients  $< 40$  years of age, there was no hint of greater or lesser harm of EVG/COBI/FTC/TAF in comparison with EFV/FTC/TDF; greater or lesser harm for this patient group is therefore not proven.

This deviates from the company’s assessment, which derived proof of an added benefit for the total population. The company described the effect modification by the characteristic “age”. However, it did not consider it in the derivation of the added benefit because it considered the effect modification to be negligible against the background of the difference in favour of EVG/COBI/FTC/TAF in the total population, which was clearly significant from the company’s point of view.

### ***Skin and subcutaneous tissue disorders***

The adjusted indirect comparison showed a statistically significant difference in favour of EVG/COBI/FTC/TAF for the outcome “skin and subcutaneous tissue disorders”. The extent of the effect in this outcome of the category non-serious/non-severe side effects was no more than marginal, however; greater or lesser harm for the outcome “skin and subcutaneous tissue disorders” is therefore not proven.

This deviates from the company’s assessment, which derived an indication of a minor added benefit.

***Gastrointestinal disorders***

The adjusted indirect comparison showed no statistically significant difference between EVG/COBI/FTC/TAF and EFV/FTC/TDF for the outcome “gastrointestinal disorders”. This resulted in no hint of greater or lesser harm of EVG/COBI/FTC/TAF in comparison with EFV/FTC/TDF; greater or lesser harm for the outcome “gastrointestinal disorders” is therefore not proven.

This deviates from the company’s assessment, which, based on an effect modification by the characteristic “CD4 cell count at the start of the study”, derived proof of greater harm for patients with a CD4 cell count of  $\leq 350$  cells/ $\mu$ L. The results in the subgroup by CD4 cell count were not interpreted separately in the present benefit assessment, however, because the effect in the respective subgroups was not statistically significant or no more than marginal and therefore not relevant (see Section 2.3.2.3).

***Renal and urinary disorders***

The adjusted indirect comparison showed no statistically significant difference between EVG/COBI/FTC/TAF and EFV/FTC/TDF for the outcome “renal and urinary disorders”. This resulted in no hint of greater or lesser harm of EVG/COBI/FTC/TAF in comparison with EFV/FTC/TDF; greater or lesser harm for the outcome “renal and urinary disorders” is therefore not proven.

This concurs with the company’s assessment.

***Infections and infestations***

The adjusted indirect comparison showed a statistically significant difference to the disadvantage of EVG/COBI/FTC/TAF for the outcome “infections and infestations”. This resulted in a hint of greater harm from EVG/COBI/FTC/TAF in comparison with EFV/FTC/TDF.

The company did not include this outcome in the assessment and derived no conclusions on the added benefit or harm on its basis.

**2.3.2.3 Subgroups and other effect modifiers**

In order to uncover possible differences between patient groups, the following subgroup characteristics were investigated:

- age ( $< 40/\geq 40$ )
- sex (men/women)
- ethnicity (Caucasian/non-Caucasian)
- baseline viral load ( $\leq 100\,000/> 100\,000$  HIV-1 RNA copies/mL)
- CD4 cell count at the start of the study ( $\leq 350/> 350$  cells/ $\mu$ L)

The company presented subgroup analyses for most outcomes included. The company conducted no subgroup analyses on the outcome “all-cause mortality” because it did not regard the consideration of subgroups to be meaningful because of the low number of events in the studies included. The company also conducted no subgroup analyses for the outcome “AIDS-defining events” because it considered this outcome in its assessment only as additional information.

Only the results on subgroups and outcomes with at least an indication of an interaction between treatment effect and subgroup characteristic and with statistically significant results and relevant effects in at least one subgroup are presented in this assessment.

The prerequisite for proof of different subgroup effects is a statistically significant interaction test ( $p < 0.05$ ). A p-value of  $\geq 0.05$  and  $< 0.2$  provides an indication of an effect modification.

The subgroup results on the indirect comparison of EVG/COBI/FTC/TAF with EFV/FTC/TDF in treatment-naïve adults with HIV-1 infection are summarized in Table 14 to Table 16. Where necessary, the data from the dossier were supplemented by the Institute’s calculations.

Table 14: Subgroups (surrogate outcome CD4 cell count) – RCT, indirect comparison: treatment-naïve adults, EVG/COBI/FTC/TAF vs. EFV/FTC/TDF (96 weeks)

Outcome Characteristic	EVG/COBI/FTC/TAF or EFV/FTC/TDF			EVG/COBI/FTC/TDF			Group difference
Study Subgroup	N <sup>a</sup>	Baseline values mean (SD)	Change at end of study mean <sup>b</sup> (SD)	N <sup>a</sup>	Baseline values mean (SD)	Change at end of study mean <sup>b</sup> (SD)	MD [95% CI]; p-value
CD4 cell count/μL							
CD4 cell count at start of study/μL							
EVG/COBI/FTC/TAF vs. EVG/COBI/FTC/TDF							
292-0104							
≤ 350	159	222 (90.9)	270 (160.9)	163	231 (96.6)	270 (152.3)	0.00 [−34.24; 34.24]; > 0.009
> 350	273	564 (176.7)	279 (223.7)	268	545 (171.3)	264 (236.9)	15.00 [−23.84; 53.84]; 0.449
292-0111							
≤ 350	168	226 (96.5)	274 (145.0)	153	214 (100.2)	285 (163.8)	−11.00 [−44.98; 22.98]; 0.526
> 350	259	536 (162.9)	269 (210.0)	279	550 (184.1)	231 (191.3)	38.00 [3.97; 72.03]; 0.029
Total	Interaction:						0.062 <sup>c</sup>
≤ 350							−5.54 [−29.66; 18.57]; 0.652
> 350							28.01 [2.42; 53.61]; 0.032
EFV/FTC/TDF vs. EVG/COBI/FTC/TDF							
236-0102							
≤ 350	147	228 (87.2)	255 (149.6)	155	239 (89.1)	261 (176.5)	−6.00 [−42.84; 30.84]; 0.750
> 350	205	492 (123.1)	241 (212.0)	193	513 (155.5)	291 (236.9)	−50.00 [−94.26; −5.74]; 0.027
Adjusted indirect comparison <sup>d</sup> :							
EVG/COBI/FTC/TAF vs. EFV/FTC/TDF							
						Interaction:	0.024 <sup>c</sup>
≤ 350							0.46 [−43.57; 44.49]; 0.984
> 350							78.01 [26.88; 129.14]; 0.003
a: Number of patients in the ITT population for whom values at the beginning and the end of the study were available.							
b: LOCF analysis.							
c: p-value based on Q test.							
d: Adjusted indirect comparison according to Bucher [11], based on the unadjusted mean differences of the individual studies.							
CD4: cluster of differentiation 4; CI: confidence interval; COBI: cobicistat; EFV: efavirenz; EVG: elvitegravir; FTC: emtricitabine; ITT: intention to treat; LOCF: last observation carried forward; MD: mean difference; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; vs.: versus							

Table 15: Subgroups (SAEs) – RCT, indirect comparison: treatment-naïve adults, EVG/COBI/FTC/TAF vs. EFV/FTC/TDF (96 weeks)

Outcome Characteristic Comparison Study Subgroup	EVG/COBI/FTC/TAF or EFV/FTC/TDF		EVG/COBI/FTC/TDF		Group difference	
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]	p-value
<b>SAEs</b>						
Ethnicity						
EVG/COBI/FTC/TAF vs. EVG/COBI/FTC/TDF						
292-0104						
Caucasian	250	33 (13.2)	255	31 (12.2)	1.09 [0.69; 1.72]	0.725
Non-Caucasian	185	21 (11.4)	177	16 (9.0)	1.26 [0.68; 2.33]	0.469
292-0111						
Caucasian	235	25 (10.6)	243	20 (8.2)	1.29 [0.74; 2.26]	0.369
Non-Caucasian	196	18 (9.2)	192	20 (10.4)	0.88 [0.48; 1.61]	0.683
Total					Interaction:	0.713 <sup>a</sup>
Caucasian					1.16 [0.82; 1.66]	0.400
Non-Caucasian					1.05 [0.68; 1.61]	0.830
EFV/FTC/TDF vs. EVG/COBI/FTC/TDF					Interaction:	0.131 <sup>a</sup>
236-0102						
Caucasian	227	16 (7.0)	214	34 (15.9)	0.44 [0.25; 0.78]	0.005
Non-Caucasian	125	17 (13.6)	134	22 (16.4)	0.83 [0.46; 1.49]	0.528
<b>Adjusted indirect comparison<sup>b</sup>:</b>						
<b>EVG/COBI/FTC/TAF vs. EFV/FTC/TDF</b>					Interaction:	0.147 <sup>a</sup>
Caucasian					2.62 [1.35; 5.11]	0.005
Non-Caucasian					1.27 [0.61; 2.62]	0.525
a: p-value based on Q test. b: Adjusted indirect comparison according to Bucher [11]. AE: adverse event; CD4: cluster of differentiation 4; CI: confidence interval; COBI: cobicistat; EFV: efavirenz; EVG: elvitegravir; FTC: emtricitabine; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RNA: ribonucleic acid; RR: relative risk; SAE: serious adverse event; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; vs.: versus						

Table 16: Subgroups (specific AEs) – RCT, indirect comparison: treatment-naïve adults, EVG/COBI/FTC/TAF vs. EFV/FTC/TDF (96 weeks)

Outcome Characteristic Comparison Study Subgroup	EVG/COBI/FTC/TAF or EFV/FTC/TDF		EVG/COBI/FTC/TDF		Group difference	
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]	p-value
<b>Nervous system disorders</b>						
HIV-1 RNA copies/mL at the start of the study						
EVG/COBI/FTC/TAF vs. EVG/COBI/FTC/TDF						
292-0104						
≤ 100 000	331	82 (24.8)	336	80 (23.8)	1.04 [0.80; 1.36]	0.772
> 100 000	104	29 (27.9)	96	28 (29.2)	0.96 [0.62; 1.48]	0.841
292-0111						
≤ 100 000	339	111 (32.7)	336	100 (29.8)	1.10 [0.88; 1.36]	0.404
> 100 000	92	29 (31.5)	99	36 (36.4)	0.87 [0.58; 1.29]	0.482
Total					Interaction:	0.326 <sup>a</sup>
≤ 100 000					1.08 [0.91; 1.28]	0.409
> 100 000					0.91 [0.67; 1.22]	0.512
EFV/FTC/TDF vs. EVG/COBI/FTC/TDF						
236-0102						
≤ 100 000	236	104 (44.1)	230	77 (33.5)	1.32 [1.04; 1.66]	0.020
> 100 000	116	55 (47.4)	118	35 (29.7)	1.60 [1.14; 2.24]	0.007
<b>Adjusted indirect comparison<sup>b</sup>:</b>						
<b>EVG/COBI/FTC/TAF vs. EFV/FTC/TDF</b>						
					Interaction:	0.179 <sup>a</sup>
≤ 100 000					0.82 [0.61; 1.09]	0.170
> 100 000					0.57 [0.36; 0.89]	0.013

(continued)

Table 16: Subgroups (specific AEs) – RCT, indirect comparison: treatment-naïve adults, EVG/COBI/FTC/TAF vs. EFV/FTC/TDF (96 weeks) (continued)

Outcome Characteristic Comparison Study Subgroup	EVG/COBI/FTC/TAF or EFV/FTC/TDF		EVG/COBI/FTC/TDF		Group difference	
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]	p-value
<b>Nervous system disorders</b>						
CD4 cell count/μL at start of study						
EVG/COBI/FTC/TAF vs. EVG/COBI/FTC/TDF						
292-0104						
≤ 350	161	49 (30.4)	164	41 (25.0)	1.22 [0.86; 1.73]	0.275
> 350	274	62 (22.6)	268	67 (25.0)	0.91 [0.67; 1.22]	0.517
292-0111						
≤ 350	169	66 (39.1)	154	43 (27.9)	1.40 [1.02; 1.92]	0.037
> 350	261	74 (28.4)	281	93 (33.1)	0.86 [0.66; 1.11]	0.234
Total					Interaction:	0.009 <sup>a</sup>
≤ 350					1.31 [1.04; 1.66]	0.023
> 350					0.88 [0.72; 1.06]	0.184
EFV/FTC/TDF vs. EVG/COBI/FTC/TDF						
236-0102						
≤ 350	147	66 (44.9)	155	50 (32.3)	1.39 [1.04; 1.86]	0.026
> 350	205	93 (45.4)	193	62 (32.1)	1.41 [1.10; 1.82]	0.008
<b>Adjusted indirect comparison<sup>b</sup>:</b>						
<b>EVG/COBI/FTC/TAF vs. EFV/FTC/TDF</b>						
					Interaction:	0.094 <sup>a</sup>
≤ 350					0.94 [0.65; 1.37]	0.766
> 350					0.62 [0.45; 0.85]	0.004

(continued)



Table 16: Subgroups (specific AEs) – RCT, indirect comparison: treatment-naïve adults, EVG/COBI/FTC/TAF vs. EFV/FTC/TDF (96 weeks) (continued)

Outcome Characteristic Comparison Study Subgroup	EVG/COBI/FTC/TAF or EFV/FTC/TDF		EVG/COBI/FTC/TDF		Group difference	
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]	p-value
<b>Psychiatric disorders</b>						
Age						
EVG/COBI/FTC/TAF vs. EVG/COBI/FTC/TDF						
292-0104						
< 40	306	79 (25.8)	273	74 (27.1)	0.95 [0.73; 1.25]	0.725
≥ 40	129	24 (18.6)	159	42 (26.4)	0.70 [0.45; 1.10]	0.122
292-0111						
< 40	288	84 (29.2)	278	74 (26.6)	1.10 [0.84; 1.43]	0.500
≥ 40	143	33 (23.1)	157	47 (29.9)	0.77 [0.53; 1.13]	0.183
Total					Interaction:	0.069 <sup>a</sup>
< 40					1.02 [0.85; 1.24]	0.812
≥ 40					0.74 [0.55; 0.99]	0.044
EFV/FTC/TDF vs. EVG/COBI/FTC/TDF						
236-0102						
< 40	197	103 (52.3)	200	85 (42.5)	1.23 [1.00; 1.52]	0.052
≥ 40	155	76 (49.0)	148	53 (35.8)	1.37 [1.05; 1.79]	0.022
<b>Adjusted indirect comparison<sup>b</sup>:</b>						
<b>EVG/COBI/FTC/TAF vs. EFV/FTC/TDF</b>						
< 40					Interaction:	0.084 <sup>a</sup>
≥ 40					0.83 [0.63; 1.10]	0.201
					0.54 [0.36; 0.80]	0.002

(continued)

Table 16: Subgroups (specific AEs) – RCT, indirect comparison: treatment-naïve adults, EVG/COBI/FTC/TAF vs. EFV/FTC/TDF (96 weeks) (continued)

Outcome Characteristic Comparison Study Subgroup	EVG/COBI/FTC/TAF or EFV/FTC/TDF		EVG/COBI/FTC/TDF		Group difference	
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]	p-value
<b>Skin and subcutaneous tissue disorders</b>						
Ethnicity						
EVG/COBI/FTC/TAF vs. EVG/COBI/FTC/TDF						
292-0104						
Caucasian	250	87 (34.8)	255	79 (31.0)	1.12 [0.88; 1.44]	0.362
Non-Caucasian	185	43 (23.2)	177	38 (21.5)	1.08 [0.74; 1.59]	0.686
292-0111						
Caucasian	235	66 (28.1)	243	87 (35.8)	0.78 [0.60; 1.02]	0.073
Non-Caucasian	196	66 (33.7)	192	54 (28.1)	1.20 [0.89; 1.62]	0.239
Total					Interaction:	0.349 <sup>a</sup>
Caucasian		Heterogeneity <sup>c</sup>		Q = 3.74; df = 1, p = 0.053; I <sup>2</sup> = 73.2%		
Non-Caucasian					1.15 [0.91; 1.46]	0.239
EFV/FTC/TDF vs. EVG/COBI/FTC/TDF					Interaction:	0.082 <sup>a</sup>
236-0102						
Caucasian	227	104 (45.8)	214	66 (30.8)	1.49 [1.16; 1.90]	0.002
Non-Caucasian	125	43 (34.4)	134	45 (33.6)	1.02 [0.73; 1.44]	0.890
<b>Adjusted indirect comparison<sup>b</sup>:</b>						
<b>EVG/COBI/FTC/TAF vs. EFV/FTC/TDF</b>					Interaction:	— <sup>c</sup>
Caucasian					— <sup>c</sup>	— <sup>c</sup>
Non-Caucasian					1.13 [0.74; 1.70]	0.576
<p>a: p-value based on Q test.</p> <p>b: Adjusted indirect comparison according to Bucher [11].</p> <p>c: The results of the subgroup analysis are not meaningfully interpretable because the studies 292-0104 and 292-0111 were not homogeneous in the subgroup of Caucasians. The adjusted indirect comparisons that only considered one of the studies 292-0104 and 292-0111 produced discrepant results regarding statistical significance.</p> <p>AE: adverse event; CD4: cluster of differentiation 4; CI: confidence interval; COBI: cobicistat; EFV: efavirenz; EVG: elvitegravir; FTC: emtricitabine; HIV-1: human immunodeficiency virus type 1; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RNA: ribonucleic acid; RR: relative risk; SOC: System Organ Class; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; vs.: versus</p>						

**Morbidity*****CD4 cell count***

In the subgroup analysis on the outcome “CD4 cell count”, the adjusted indirect comparison showed proof of an effect modification by the characteristic “CD4 cell count at the start of the study” ( $\leq 350 / > 350$  cells/ $\mu$ L). No statistically significant difference between EVG/COBI/FTC/TAF and EFV/FTC/TDF was shown for patients with a CD4 cell count of  $\leq 350$  cells/ $\mu$ L, whereas there was a statistically significant difference in favour of EVG/COBI/FTC/TAF for patients with a CD4 cell count of  $> 350$  cells/ $\mu$ L. In the present benefit assessment, CD4 cell count was only considered as additional information to AIDS-defining events, which was the actual patient-relevant outcome, for which the company had presented no subgroup analyses. Furthermore, the subgroup analyses for the outcome “virologic response”, which is also considered as additional information, showed no indication of this effect modification. An isolated interpretation of the subgroup results for the outcome “CD4 cell count” was therefore not considered to be meaningful.

This concurs with the assessment of the company in so far as the company rated the statistically significant effect at week 96 in favour of EVG/COBI/FTC/TAF in patients with CD4 cell count of  $> 350$  cells/ $\mu$ L as clinically irrelevant. However, it considered the effect modification by CD4 cell count in the derivation of the added benefit on the basis of the results at 48 weeks.

**Side effects*****Serious adverse events***

In the subgroup analysis on the outcome “SAEs”, the adjusted indirect comparison showed an indication of an effect modification by the characteristic “ethnicity” (Caucasian/non-Caucasian).

No statistically significant difference between EVG/COBI/FTC/TAF and EFV/FTC/TDF was shown for non-Caucasian patients. This resulted in no hint of an added benefit of EVG/COBI/FTC/TAF in comparison with EFV/FTC/TDF in non-Caucasian patients; an added benefit for these patients is therefore not proven.

A statistically significant difference to the disadvantage of EVG/COBI/FTC/TAF in comparison with EFV/FTC/TDF was shown for Caucasians. For the outcome “SAEs”, this resulted in a hint of greater harm from EVG/COBI/FTC/TAF in comparison with EFV/FTC/TDF in Caucasians.

As the patients of Caucasian origin represent the main ethnicity for the health care area of the present benefit assessment, the subgroup of non-Caucasians were not considered further in the present benefit assessment.

The company also considered the indication of effect modification by ethnicity and described a statistically significant difference to the disadvantage of EVG/COBI/FTC/TAF only for Caucasians. It derived no greater harm from this, however (see Section 2.3.2.2).

### ***Nervous system disorders***

In the subgroup analysis on the outcome “nervous system disorders”, the adjusted indirect comparison showed an indication of an effect modification by the characteristics “baseline viral load” ( $\leq 100\,000 / > 100\,000$  HIV-1 RNA copies/mL) and “CD4 cell count at the start of the study” ( $\leq 350 / > 350$  cells/ $\mu$ L). In the final result, these effect modifications resulted in a statistically significant difference in favour of EVG/COBI/FTC/TAF both in patients with a baseline viral load of  $> 100\,000$  HIV-1 RNA copies/mL and in patients with a CD4 cell count of  $> 350$  cells/ $\mu$ L. No statistically significant differences between the treatment options were shown for the remaining subgroups. Since an advantage of EVG/COBI/FTC/TAF was associated both with patients with a more severe disease stage (baseline viral load  $> 100\,000$  HIV-1 RNA copies/mL) and with patients with a less severe disease stage (CD4 cell count of  $> 350$  cells/ $\mu$ L), the result of the subgroup analyses could not be meaningfully interpreted for this outcome and was not considered further in the benefit assessment.

This concurs with the company’s assessment.

### ***Psychiatric disorders***

The adjusted indirect comparison showed an indication of an effect modification by the characteristic “age” ( $< 40 / \geq 40$ ) for the outcome “psychiatric disorders”.

No statistically significant difference between EVG/COBI/FTC/TAF and EFV/FTC/TDF was shown for patients  $< 40$  years. This resulted in no hint of an added benefit of EVG/COBI/FTC/TAF in comparison with EFV/FTC/TDF in patients  $< 40$  years; an added benefit for these patients is therefore not proven.

A statistically significant difference in favour of EVG/COBI/FTC/TAF was shown for patients  $\geq 40$  years. For the outcome “psychiatric disorders”, this resulted in a hint of lesser harm from EVG/COBI/FTC/TAF in comparison with EFV/FTC/TDF in patients  $\geq 40$  years.

This deviates from the company’s assessment, which described the indication of effect modification, but did not consider the results of the subgroup analysis in the derivation of the added benefit because it regarded the effect modification to be negligible against the background of the difference in the total population, which was clearly significant from the company’s point of view.

### ***Skin and subcutaneous tissue disorders***

There was an indication of an effect modification by the characteristic “ethnicity” (Caucasian/non-Caucasian) for the outcome “skin and subcutaneous tissue disorders”. However, the meta-analysis of the studies with the intervention showed unexplained

heterogeneity without effects in the same direction in the group of Caucasians. The result of the subgroup analyses for this outcome could therefore not be meaningfully interpreted for the patients of Caucasian origin and was not further considered in the benefit assessment.

This concurs with the company's assessment.

### **2.3.3 Extent and probability of added benefit**

The derivation of extent and probability of added benefit for treatment-naïve adults (research question 1) at outcome level is shown below, taking into account the various 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.

#### **2.3.3.1 Assessment of added benefit at outcome level**

The data presented in Section 2.3.2 resulted in a hint of lesser benefit for the outcome “AIDS-defining events” and hints of greater harm for the outcomes “SAEs” and “infections and infestations”. There was a hint of lesser harm for the outcome “psychiatric disorders”. Moreover, there were relevant indications of an effect modification for the subgroup characteristics “ethnicity” and “age”.

The extent of the respective added benefit at outcome level was estimated from these results (see Table 17).

Table 17: Extent of added benefit at outcome level: treatment-naïve adults,  
EVG/COBI/FTC/TAF vs. EFV/FTC/TDF

Outcome category Outcome Effect modifier Subgroup	EVG/COBI/FTC/TDF vs. EFV/FTC/TDF Effect estimates [95% CI]; p-value Probability <sup>a</sup>	Derivation of extent <sup>b</sup>
<b>Mortality</b>		
All-cause mortality	POR: 0.35 [0.02; 6.12] p = 0.471	Added benefit not proven
<b>Morbidity</b>		
AIDS-defining events	RR: 11.88 [1.23; 114.99] <sup>c</sup> RR <sup>d</sup> 0.08 [0.01; 0.81] p = 0.033 <sup>c</sup> probability: “hint”	Outcome category: serious/severe symptoms/late complications $0.75 \leq CI_u < 0.90$ lesser benefit, extent: “considerable”
Surrogate outcomes additionally presented Virologic response (snapshot) CD4 cell count	RR: 1.05 [0.97; 1.13] p = 0.233 MD (cells/ $\mu$ L: 47.06 [12.08; 82.04] p = 0.008	
Health status (VAS of the EQ-5D)	There were no data for an adjusted indirect comparison.	
<b>Health-related quality of life</b>		
	Not investigated in the studies included	
<b>Side effects</b>		
Serious adverse events	RR: 1.91 [1.18; 3.12] RR <sup>d</sup> 0.52 [0.32; 0.85] p = 0.009 probability: “hint”	
Ethnicity		
Caucasian	RR: 2.62 [1.35; 5.11] RR <sup>d</sup> 0.38 [0.20; 0.74] p = 0.005 probability: “hint”	Outcome category: serious/severe side effects $CI_u < 0.75^e$ greater harm, extent: “major”
Non-Caucasian	RR: 1.27 [0.61; 2.62] p = 0.525	Greater/lesser harm not proven
Severe AEs (grade 3-4)	Heterogeneous data <sup>f</sup>	Greater/lesser harm not proven
Discontinuation due to adverse events	RR: 0.36 [0.14; 0.94] p = 0.038	Outcome category: non-serious/non-severe side effects $0.90 \leq CI_u < 1$ Greater/lesser harm not proven <sup>g</sup>

(continued)

Table 17: Extent of added benefit at outcome level: treatment-naïve adults,  
EVG/COBI/FTC/TAF vs. EFV/FTC/TDF (continued)

Outcome category Outcome Effect modifier Subgroup	EVG/COBI/FTC/TDF vs. EFV/FTC/TDF Effect estimates [95% CI]; p-value Probability <sup>a</sup>	Derivation of extent <sup>b</sup>
Nervous system disorders	RR: 0.73 [0.58; 0.94] p = 0.013	Outcome category: non-serious/non-severe side effects $0.90 \leq CI_u < 1$ Greater/lesser harm not proven <sup>g</sup>
Psychiatric disorders	RR: 0.73 [0.58; 0.91] p = 0.006	
Age		
< 40 years	RR: 0.83 [0.63; 1.10] p = 0.201	Greater/lesser harm not proven
≥ 40 years	RR: 0.54 [0.36; 0.80] <sup>h</sup> p = 0.002 probability: “hint”	Outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ lesser harm, extent: “minor”
Skin and subcutaneous tissue disorders	RR: 0.78 [0.61; 0.99] p = 0.046	Outcome category: non-serious/non-severe side effects $0.90 \leq CI_u < 1$ Greater/lesser harm not proven <sup>g</sup>
Gastrointestinal disorders	RR: 1.11 [0.95; 1.30] p = 0.176	Greater/lesser harm not proven
Renal and urinary disorders	RR: 0.87 [0.51; 1.46] p = 0.590	Greater/lesser harm not proven
Infections and infestations (SAEs)	RR: 3.90 [1.67; 9.12] RR <sup>d</sup> 0.26 [0.11; 0.60] p = 0.002 probability: “hint”	Outcome category: serious/severe side effects $CI_u \leq 0.90$ greater harm, extent: “considerable”

(continued)

Table 17: Extent of added benefit at outcome level: treatment-naïve adults, EVG/COBI/FTC/TAF vs. EFV/FTC/TDF (continued)

a: Probability provided if statistically significant and relevant differences are present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the $CI_u$ .
c: Institute's calculation.
d: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
e: Risk must be at least 5% for at least 1 of the 2 groups compared.
f: Result of the adjusted indirect comparison not meaningfully interpretable due to heterogeneity in the comparison of EVG/COBI/FTC/TAF vs. EVG/COBI/FTC/TDF.
g: Greater/lesser harm is not proven because the effect size is only marginal.
h: $CI_u$ : 0.80466
AE: adverse event; AIDS: acquired immunodeficiency syndrome; CD4: cluster of differentiation 4;
CI: confidence interval; $CI_u$ : upper limit of confidence interval; COBI: cobicistat; EFV: efavirenz;
EQ-5D: European Quality of Life-5 Dimensions; EVG: elvitegravir; FTC: emtricitabine; MD: mean difference; POR: Peto odds ratio; RR: relative risk; SAE: serious adverse event; TAF: tenofovir alafenamide;
TDF: tenofovir disoproxil; VAS: visual analogue scale; vs.: versus

### 2.3.3.2 Overall conclusion on added benefit

Table 18 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 18: Positive and negative effects from the assessment of EVG/COBI/FTC/TAF compared with EFV/FTC/TDF

Positive effects	Negative effects
Non-serious/non-severe side effects <ul style="list-style-type: none"> <li>Psychiatric disorders <ul style="list-style-type: none"> <li>age (<math>\geq 40</math> years): hint of lesser harm – extent: “minor”</li> </ul> </li> </ul>	Serious/severe symptoms/late complications <ul style="list-style-type: none"> <li>AIDS-defining events: hint of a lesser benefit – extent: “considerable”</li> </ul>
	Serious/severe side effects <ul style="list-style-type: none"> <li>Serious adverse events <ul style="list-style-type: none"> <li>ethnicity (Caucasian): hint of greater harm – extent: “major”</li> </ul> </li> <li>Infections and infestations: hint of greater harm – extent: “considerable”</li> </ul>
AIDS: acquired immunodeficiency syndrome; COBI: cobicistat; EFV: efavirenz; EVG: elvitegravir; FTC: emtricitabine; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil	

Overall, one positive effect and several negative effects with the same probability (“hint”) remain.

The positive effect in the outcome category “non-serious/non-severe side effects” for the outcome “psychiatric disorders” was only shown in the subgroup of patients 40 years of age or older (extent: “minor”).



On the negative side, lesser benefit was shown for the outcome “AIDS-defining events” (extent: “considerable”) and greater harm for the outcomes “SAEs” (extent: “major”) and “infections and infestations” (extent: “considerable”).

Balancing these effects, the positive effect of minor extent, which, in addition, only existed in the subgroup of patients  $\geq 40$  years of age, did not outweigh the negative effects. It should be particularly highlighted that the negative effects were from the categories “serious/severe symptoms/late complications” or “side effects”.

In summary, there is a hint of lesser benefit of EVG/COBI/FTC/TAF in comparison with the ACT for treatment-naïve adults with HIV-1 infection.

This deviates from the company’s approach, which derived proof of a minor added benefit based on the results of the adjusted indirect comparison.

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

#### **2.3.4 List of included studies**

##### **236-0102**

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-naïve adults: study GS-US-236-0102; interim week 48 clinical study report [unpublished]. 2011.

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-naïve adults: study GS-US-236-0102; interim week 96 clinical study report [unpublished]. 2012.

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-naïve adults: study GS-US-236-0102; week 48; Zusatzanalysen [unpublished]. 2015.

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-naïve adults: study GS-US-236-0102; week 96; Zusatzanalysen [unpublished]. 2015.

Gilead Sciences. Study to evaluate the safety and efficacy of Stribild versus Atripla in human immunodeficiency virus, type 1 (HIV-1) infected, antiretroviral treatment-naïve adults: full text view [online]. In: ClinicalTrials.gov. 09.2015 [accessed: 21.10.2015]. URL: <https://ClinicalTrials.gov/show/NCT01095796>.

Gilead Sciences. Study to evaluate the safety and efficacy of Stribild versus Atripla in human immunodeficiency virus, type 1 (HIV-1) infected, antiretroviral treatment-naïve adults: study results [online]. In: ClinicalTrials.gov. 15.10.2015 [accessed: 16.02.2016]. URL: <https://clinicaltrials.gov/ct2/show/results/NCT01095796>.

Sax PE, DeJesus E, Mills A. Erratum: "Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3 trial, analysis of results after 48 weeks" (Lancet 2012; 379(9835): 2439-2448). Lancet 2012; 380(9843): 730.

Sax PE, DeJesus E, Mills A, Zolopa A, Cohen C, Wohl D et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3 trial, analysis of results after 48 weeks. Lancet 2012; 379(9835): 2439-2448.

Zolopa A, Sax PE, DeJesus E, Mills A, Cohen C, Wohl D et al. A randomized double-blind comparison of coformulated elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate versus efavirenz/emtricitabine/tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: analysis of week 96 results. J Acquir Immune Defic Syndr 2013; 63(1): 96-100.

#### **236-0104**

Cohen C, Elion R, Ruane P, Shamblaw D, DeJesus E, Rashbaum B et al. Randomized, phase 2 evaluation of two single-tablet regimens elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate versus efavirenz/emtricitabine/tenofovir disoproxil fumarate for the initial treatment of HIV infection. AIDS 2011; 25(6): F7-F12.

Gilead Sciences. A phase 2, randomized, double-blinded study of the safety and efficacy of elvitegravir/emtricitabine/tenofovir disoproxil fumarate/GS-9350 versus Atripla (efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) in HIV-1 infected, antiretroviral treatment-naïve adults: study GS-US-236-0104; week 96 interim clinical study report [unpublished]. 2011.

Gilead Sciences. A phase 2, randomized, double-blinded study of the safety and efficacy of elvitegravir/emtricitabine/tenofovir disoproxil fumarate/GS-9350 versus Atripla (efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) in HIV-1 infected, antiretroviral treatment-naïve adults: study GS-US-236-0104; week 48; Zusatzanalysen [unpublished]. 2015.

Gilead Sciences. Study of the safety and efficacy of Stribild versus Atripla in human immunodeficiency virus, type 1 (HIV-1) infected, antiretroviral treatment-naïve adults: full text view [online]. In: ClinicalTrials.gov. 22.05.2014 [accessed: 21.10.2015]. URL: <https://clinicaltrials.gov/ct2/show/study/NCT00869557>.

Gilead Sciences. Study of the safety and efficacy of Stribild versus Atripla in human immunodeficiency virus, type 1 (HIV-1) infected, antiretroviral treatment-naïve adults: study results [online]. In: ClinicalTrials.gov. 22.05.2014 [accessed: 16.02.2016]. URL: <https://clinicaltrials.gov/ct2/show/results/NCT00869557>.

## **292-0102**

Gilead Sciences. A phase 2, randomized, double-blinded study of the safety and efficacy of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide single tablet regimen versus elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate single tablet regimen in HIV-1 infected, antiretroviral treatment-naïve adults: study GS-US-292-0102; week 96 interim clinical study report [unpublished]. 2014.

Gilead Sciences. A phase 2, randomized, double-blinded study of the safety and efficacy of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide single tablet regimen versus elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate single tablet regimen in HIV-1 infected, antiretroviral treatment-naïve adults: study GS-US-292-0102; week 48; Zusatzanalysen [unpublished]. 2015.

Gilead Sciences. Safety and efficacy of E/C/F/TAF (Genvoya) versus E/C/F/TDF (Stribild) in HIV-1 infected, antiretroviral treatment-naïve adults: full text view [online]. In: ClinicalTrials.gov. 08.2015 [accessed: 20.10.2015]. URL: <https://ClinicalTrials.gov/show/NCT01497899>.

Gilead Sciences. Safety and efficacy of E/C/F/TAF (Genvoya) versus E/C/F/TDF (Stribild) in HIV-1 infected, antiretroviral treatment-naïve adults: study results [online]. In: ClinicalTrials.gov. 04.12.2015 [accessed: 16.02.2016]. URL: <https://clinicaltrials.gov/ct2/show/results/NCT01497899>.

Sax PE, Zolopa A, Brar I, Elion R, Ortiz R, Post F et al. Tenofovir alafenamide vs. tenofovir disoproxil fumarate in single tablet regimens for initial HIV-1 therapy: a randomized phase 2 study. J Acquir Immune Defic Syndr 2014; 67(1): 52-58.

## **292-0104**

Gilead Sciences. A phase 3, randomized, double-blind study to evaluate the safety and efficacy of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide versus elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate in HIV-1 positive, antiretroviral treatment-naïve adults [online]. In: EU Clinical Trials Register. [Accessed: 20.10.2015]. URL: [https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract\\_number:2012-004458-27](https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-004458-27).

Gilead Sciences. A phase 3, randomized, double-blind study to evaluate the safety and efficacy of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide versus elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate in HIV-1 positive, antiretroviral treatment-naïve adults: study GS-US-292-0104; interim week 48 clinical study report [unpublished]. 2014.

Gilead Sciences. A phase 3, randomized, double-blind study to evaluate the safety and efficacy of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide versus elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate in HIV-1 positive, antiretroviral treatment-naïve adults: study GS-US-292-0104; week 48; Zusatzanalysen [unpublished]. 2015.

Gilead Sciences. A phase 3, randomized, double-blind study to evaluate the safety and efficacy of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide versus elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate in HIV-1 positive, antiretroviral treatment-naïve adults: study GS-US-292-0104; interim week 96 clinical study report [unpublished]. 2015.

Gilead Sciences. A phase 3, randomized, double-blind study to evaluate the safety and efficacy of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide versus elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate in HIV-1 positive, antiretroviral treatment-naïve adults: study GS-US-292-0104; week 96; Zusatzanalysen [unpublished]. 2015.

Gilead Sciences. Study to evaluate the safety and efficacy of E/C/F/TAF (Genvoya) versus E/C/F/TDF (Stribild) in HIV-1 positive, antiretroviral treatment-naïve adults: full text view [online]. In: ClinicalTrials.gov. 07.2015 [accessed: 20.10.2015]. URL: <https://ClinicalTrials.gov/show/NCT01780506>.

Gilead Sciences. Study to evaluate the safety and efficacy of E/C/F/TAF (Genvoya) versus E/C/F/TDF (Stribild) in HIV-1 positive, antiretroviral treatment-naïve adults: study results [online]. In: ClinicalTrials.gov. 04.12.2015 [accessed: 16.02.2016]. URL: <https://clinicaltrials.gov/ct2/show/results/NCT01780506>.

Sax PE, Wohl D, Yin MT, Post F, DeJesus E, Saag M et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. *Lancet* 2015; 385(9987): 2606-2615.

## **292-0111**

Gilead Sciences. A phase 3, randomized, double-blind study to evaluate the safety and efficacy of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide versus elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate in HIV-1 positive, antiretroviral treatment-naïve adults [online]. In: EU Clinical Trials Register. [Accessed: 20.10.2015]. URL: [https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract\\_number:2013-000102-37](https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-000102-37).

Gilead Sciences. A phase 3, randomized, double-blind study to evaluate the safety and efficacy of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide versus elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate in HIV-1 positive, antiretroviral treatment-naïve adults: study GS-US-292-0111; interim week 48 clinical study report [unpublished]. 2014.

Gilead Sciences. A phase 3, randomized, double-blind study to evaluate the safety and efficacy of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide versus elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate in hiv-1 positive, antiretroviral treatment-naïve adults: study GS-US-292-0111; interim week 96 clinical study report [unpublished]. 2015.

Gilead Sciences. A phase 3, randomized, double-blind study to evaluate the safety and efficacy of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide versus elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate in HIV-1 positive, antiretroviral treatment-naïve adults: study GS-US-292-0111; week 48; Zusatzanalysen [unpublished]. 2015.

Gilead Sciences. A phase 3, randomized, double-blind study to evaluate the safety and efficacy of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide versus elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate in HIV-1 positive, antiretroviral treatment-naïve adults: study GS-US-292-0111; week 96; Zusatzanalysen [unpublished]. 2015.

Gilead Sciences. Study to evaluate the safety and efficacy of E/C/F/TAF (Genvoya) versus E/C/F/TDF (Stribild) in HIV-1 positive, antiretroviral treatment-naïve adults: full text view [online]. In: ClinicalTrials.gov. 07.2015 [accessed: 20.10.2015]. URL: <https://ClinicalTrials.gov/show/NCT01797445>.

Gilead Sciences. Study to evaluate the safety and efficacy of E/C/F/TAF (Genvoya) versus E/C/F/TDF (Stribild) in HIV-1 positive, antiretroviral treatment-naïve adults: study results [online]. In: ClinicalTrials.gov. 04.12.2015 [accessed: 16.02.2016]. URL: <https://clinicaltrials.gov/ct2/show/results/NCT01797445>.

Sax PE, Wohl D, Yin MT, Post F, DeJesus E, Saag M et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. Lancet 2015; 385(9987): 2606-2615.

## **2.4 Research question 2: treatment-naïve adolescents 12 years of age and older**

### **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 list on EVG/COBI/FTC/TAF (status: 15 October 2015)
- bibliographical literature search on EVG/COBI/FTC/TAF (last search on 19 October 2015)
- search in trial registries for studies on EVG/COBI/FTC/TAF (last search on 20 October 2015)

To check the completeness of the study pool:

- search in trial registries for studies on EVG/COBI/FTC/TAF (last search on 13 January 2016)

No relevant study was identified from the company's search and the check.

### **2.4.2 Results on added benefit**

No data for the assessment of the added benefit were available for treatment-naïve adolescents. Hence an added benefit of EVG/COBI/FTC/TAF in comparison with the ACT for this population is not proven.

### **2.4.3 Extent and probability of added benefit**

As the company presented no data for the assessment of the added benefit for treatment-naïve adolescents, an added benefit of EVG/COBI/FTC/TAF is not proven for this population.

## 2.5 Research question 3: pretreated adults

### 2.5.1 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 list on EVG/COBI/FTC/TAF (status: 15 October 2015)
- bibliographical literature search on EVG/COBI/FTC/TAF (last search on 19 October 2015)
- search in trial registries for studies on EVG/COBI/FTC/TAF (last search on 20 October 2015)

To check the completeness of the study pool:

- search in trial registries for studies on EVG/COBI/FTC/TAF (last search on 13 January 2016)

No additional relevant study was identified from the check.

#### 2.5.1.1 Studies included

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

Table 19: Study pool – RCT, direct comparison: pretreated adults, EVG/COBI/FTC/TAF vs. continuation of ongoing treatment (FTC/TDF + third agent<sup>a</sup>)

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study <sup>b</sup> (yes/no)	Third-party study (yes/no)
GS-US-292-0109 (292-0109) <sup>c</sup>	Yes	Yes	No
a: EVG/COBI or EFV or ATV/co or ATV/r. b: Study for which the company was sponsor. c: Hereinafter, the study is referred to with its abbreviated form. ATV/co: cobicistat-boosted atazanavir; ATV/r: ritonavir-boosted atazanavir; COBI: cobicistat; EFV: efavirenz; EVG: elvitegravir; FTC: emtricitabine; RCT: randomized controlled trial; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; vs.: versus			

The company used study 292-0109 for the assessment of the added benefit of EVG/COBI/FTC/TAF for patients without indication for a treatment switch (e.g. due to virologic failure or side effects). This approach was followed (see also Section 2.8.2.4.1 of the full dossier assessment).

An assessment of the added benefit for pretreated adults with indication for a treatment switch, e.g. due to virologic failure or side effects, was not possible on the basis of study 292-0109. Hence no studies were available for these patients.

Section 2.5.4 contains a reference list for the study included.

#### **2.5.1.2 Study characteristics**

Table 20 and Table 21 describe the study used for the benefit assessment.



Table 20: Characteristics of the study included – RCT, direct comparison: pretreated adults, EVG/COBI/FTC/TAF vs. continuation of ongoing treatment (FTC/TDF + third agent<sup>a</sup>)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes <sup>b</sup>
292-0109	RCT, open-label, parallel	HIV-infected adults <sup>c</sup> with antiretroviral pretreatment with an HIV-1 RNA viral load of < 50 copies/mL for at least 6 consecutive months prior to and at screening and eGFR of ≥ 50 mL/min	EVG/COBI/FTC/TAF (N = 963) Continuation of ongoing treatment (N = 480) consisting of <ul style="list-style-type: none"> <li>▪ EVG/COBI/FTC/TDF or</li> <li>▪ EFV/FTC/TDF or</li> <li>▪ ATV/co + FTC/TDF or</li> <li>▪ ATV/r + FTC/TDF</li> </ul>	Screening: 30 days prior to the start of treatment Planned treatment duration: 96 weeks <sup>d</sup> Follow-up: 30 days	168 centres in Australia, Austria, Belgium, Brazil, Canada, Denmark, Dominican Republic, France, Germany, Italy, Mexico, Netherlands, Portugal, Puerto Rico, Sweden, Switzerland, Spain, Thailand, United Kingdom, USA 3/2013–ongoing Data cut-off at week 48: 3/2015	Primary: virologic response at week 48 Secondary: AIDS-defining events (CDC class C events), change in CD4 cell count, health status, health-related quality of life, mortality, AEs
<p>a: EVG/COBI or EFV or ATV/co or ATV/r.  b: 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.  c: Pretreatment with EVG/COBI/FTC/TDF or EFV/FTC/TDF or ATV/r + FTC/TDF or ATV/co + FTC/TDF for ≥ 6 consecutive months preceding the final visit in an earlier study.  d: Then all study participants have the possibility to receive unblinded EVG/COBI/FTC/TAF treatment until the product is commercially available or until Gilead stops the research programme.</p> <p>ACT: appropriate comparator therapy; AE: adverse event; AIDS: acquired immunodeficiency syndrome; ATV/co: cobicistat-boosted atazanavir; ATV/r: ritonavir-boosted atazanavir; CD4: cluster of differentiation 4; CDC: Centers for Disease Control and Prevention; COBI: cobicistat; EFV: efavirenz; eGFR: estimated glomerular filtration rate (according to Cockcroft-Gault equation); EVG: elvitegravir; FTC: emtricitabine; HIV-1: human immunodeficiency virus type 1; N: number of randomized patients; RCT: randomized controlled trial; RNA: ribonucleic acid; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; vs: versus</p>						

Table 21: Characteristics of the intervention – RCT, direct comparison: pretreated adults, EVG/COBI/FTC/TAF vs. continuation of ongoing treatment (FTC/TDF + third agent<sup>a</sup>)

Study	Intervention	Comparison	Prior and concomitant medication
292-0109	EVG 150 mg/COBI 150 mg/ FTC 200 mg/TAF 10 mg (fixed-dose combination) once daily orally with food	<ul style="list-style-type: none"> <li>▪ EVG 150 mg/COBI 150 mg/ FTC 200 mg/TDF 300 mg<sup>b</sup> (fixed-dose combination) once daily orally with food</li> <li><b>or</b></li> <li>▪ EFV 600 mg/FTC 200 mg/ TDF 300 mg<sup>b</sup> (fixed-dose combination) once daily orally on an empty stomach preferably prior to bedtime</li> <li><b>or</b></li> <li>▪ ATV/r 300 mg/100 mg (individual substances) + FTC 200 mg/TDF 300 mg<sup>b</sup> (fixed-dose combination) once daily orally with food</li> <li><b>or</b></li> <li>▪ ATV/co 300 mg/150 mg (individual substances) + FTC 200 mg/TDF 300 mg<sup>b</sup> (fixed-dose combination) once daily orally with food</li> </ul>	<p><b>Pretreatment:</b> EVG/COBI/FTC/TDF or EFV/FTC/TDF or ATV/r + FTC/TDF or ATV/co + FTC/TDF for ≥ 6 consecutive months preceding the final visit in an earlier study</p> <p><b>Non-permitted concomitant medication:</b> drugs with high interaction potential (e.g. carbamazepine, HMG-CoA reductase inhibitors, St. John's Wort)</p>
<p>a: EVG/COBI or EFV or ATV/co or ATV/r. b: Equivalent to 245 mg tenofovir disoproxil. ATV/co: cobicistat-boosted atazanavir; ATV/r: ritonavir-boosted atazanavir; COBI: cobicistat; EFV: efavirenz; EVG: elvitegravir; FTC: emtricitabine; HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme-A; RCT: randomized controlled trial; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate; vs.: versus</p>			

The 292-0109 study was an open-label, active-controlled randomized trial with patients with prior antiretroviral therapy. Virologically suppressed adults who had participated in different clinical studies conducted by the company with a treatment regimen consisting of the fixed FTC/TDF backbone therapy and a third antiretroviral agent were enrolled in the study. Efavirenz (EFV), cobicistat-boosted elvitegravir (EVG/COBI) or cobicistat-boosted or ritonavir-boosted atazanavir (ATV/co or ATV/r) were possible third agents. Patients also had to have an eGFR of  $\geq 50$  mL/min.

A total of 1443 patients were randomized in a ratio of 2:1 to the 2 study arms, 963 patients to the EVG/COBI/FTC/TAF arm, and 480 patients to the comparator arm (continuation of ongoing treatment). Randomization was stratified by pretreatment (EVG/COBI/FTC/TDF, EFV/FTC/TDF or ATV/booster/FTC/TDF).

The planned treatment duration in the study is 96 weeks; at the time point of the benefit assessment, however, only results for the period of analysis of 48 weeks were available.

The antiretroviral agents used in the studies were administered in compliance with their approval, either with food or on an empty stomach once daily orally [3,6,14-18]. In addition, according to the SPCs of the substances used in the study [3,6,15,17], there were to be no resistances to the agents or drug classes used in the study. Yet there was no specification regarding resistance testing or genotyping in study 292-0109. However, the company comprehensibly explained that, in compliance with the approval, the patients included had no resistances to the agents used in the study (see Section 2.8.2.4.1 of the full dossier assessment). According to the SPC of EVG/COBI/FTC/TDF, discontinuation of treatment should be considered if creatinine clearance declines below 70 mL/min [17]. According to the information provided by the company, this only applied to 9 patients treated with EVG/COBI/FTC/TDF in the study (corresponding to 1.9% of the patients in the comparator arm). The proportion of patients in the study population was therefore markedly < 20% so that it was possible to use the entire study population for the assessment.

An evaluation regarding content of the investigated patient population showed that mostly patients without medically required indication for a treatment switch (e.g. due to virologic failure or side effects) were enrolled in study 292-0109 [see Section 2.8.2.3.2 of the full dossier assessment]). Hence on the basis of the total population, study 292-0109 could be used for the assessment of the added benefit in treatment-naïve adults without indication for a treatment switch. Some uncertainty remained, however, whether a small proportion of patients with necessary treatment switch due to side effects were also included in the study. This uncertainty had to be considered in the interpretation of the results on the outcome “discontinuation due to AEs” (see Section 2.8.2.4.1 of the full dossier assessment).

It was not possible to assess the added benefit of EVG/COBI/FTC/TAF for pretreated adults with indication for a treatment switch on the basis of study 292-0109.

Table 22 shows the characteristics of the patients in the study included.

Table 22: Characteristics of the study population – RCT, direct comparison: pretreated adults, EVG/COBI/FTC/TAF vs. continuation of ongoing treatment (FTC/TDF + third agent<sup>a</sup>)

<b>Study Characteristics Category</b>	<b>EVG/COBI/FTC/TAF</b>	<b>EVG/COBI/FTC/TDF, EFV/FTC/TDF, ATV/co + FTC/TDF or ATV/r + FTC/TDF</b>
<b>292-0109</b>	<b>N<sup>b</sup> = 959</b>	<b>N<sup>b</sup> = 477</b>
Age [years], mean (SD)	41 (10)	41 (10)
Sex [F/M], %	10.7/89.3	10.5/89.5
Ethnicity, %		
Caucasian	67.9	65.8
Asian	6.2	7.3
Other <sup>c</sup>	26.0 <sup>d</sup>	26.8 <sup>d</sup>
Pretreatment, n (%)		
EVG/COBI/FTC/TDF	306 (31.9)	153 (32.1)
EFV/FTC/TDF	251 (26.2)	125 (26.2)
ATV/co + FTC/TDF	147 (15.3) <sup>d</sup>	69 (14.5) <sup>d</sup>
ATV/r + FTC/TDF	255 (26.6) <sup>d</sup>	130 (27.3) <sup>d</sup>
Duration of pretreatment	ND	ND
eGFR [mL/min], median (Q1; Q3)	105.7 (89.4; 126.0)	107.7 (88.7; 128.2)
Baseline viral load [HIV-1 RNA copies/mL], n (%)		
< 50	943 (98.3)	466 (97.7)
≥ 50	16 (1.7)	11 (2.3)
Median (Q1; Q3)	ND	ND
CD4 cell count/μL, n (%)		
< 350	59 (6.2) <sup>d</sup>	29 (6.1) <sup>d</sup>
≥ 350	900 (93.8) <sup>d</sup>	448 (93.9) <sup>d</sup>
Median (Q1; Q3)	675 (520; 833)	662 (525; 831)
HIV disease stage, n (%)	ND	ND
Treatment discontinuation, week 48, n (%)	32 (3.3)	40 (8.4)
Study discontinuation, week 48, n (%)	28 (2.9)	26 (5.5)
<p>a: EVG/COBI or EFV or ATV/co or ATV/r.</p> <p>b: Number of patients in the safety population, which includes all patients who were randomized and received at least one dose of the study treatment.</p> <p>c: This group includes blacks or patients of African origin, native Americans/native Alaskans, Hawaiians/Pacific Islanders, missing data, and others.</p> <p>d: Institute's calculation.</p> <p>ATV/co: cobicistat-boosted atazanavir; ATV/r: ritonavir-boosted atazanavir; CD4: cluster of differentiation 4; COBI: cobicistat; EFV: efavirenz; eGFR: estimated glomerular filtration rate (according to Cockcroft-Gault equation); EVG: elvitegravir; F: female; FTC: emtricitabine; HIV: human immunodeficiency virus; ND: no data; M: male; n: number of patients in the category; N: number of patients included; Q: quartile; RCT: randomized controlled trial; RNA: ribonucleic acid; SD: standard deviation; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; vs.: versus</p>		

There were no important differences regarding the demographic characteristics “age”, “sex” and “ethnicity” between the 2 treatment arms in study 292-0109. The mean age of the patients was 41 years, and markedly more men (about 90%) than women (about 10%) were included in both treatment arms, reflecting the higher prevalence of HIV-1 infection in men [10]. The majority of the patients included in the studies were of Caucasian origin (about 66% each). Antiretroviral pretreatment was also mostly equally distributed between both treatment arms. Approximately one third of the patients were pretreated with EVG/COBI/FTC/TDF, about one quarter each with EFV/FTC/TDF or ATV/r/FTC/TDF, and about 15% with ATV/co/FTC/TDF. According to the inclusion criterion of the study, almost all patients in both treatment arms had a viral load of < 50 HIV-1 RNA copies/mL (about 98% in each case). The median CD4 cell count in both treatment arms was about 670 cells/μL each. Notably fewer patients discontinued treatment or the study in the intervention arm (3.3% and 2.9%) than in the comparator arm (8.4% and 5.5%). Table 23 shows the risk of bias at study level.

Table 23: Risk of bias at study level – RCT, direct comparison: pretreated adults, EVG/COBI/FTC/TAF vs. continuation of ongoing treatment (FTC/TDF + third agent<sup>a</sup>)

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			
292-0109	Yes	Yes	No	No	Yes	Yes	Low
a: EVG/COBI or EFV or ATV/co or ATV/r. ATV/co: cobicistat-boosted atazanavir; ATV/r: ritonavir-boosted atazanavir; COBI: cobicistat; EFV: efavirenz; EVG: elvitegravir; FTC: emtricitabine; RCT: randomized controlled trial; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; vs.: versus							

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

Limitations resulting from the open-label study design are described in Section 2.5.2.2 with the outcome-specific risk of bias.

## **2.5.2 Results on added benefit**

### **2.5.2.1 Outcomes included**

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.8.2.4.3 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity
  - AIDS-defining events (CDC class C events)
  - presented as additional information: virologic response and CD4 cell count as surrogate outcomes for the patient-relevant outcome “AIDS-defining illnesses/death”
  - health status measured with the EQ-5D VAS
- Health-related quality of life
  - SF-36 Version 2 (SF-36v2)
- Side effects
  - SAEs
  - discontinuation due to AEs
  - severe AEs (grade 3-4)
  - 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) and presented the outcome “AIDS-defining events (CDC class C events)” only as additional information (see Section 2.8.2.4.3 of the full dossier assessment).

Table 24 shows for which outcomes data were available in the study included.

Table 24: Matrix of outcomes – RCT, direct comparison: pretreated adults, EVG/COBI/FTC/TAF vs. continuation of ongoing treatment (FTC/TDF + third agent<sup>a</sup>)

Study	Outcomes									
	All-cause mortality	AIDS-defining events (CDC class C events)	Virologic response (snapshot) <sup>b</sup>	CD4 cell count <sup>b</sup>	Health status (EQ-5D VAS)	Health-related quality of life (SF-36)	SAEs	Discontinuation due to AEs	Severe AEs (grade 3-4) <sup>c</sup>	Further specific AEs <sup>d</sup>
292-0109 <sup>e</sup>	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
<p>a: EVG/COBI or EFV or ATV/co or ATV/r.</p> <p>b: Virologic response and CD4 cell count as surrogate outcomes for the composite outcome “AIDS-defining illnesses/death” are presented as additional information.</p> <p>c: Classification based on the “Gilead Sciences Grading Scale for Severity of Adverse Events and Laboratory Abnormalities”.</p> <p>d: The following events (MedDRA coding) are considered: nervous system disorders (SOC), psychiatric disorders (SOC), skin and subcutaneous tissue disorders (SOC), gastrointestinal disorders (SOC), and renal and urinary disorders (SOC).</p> <p>e: The information on data availability refers to the analysis date of 48 weeks.</p> <p>AE: adverse event; AIDS: acquired immunodeficiency syndrome; ATV/co: cobicistat-boosted atazanavir; ATV/r: ritonavir-boosted atazanavir; CD4: cluster of differentiation 4; CDC: Centers for Disease Control and Prevention; COBI: cobicistat; EFV: efavirenz; EQ-5D: European Quality of Life-5 Dimensions; EVG: elvitegravir; FTC: emtricitabine; MedDRA: Medical Dictionary for Regulatory Activities; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; SOC: System Organ Class; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; VAS: visual analogue scale; vs.: versus</p>										

### 2.5.2.2 Risk of bias

Table 25 shows the risk of bias for the relevant outcomes.

Table 25: Risk of bias at study and outcome level – RCT, direct comparison: pretreated adults, EVG/COBI/FTC/TAF vs. continuation of ongoing treatment (FTC/TDF + third agent<sup>a</sup>)

Study	Study level	Outcomes									
		All-cause mortality	AIDS-defining events (CDC class C events)	Virologic response (snapshot)	CD4 cell count	Health status (EQ-5D VAS)	Health-related quality of life (SF-36)	SAEs	Discontinuation due to AEs	Severe AEs (grade 3-4) <sup>e</sup>	Further specific AEs <sup>f</sup>
292-0109	L	L	H <sup>b</sup>	H <sup>c</sup>	L	H <sup>d</sup>	H <sup>d</sup>	L	H <sup>d</sup>	L	H <sup>d</sup>
<p>a: EVG/COBI or EFV or ATV/co or ATV/r.  b: It was not clear from the study documents whether the rating of an AE as an AIDS-defining event was blinded or unblinded.  c: Differential proportions of patients who discontinued treatment with a last measurement of &lt; 50 HIV-1 RNA copies/mL without blinding.  d: Due to lack of blinding in subjective recording of outcomes.  e: Classification based on the “Gilead Sciences Grading Scale for Severity of Adverse Events and Laboratory Abnormalities”.  f: The following events (MedDRA coding) are considered: nervous system disorders (SOC), psychiatric disorders (SOC), skin and subcutaneous tissue disorders (SOC), gastrointestinal disorders (SOC), and renal and urinary disorders (SOC).  AE: adverse event; AIDS: acquired immunodeficiency syndrome; ATV/co: cobicistat-boosted atazanavir; ATV/r: ritonavir-boosted atazanavir; CD4: cluster of differentiation 4; CDC: Centers for Disease Control and Prevention; COBI: cobicistat; EFV: efavirenz; EQ-5D: European Quality of Life-5 Dimensions; EVG: elvitegravir; FTC: emtricitabine; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; SOC: System Organ Class; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; VAS: visual analogue scale; vs.: versus</p>											

The risk of bias for the outcome “all-cause mortality” was rated as low. This deviates from the company’s assessment, which considered the outcome together with the side effects and rated the risk of bias for these outcomes as high due to the open-label study design.

The risk of bias for the outcome “virologic response” (snapshot) was rated as high due to the differential proportions of patients who discontinued treatment with a last measurement of < 50 HIV-1 RNA copies/mL (for detailed reasons, see Section 2.8.2.4.2 of the full dossier assessment). This assessment deviates from that of the company. Concurring with the company’s assessment, the risk of bias for CD4 cell count was rated as low.



The risk of bias for the patient-relevant outcomes “EQ-5D VAS” and “SF-36” was rated as high due to a lack of blinding in subjective recording of outcomes. This concurs with the company’s assessment.

Concurring with the company, the AE outcomes “discontinuation due to AEs” and “further specific AEs” were rated as having a high risk of bias due to the open-label study design. The risk of bias of the outcome “AIDS-defining events” was rated as high because it was not clear from the available study documents whether the rating of an AE as AIDS-defining event was blinded or unblinded.

The risk of bias of the AE outcomes “SAEs” and “severe AEs (grade 3-4)” was rated as low because it was not assumed that the recording of the severe/serious side effects is influenced by subjective expectations. This deviates from the company’s assessment, which assumed a high risk of bias also for severe/serious AEs due to the open-label study design.

### **2.5.2.3 Results**

The results on the comparison of EVG/COBI/FTC/TAF with continuation of ongoing treatment in pretreated adults with HIV-1 infection are summarized in Table 26 and Table 27. Where necessary, the data from the company’s dossier were supplemented by the Institute’s calculations.

Table 26: Results (mortality, morbidity and quality of life) – RCT, direct comparison: pretreated adults, EVG/COBI/FTC/TAF vs. continuation of ongoing treatment (FTC/TDF + third agent<sup>a</sup>)

Study Outcome category Outcome	EVG/COBI/FTC/TAF		EVG/COBI/FTC/TDF, EFV/FTC/TDF, ATV/co + FTC/TDF or ATV/r + FTC/TDF		EVG/COBI/FTC/TAF vs. EVG/COBI/FTC/TDF, EFV/FTC/TDF, ATV/co + FTC/TDF or ATV/r + FTC/TDF		
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value <sup>b</sup>		
292-0109 (48 weeks)							
Mortality							
All-cause mortality	959	4 (0.4)	477	0 (0)	4.48 [0.24; 83.06]; 0.175		
Morbidity							
AIDS-defining events (CDC class C)	959	26 (2.7) <sup>c</sup>	477	18 (3.8) <sup>c</sup>	0.72 [0.40; 1.30] <sup>d</sup> ; 0.310		
Additional information: surrogate outcome “virologic response” (HIV-1 RNA < 50 copies/mL)							
Snapshot <sup>e</sup>	959	932 (97.2)	477	444 (93.1)	1.04 [1.02; 1.07]; 0.002		
Imputation strategy <sup>f</sup>	959	(97.9)	477	(97.2)	1.01 [0.99; 1.03]; 0.413		
Missing = failure <sup>g</sup>	959	939 (97.9)	477	456 (95.6)	1.02 [1.00; 1.05] <sup>h</sup> ; 0.013		
Missing = excluded <sup>g</sup>	946	939 (99.3)	460	456 (99.1)	1.00 [0.99; 1.01] <sup>d</sup> ; 0.837		
	N <sup>i</sup>	Base- line values mean (SD)	Change at end of study mean <sup>j</sup> (SD)	N <sup>i</sup>	Base- line values mean (SD)	Change at end of study mean <sup>j</sup> (SD)	MD [95% CI]; p-value
Additional information: surrogate outcome: CD4 cell count/μL	958	701 (261.8)	34 (164.5)	476	689 (248.0)	23 (158.1)	11.0 <sup>k</sup> [−6.61; 28.61]; 0.221
EQ-5D VAS	876 <sup>l</sup>	87.9 (12.62)	−0.5 (12.38)	424 <sup>l</sup>	87.4 (13.81)	0.3 (15.15)	−0.80 [−2.46; 0.86]; 0.345
Health-related quality of life							
SF-36							
Physical sum score	907 <sup>l</sup>	55.1 (6.55)	−0.5 (5.88)	440 <sup>l</sup>	55.1 (6.61)	−0.5 (6.84)	0.00 [−0.74; 0.74]; > 0.999
Mental sum score	907 <sup>l</sup>	51.0 (9.84)	−0.2 (9.01)	440 <sup>l</sup>	51.2 (10.49)	−1.7 (9.26)	1.50 [0.45; 2.55]; 0.005
Hedges’ g 0.16 [0.05; 0.28]							

(continued)

Table 26: Results (mortality, morbidity and quality of life) – RCT, direct comparison: pretreated adults, EVG/COBI/FTC/TAF vs. continuation of ongoing treatment (FTC/TDF + third agent<sup>a</sup>) (continued)

<p>a: EVG/COBI or EFV or ATV/co or ATV/r.</p> <p>b: Institute's calculation, unconditional exact test (CSZ method according to [19]).</p> <p>c: In Module 4 A of the dossier, the company only stated 16 patients with (at least) one AIDS-defining event in the EVG/COBI/FTC/TAF arm, and 9 patients in the arm of continuation of ongoing treatment.</p> <p>d: Institute's calculation, asymptotic.</p> <p>e: Calculated with FDA snapshot algorithm, primary analysis of the company. Time window for the analysis: day 294 to 377; if results from several samples are available within the time window, the last measurement is relevant [12].</p> <p>f: Institute's calculation: For patients who discontinued treatment for reasons other than AEs or death and whose last HIV-1 RNA measurement was &lt; 50 copies/mL, it was assumed in both treatment arms that they achieved the outcome with the probability of the respective treatment arm without consideration of these patients. The variances were adapted according to the data-set re-sizing approach (approach W3 in [20]); p-value asymptotic.</p> <p>g: Time window for the analysis: week 48 ± 6 weeks. Based on other approval processes in the therapeutic indication [13], it is assumed that in the algorithms M = E and M = F, in contrast to the snapshot algorithm, the value that is closer to week 96 is relevant if several measurements are available within the analysis time window. There is no detailed description of the algorithms in the study documents.</p> <p>h: Institute's calculation, asymptotic. Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.</p> <p>i: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.</p> <p>j: LOCF analysis.</p> <p>k: Difference of adjusted mean values (95% CI, p-value) from an ANOVA of the ITT population; the adjusted mean value is the average change in CD4 cell count from baseline to week 48 in each study arm with the covariable "pretreatment" (EVG/COBI/FTC/TDF, EFV/FTC/TDF, ATV/co + FTC/TDF or ATV/r + FTC/TDF).</p> <p>l: Number of patients in the safety population, which includes all patients who were randomized and received at least one dose of the study treatment.</p> <p>AE: adverse event; AIDS: acquired immunodeficiency syndrome; ANOVA: analysis of variance; ATV/co: cobicistat-boosted atazanavir; ATV/r: ritonavir-boosted atazanavir; CDC: Centers for Disease Control and Prevention; CD4: cluster of differentiation 4; CI: confidence interval; COBI: cobicistat; CSZ: convexity, symmetry, z score; EFV: efavirenz; EVG: elvitegravir; EQ-5D: European Quality of Life-5 Dimensions; FDA: Food and Drug Administration; FTC: emtricitabine; HIV-1: human immunodeficiency virus type 1; ITT: intention to treat; LOCF: last observation carried forward; MD: mean difference; M = E: missing = excluded; M = F: missing = failure; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RNA: ribonucleic acid; RR: relative risk; SD: standard deviation; SF-36: Short Form (36) Health Survey; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; VAS: visual analogue scale; vs.: versus</p>
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Table 27: Results (side effects) – RCT, direct comparison: pretreated adults, EVG/COBI/FTC/TAF vs. continuation of ongoing treatment (FTC/TDF + third agent<sup>a</sup>)

Study Outcome category Outcome	EVG/COBI/FTC/TAF		EVG/COBI/FTC/TDF, EFV/FTC/TDF, ATV/co + FTC/TDF or ATV/r + FTC/TDF		EVG/COBI/FTC/TAF vs. EVG/COBI/FTC/TDF, EFV/FTC/TDF, ATV/co + FTC/TDF or ATV/r + FTC/TDF
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value <sup>b</sup>
<b>292-0109 (48 weeks)</b>					
AEs (supplementary information)	959	828 (86.3)	477	399 (83.6)	–
SAEs	959	65 (6.8)	477	35 (7.3)	0.92 [0.62; 1.37]; 0.736
Severe AEs (grade 3-4) <sup>c</sup>	959	84 (8.8)	477	54 (11.3)	0.77 [0.56; 1.07]; 0.128
Discontinuation due to AEs	959	9 (0.9)	477	12 (2.5)	0.37 [0.16; 0.88]; 0.019
Nervous system disorders	959	199 (20.8)	477	60 (12.6)	1.65 [1.26; 2.15]; < 0.001
Psychiatric disorders	959	161 (16.8)	477	94 (19.7)	0.85 [0.68; 1.07]; 0.182
Skin and subcutaneous tissue disorders	959	166 (17.3)	477	75 (15.7)	1.10 [0.86; 1.41]; 0.465
Gastrointestinal disorders	959	312 (32.5)	477	136 (28.5)	1.14 [0.96; 1.35]; 0.128
Renal and urinary disorders	959	71 (7.4)	477	34 (7.1)	1.04 [0.70; 1.54]; 0.891
a: EVG/COBI or EFV or ATV/co or ATV/r. b: Institute's calculation, unconditional exact test (CSZ method according to [19]). c: Classification based on the "Gilead Sciences Grading Scale for Severity of Adverse Events and Laboratory Abnormalities". AE: adverse event; AIDS: acquired immunodeficiency syndrome; ATV/co: cobicistat-boosted atazanavir; ATV/r: ritonavir-boosted atazanavir; CI: confidence interval; COBI: cobicistat; CSZ: convexity, symmetry, z score; EFV: efavirenz; EVG: elvitegravir; FTC: emtricitabine; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; vs.: versus					

Only one study with a low risk of bias was available for the assessment of the added benefit of EVG/COBI/FTC/TAF in comparison with continuation of ongoing treatment (292-0109). Study 292-0109 did not meet the particular requirements placed on the derivation of proof, e.g. of an added benefit, from a single study [1]. Hence at most indications, e.g. of an added benefit, can be derived from the data. This concurs with the company's assessment.

## Mortality

### All-cause mortality

There was no statistically significant difference between the treatment groups for the outcome "all-cause mortality". This resulted in no hint of an added benefit of EVG/COBI/FTC/TAF in

comparison with continuation of ongoing treatment; an added benefit for the outcome “all-cause mortality” is therefore not proven.

This concurs with the company’s assessment.

### **Morbidity**

#### ***AIDS-defining events (CDC class C events); supplementary consideration of the surrogate outcomes “virologic response” and “CD4 cell count”***

There was no statistically significant difference between the treatment groups for the outcome “AIDS-defining events”.

A statistically significant difference in favour of EVG/COBI/FTC/TAF was shown for virologic response (snapshot algorithm). It is possible, however, that this result was influenced by the algorithm used for the analysis of virologic response (see Section 2.8.2.2 of the full dossier assessment). For this reason, results of the sensitivity analyses presented in the CSR were additionally considered using other algorithms (missing = failure and missing = excluded). These analyses resulted in discrepant results regarding statistical significance; these analyses did therefore not support the statistically significant effect presented by the company.

However, all 3 analyses (snapshot, missing = failure and missing = excluded) may be biased if the proportions of patients without virologic data in the analysis time window who had discontinued treatment and whose last measurement was < 50 HIV-1 RNA copies/mL differed between the study arms. In the analyses, these patients were not rated as patients with virologic response (snapshot, missing = failure) or excluded from the analyses (missing = excluded). The bias can be caused by not rating these patients as responders although they had responded to treatment at the last time point of measurement (see Section 2.8.2.2 of the full dossier assessment).

The proportion of patients without virologic data in the period of analysis whose last measurement was < 50 HIV-1 RNA copies/mL and who discontinued treatment for reasons other than AEs or death differed notably between the treatment arms in the snapshot algorithm (7/959 [0.7%] in the intervention arm, 20/477 [4.2%] in the comparator arm). Hence an imputation strategy was used for the outcome “virologic response” to check the robustness of the effect. For this purpose, the values for patients without virologic data in the period of analysis was imputed as follows: for patients whose last measurement before the 48-week period of analysis was < 50 HIV-1 RNA copies/mL and who discontinued treatment for reasons other than AEs or death, it was assumed that the response rates corresponded to the response rates observed in the treatment arms. The result of the imputation strategy showed no statistically significant difference between the treatment arms. Hence the result on virologic response with the snapshot algorithm was not robust and was biased by events such as treatment discontinuation of patients with a last measurement of < 50 HIV1 RNA copies/mL.

Likewise, the analysis of patients with virologic failure, considered meaningful in pretreated patients, showed no statistically significant difference between the treatment groups (EVG/COBI/FTC/TAF: 25 patients [2.6%], and continuation of ongoing treatment: 9 patients [1.9%]; relative risk [RR]: 1.38 [0.65; 2.94]; 0.450).

In summary, the result on the outcome “virologic response” is not robust.

No statistically significant difference between the treatment arms was shown for change in CD4 cell count.

In the overall consideration of the results, there was therefore no hint of an added benefit of EVG/COBI/FTC/TAF in comparison with continuation of ongoing treatment for the outcome “AIDS-defining events”; an added benefit is therefore not proven.

This assessment deviates from that of the company in several aspects. The company considered the outcomes “virologic response” and “CD4 cell count” separately. Based on the results of the snapshot algorithm, the company saw a statistically significant difference in favour of EVG/COBI/FTC/TAF for the outcome “virologic response”. It derived an added benefit for this outcome, which, from the company’s point of view, had a different probability in the USA population (“hint”) and in the ex-USA population (“indication”). The company presented no sensitivity analyses for this outcome.

The company also saw no statistically significant difference between the treatment arms for the outcome “CD4 cell count”.

The company presented the outcome “AIDS-defining events” only as additional information because, from the company’s point of view, the outcome is no informative parameter for the assessment of the efficacy and the treatment (see Section 2.8.2.4.3 of the full dossier assessment). In addition, the company discussed the results for the outcome “AIDS-defining events” on the basis of a deviating operationalization.

### ***Health status (EQ-5D VAS)***

No statistically significant difference between the treatment groups was shown for the outcome “health status measured with the EQ-5D VAS”. This resulted in no hint of an added benefit of EVG/COBI/FTC/TAF in comparison with continuation of ongoing treatment; an added benefit is therefore not proven.

This concurs with the company’s assessment.

### **Health-related quality of life**

#### ***SF-36 – physical sum score***

No statistically significant difference between the treatment groups was shown for the outcome “physical sum score of the SF-36”. This resulted in no hint of an added benefit of

EVG/COBI/FTC/TAF in comparison with continuation of ongoing treatment; an added benefit is therefore not proven.

This concurs with the company's assessment.

### ***SF-36 – mental sum score***

A statistically significant difference in favour of EVG/COBI/FTC/TAF was shown for the mental sum score of the SF-36. The SMD in the form of Hedges' g was considered to check the relevance of the result [1]. The 95% CI was not completely above the irrelevance threshold of 0.2. It can therefore not be inferred that the effect is relevant. This resulted in no hint of an added benefit of EVG/COBI/FTC/TAF in comparison with continuation of ongoing treatment; an added benefit is therefore not proven.

This concurs with the company's assessment.

## **Side effects**

### ***Serious adverse events***

There was no statistically significant difference between the treatment groups for the outcome "SAEs". This resulted in no hint of greater or lesser harm of EVG/COBI/FTC/TAF in comparison with continuation of ongoing treatment for the outcome "SAEs"; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

### ***Severe adverse events (grade 3-4)***

No statistically significant difference between the treatment groups was shown for the outcome "severe AEs (grade 3-4)".

However, there was an indication of an effect modification by the characteristic "ethnicity" (Caucasian/non-Caucasian) for this outcome (see Section 2.5.2.4). For Caucasian patients, there was a hint of a lesser harm of EVG/COBI/FTC/TAF for the outcome "severe AEs (grade 3-4)". For non-Caucasian patients, there was no hint of greater or lesser harm of EVG/COBI/FTC/TAF in comparison with continuation of ongoing treatment; greater or lesser harm for this patient group is therefore not proven.

This concurs with the company's assessment.

### ***Discontinuation due to adverse events***

A statistically significant difference in favour of EVG/COBI/FTC/TAF was shown for the outcome "discontinuation due to AEs". There was an uncertainty for this outcome, however, because patients with indication for a treatment switch might have been included in the study (see Section 2.8.2.4.1 of the full dossier assessment).

Considering the rate of patients with treatment discontinuation (of any cause), it was shown in study 292-0109 already after 4 weeks of treatment that fewer patients in the intervention arm than in the comparator arm tended to discontinue treatment (0.1% vs. 1.0%). In comparison, the difference for the outcome “discontinuation due to AEs” between the treatment arms was only 1.6%. It is therefore not excluded that the statistically significant effect in discontinuation due to AEs was due to patients who had experienced burdensome side effects under their prior therapy already before the start of the study. The result for the outcome “discontinuation due to AEs” was therefore overall considered to be not interpretable with certainty. Hence greater or lesser harm for this outcome is not proven.

This deviates from the company’s assessment, which derived a hint of an added benefit on the basis of the statistically significant difference in favour of EVG/COBI/FTC/TAF.

### ***Nervous system disorders***

A statistically significant difference to the disadvantage of EVG/COBI/FTC/TAF was shown for the outcome “nervous system disorders”.

However, there was proof of an effect modification by the characteristic “sex” for this outcome (see Section 2.5.2.4). For men, there was a hint of greater harm from EVG/COBI/FTC/TAF in comparison with continuation of ongoing treatment for the outcome “nervous system disorders”. For women, there was no hint of greater or lesser harm of EVG/COBI/FTC/TAF in comparison with continuation of ongoing treatment; greater or lesser harm in this patient group is therefore not proven.

This concurs with the company’s assessment.

### ***Psychiatric disorders***

There was no statistically significant difference between the treatment groups for the outcome “psychiatric disorders”.

This resulted in no hint of greater or lesser harm of EVG/COBI/FTC/TAF in comparison with continuation of ongoing treatment for the outcome “psychiatric disorders”; greater or lesser harm is therefore not proven.

This concurs with the company’s assessment.

### ***Skin and subcutaneous tissue disorders***

There was no statistically significant difference between the treatment groups for the outcome “skin and subcutaneous tissue disorders”. This resulted in no hint of greater or lesser harm of EVG/COBI/FTC/TAF in comparison with continuation of ongoing treatment for the outcome “skin and subcutaneous tissue disorders”; greater or lesser harm is therefore not proven.

This concurs with the company’s assessment.



***Gastrointestinal disorders***

There was no statistically significant difference between the treatment groups for the outcome “gastrointestinal disorders”. This resulted in no hint of greater or lesser harm of EVG/COBI/FTC/TAF in comparison with continuation of ongoing treatment for the outcome “gastrointestinal disorders”; greater or lesser harm is therefore not proven.

This concurs with the company’s assessment.

***Renal and urinary disorders***

There was no statistically significant difference between the treatment groups for the outcome “renal and urinary disorders”. This resulted in no hint of greater or lesser harm of EVG/COBI/FTC/TAF in comparison with continuation of ongoing treatment for the outcome “renal and urinary disorders”; greater or lesser harm is therefore not proven.

This concurs with the company’s assessment.

**2.5.2.4 Subgroups and other effect modifiers**

In order to uncover possible differences between patient groups, the following subgroup characteristics were investigated:

- age ( $< 50/\geq 50$ )
- sex (men/women)
- ethnicity (Caucasian/non-Caucasian)
- type of antiretroviral pretreatment (EVG/COBI/FTC/TDF versus EFV/FTC/TDF versus ATV/booster + FTC/TDF)

The company presented subgroup analyses for most outcomes included. The company conducted no subgroup analyses on the outcome “all-cause mortality” because it did not regard the consideration of subgroups to be meaningful because of the low number of events in the studies included. The company also conducted no subgroup analyses for the outcome “AIDS-defining events” because it considered this outcome in its assessment only as additional information.

Only the results on subgroups and outcomes with at least an indication of an interaction between treatment effect and subgroup characteristic and with statistically significant results and relevant effects in at least one subgroup are presented in this assessment.

The prerequisite for proof of different subgroup effects is a statistically significant interaction test ( $p < 0.05$ ). A p-value of  $\geq 0.05$  and  $< 0.2$  provides an indication of an effect modification.

The subgroup analyses on the direct comparison of EVG/COBI/FTC/TAF with continuation of ongoing treatment in pretreated adults with HIV-1 infection are summarized in Table 28. Where necessary, the data from the dossier were supplemented by the Institute's calculations.

Table 28: Subgroups (side effects) – RCT, direct comparison: pretreated adults, EVG/COBI/FTC/TAF vs. continuation of ongoing treatment (FTC/TDF + third agent<sup>a</sup>)

Study Outcome Characteristic Subgroup	EVG/COBI/FTC/TAF		EVG/COBI/FTC/TDF, EFV/FTC/TDF, ATV/co + FTC/TDF or ATV/r + FTC/TDF		EVG/COBI/FTC/TAF vs. EVG/COBI/FTC/TDF, EFV/FTC/TDF, ATV/co + FTC/TDF or ATV/r + FTC/TDF	
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]	p-value
<b>292-0109 (48 weeks)</b>						
Severe AEs (grade 3-4) <sup>c</sup>						
Ethnicity						
Caucasian	651	53 (8.1)	314	40 (12.7)	0.64 [0.43; 0.94]	0.024
Non-Caucasian	306	31 (10.1)	162	14 (8.6)	1.17 [0.64; 2.14]	0.605
					Interaction:	0.097 <sup>b</sup>
Nervous system disorders						
Sex						
Men	856	177 (20.7)	427	48 (11.2)	1.84 [1.37; 2.48]	< 0.001
Women	103	22 (21.4)	50	12 (24.0)	0.89 [0.48; 1.65]	0.711
					Interaction:	0.038 <sup>b</sup>
a: EVG/COBI or EFV or ATV/co or ATV/r. b: p-value based on Q test. c: Classification based on the “Gilead Sciences Grading Scale for Severity of Adverse Events and Laboratory Abnormalities”. AE: adverse event; ATV/co: cobicistat-boosted atazanavir; ATV/r: ritonavir-boosted atazanavir; CI: confidence interval; COBI: cobicistat; EFV: efavirenz; EVG: elvitegravir; FTC: emtricitabine; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; vs.: versus						

## Side effects

### Severe adverse events (grade 3-4)

The subgroup analysis on the outcome “severe AEs (grade 3-4)” showed an indication of an effect modification by the characteristic “ethnicity” (Caucasian/non-Caucasian).

A statistically significant difference in favour of EVG/COBI/FTC/TAF was shown for Caucasians. For this outcome, this resulted in a hint of lesser harm from EVG/COBI/FTC/TAF in comparison with continuation of ongoing treatment in Caucasians. As the patients of Caucasian origin represent the main ethnicity for the health care area of the present

benefit assessment, the subgroup of the other ethnicities were not considered further in the present assessment.

This concurs with the company's assessment.

### ***Nervous system disorders***

The subgroup analysis on the outcome “nervous system disorders” showed proof of an effect modification by the characteristic “sex”.

A statistically significant difference to the disadvantage of EVG/COBI/FTC/TAF was shown for men. For this outcome, this resulted in a hint of greater harm from EVG/COBI/FTC/TAF in comparison with continuation of ongoing treatment in men.

For women, there was no statistically significant difference between the treatment groups. This resulted in no hint of greater or lesser harm of EVG/COBI/FTC/TAF in comparison with continuation of ongoing treatment; greater or lesser harm for women is therefore not proven.

This concurs with the company's assessment.

## **2.5.3 Extent and probability of added benefit**

The derivation of extent and probability of added benefit for pretreated adults without indication for a treatment switch at outcome level is shown below, taking into account the various 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.

### **2.5.3.1 Assessment of added benefit at outcome level**

The data presented in Section 2.5.2 showed no hint of an added benefit or greater or lesser harm for any outcome on the basis of the total study population. Under consideration of effect modifications for ethnicity and sex however, there was a hint of lesser harm for the outcome “severe AEs (grade 3-4)” for Caucasian patients and a hint of greater harm for men for the outcome “nervous system disorders”. The extent of the respective harm at outcome level was estimated from these results (see Table 29).

Table 29: Extent of added benefit at outcome level: EVG/COBI/FTC/TAF vs. continuation of ongoing treatment (FTC/TDF + third agent<sup>a</sup>)

Outcome category Outcome Effect modifier Subgroup	EVG/COBI/FTC/TAF vs. EVG/COBI/FTC/TDF, EFV/FTC/TDF, ATV/co + FTC/TDF or ATV/r + FTC/TDF Proportion of events or mean Effect estimates [95% CI]; p-value Probability <sup>b</sup>	Derivation of extent <sup>c</sup>
<b>Mortality</b>		
All-cause mortality	0.4% vs. 0% RR: 4.48 [0.24; 83.06] p = 0.175	Lesser benefit/added benefit not proven
<b>Morbidity</b>		
AIDS-defining events	2.7% vs. 3.8% 0.72 [0.40; 1.30] p = 0.310	Lesser benefit/added benefit not proven
Supplementary information: Virologic response	result not robust <sup>d</sup>	
CD4 cell count	mean (cells/μL): 34 vs. 23 MD: 11.0 [-6.61; 28.61] p = 0.221	
Health status (EQ-5D VAS)	mean: -0.5 vs. 0.3 MD: -0.80 [-2.46; 0.86]; p = 0.345	Lesser benefit/added benefit not proven
<b>Health-related quality of life</b>		
SF-36		
Physical sum score	mean: -0.5 vs. -0.5 MD: 0.00 [-0.74; 0.74] p = 0.999	Lesser benefit/added benefit not proven
Mental sum score	mean: -0.2 vs. -1.7 MD: 1.50 [0.45; 2.55] p = 0.005 Hedges' g 0.16 [0.05; 0.28] <sup>e</sup>	Lesser benefit/added benefit not proven

(continued)

Table 29: Extent of added benefit at outcome level: EVG/COBI/FTC/TAF vs. continuation of ongoing treatment (FTC/TDF + third agent<sup>a</sup>) (continued)

Outcome category Outcome Effect modifier Subgroup	EVG/COBI/FTC/TAF vs. EVG/COBI/FTC/TDF, EFV/FTC/TDF, ATV/co + FTC/TDF or ATV/r + FTC/TDF Proportion of events or mean Effect estimates [95% CI]; p-value Probability <sup>b</sup>	Derivation of extent <sup>c</sup>
<b>Side effects</b>		
Serious adverse events	6.8% vs. 7.3% RR: 0.92 [0.62; 1.37] p = 0.736	Greater/lesser harm not proven
Severe AEs (grade 3-4)	8.8% vs. 11.3% RR: 0.77 [0.56; 1.07] p = 0.128	
Ethnicity		
Caucasian	8.1% vs. 12.7% RR: 0.64 [0.43; 0.94] p = 0.024 probability: “hint”	Outcome category: serious/severe side effects $1.0 \leq CI_u < 0.9$ lesser harm, extent: “minor”
Non-Caucasian	10.1% vs. 8.6% RR: 1.17 [0.64; 2.14] p = 0.605	Greater/lesser harm not proven
Discontinuation due to adverse events	Results not interpretable	Greater/lesser harm not proven
<b>Nervous system disorders</b>		
Sex		
Men	20.7% vs. 11.2% RR: 1.84 [1.37; 2.48] RR <sup>f</sup> : 0.54 [0.40; 0.73] p = < 0.001 probability: “hint”	Outcome category: non-serious/non-severe side effects $CI_u < 0.8$ greater harm; extent: “considerable”
Women	21.4% vs. 24.0% RR: 0.89 [0.48; 1.65] p = 0.711	Greater/lesser harm not proven
Psychiatric disorders	16.8% vs. 19.7% RR: 0.85 [0.68; 1.07] p = 0.182	Greater/lesser harm not proven
Skin and subcutaneous tissue disorders	17.3% vs. 15.7% RR: 1.10 [0.86; 1.41] p = 0.465	Greater/lesser harm not proven
Gastrointestinal disorders	32.5% vs. 28.5% RR: 1.14 [0.96; 1.35] p = 0.128	Greater/lesser harm not proven
Renal and urinary disorders	7.4% vs. 7.1% RR: 1.04 [0.70; 1.54] p = 0.891	Greater/lesser harm not proven

(continued)

Table 29: Extent of added benefit at outcome level: EVG/COBI/FTC/TAF vs. continuation of ongoing treatment (FTC/TDF + third agent<sup>a</sup>) (continued)

a: EVG/COBI or EFV or ATV/co or ATV/r.
b: Probability given if statistically significant differences are present.
c: Estimations of effect size are made depending on the outcome category with different limits based on the CI <sub>u</sub> .
d: See results of the sensitivity analyses in Section 2.5.2.3.
e: Added benefit assumed with lower CI limits > 0.2.
f: Institute's calculation: reversed direction of effect to enable use of limits to derive the extent of the added benefit.
AE: adverse event; AIDS: acquired immunodeficiency syndrome; ATV/co: cobicistat-boosted atazanavir; ATV/r: ritonavir-boosted atazanavir; CD4: cluster of differentiation 4; CI: confidence interval; CI <sub>u</sub> : upper limit of confidence interval; COBI: cobicistat; EFV: efavirenz; EQ-5D: European Quality of Life-5 Dimensions; EVG: elvitegravir; FTC: emtricitabine; HIV-1: human immunodeficiency virus type 1; MD: mean difference; RR: relative risk; SF-36: Short Form (36) Health Survey; SAE: serious adverse event; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; VAS: visual analogue scale; vs.: versus

### 2.5.3.2 Overall conclusion on added benefit

Table 30 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 30: Positive and negative effects from the assessment of EVG/COBI/FTC/TAF compared with continuation of ongoing treatment (FTC/TDF + third agent<sup>a</sup>)

Positive effects	Negative effects
Serious/severe side effects <ul style="list-style-type: none"> <li>Severe AEs (grade 3-4) <ul style="list-style-type: none"> <li>ethnicity (Caucasian): hint of lesser harm – extent: “minor”</li> </ul> </li> </ul>	Non-serious/non-severe side effects <ul style="list-style-type: none"> <li>Nervous system disorders <ul style="list-style-type: none"> <li>sex (men): hint of greater harm – extent “considerable”</li> </ul> </li> </ul>
a: EVG/COBI or EFV or ATV/co or ATV/r. AE: adverse event; ATV/co: cobicistat-boosted atazanavir; ATV/r: ritonavir-boosted atazanavir; COBI: cobicistat; EFV: efavirenz; EVG: elvitegravir; FTC: emtricitabine; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; vs.: versus	

Overall, one positive effect and one negative effect remain.

For severe AEs, there was a hint of lesser harm (extent: “minor”) in Caucasians. However, since patients of Caucasian origin represent the main ethnicity for the health care area of the present benefit assessment, no separate balancing for Caucasians and non-Caucasians was conducted. There was a hint of greater harm (extent: “considerable”) for the outcome “nervous system disorders”, which only applied to men. This led to a separate balancing of the added benefit in men and women.

For women, only a positive effect in the category “severe/serious side effects” remained so that a hint of a minor added benefit was derived for women.

For men, a positive effect in the category “severe/serious side effects” and a negative effect in the category “non-serious/non-severe side effects”, each with the same certainty of results (“hint”), remain. The extent of the positive effect for the outcome “severe AEs (grade 3-4)” was only minor and was therefore outweighed by considerable greater harm for the outcome of “(non-serious) nervous system disorders”. Overall, there was therefore no hint of an added benefit for men; an added benefit is not proven.

In summary, there was a hint of a minor added benefit of EVG/COBI/FTC/TAF in comparison with the ACT for pretreated HIV-1 infected women (without indication for a treatment switch), and no hint of an added benefit for pretreated HIV-1 infected men (without indication for a treatment switch); an added benefit for men is therefore not proven.

No data were available for pretreated HIV-infected patients with indication for a treatment switch. There was no hint of an added benefit of EVG/COBI/FTC/TAF in comparison with the ACT for this patient population; an added benefit for these patients is not proven.

This assessment deviates from that of the company, which derived an indication of a minor added benefit for all pretreated adults and did not distinguish between patients with and without indication for a treatment switch.

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

#### **2.5.4 List of included studies**

##### **292-0109**

Gilead Sciences. Open-label study to evaluate switching from a tdf-containing combination regimen to a TAF-containing combination single tablet regimen (STR) in virologically-suppressed, HIV-1 positive subjects: full text view [online]. In: ClinicalTrials.gov. 03.2015 [accessed: 20.10.2015]. URL: <https://clinicaltrials.gov/ct2/show/study/NCT01815736>.

Gilead Sciences. A phase 3, open-label study to evaluate switching from a TDF-containing combination regimen to a TAF-containing combination single tablet regimen (STR) in virologically-suppressed, HIV-1 positive subjects [online]. In: EU Clinical Trials Register. [Accessed: 20.10.2015]. URL: [https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract\\_number:2012-005114-20](https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-005114-20).

Gilead Sciences. A phase 3, open-label study to evaluate switching from a TDF-containing combination regimen to a TAF-containing combination single tablet regimen (STR) in virologically-suppressed, HIV-1 positive subjects: study GS-US-292-0109; week 48 final (all subjects) clinical study report [unpublished]. 2014.

Gilead Sciences. A phase 3, open-label study to evaluate switching from a TDF-containing combination regimen to a TAF-containing combination single tablet regimen (STR) in virologically-suppressed, HIV-1 positive subjects: study GS-US-292-0109; week 96; Zusatzanalysen [unpublished]. 2015.



## **2.6 Research question 4: pretreated adolescents 12 years of age and older**

### **2.6.1 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 list on EVG/COBI/FTC/TAF (status: 15 October 2015)
- bibliographical literature search on EVG/COBI/FTC/TAF (last search on 19 October 2015)
- search in trial registries for studies on EVG/COBI/FTC/TAF (last search on 20 October 2015)

To check the completeness of the study pool:

- search in trial registries for studies on EVG/COBI/FTC/TAF (last search on 13 January 2016)

No relevant study was identified from the company's search and the check.

### **2.6.2 Results on added benefit**

No data for the assessment of the added benefit were available for pretreated adolescents. Hence an added benefit of EVG/COBI/FTC/TAF in comparison with the ACT for this population is not proven.

### **2.6.3 Extent and probability of added benefit**

As the company presented no data for the assessment of the added benefit for pretreated adolescents, an added benefit of EVG/COBI/FTC/TAF is not proven for this population.

## 2.7 Extent and probability of added benefit – summary

The result of the assessment of the added benefit of EVG/COBI/FTC/TAF in comparison with the ACT is summarized in Table 31.

Table 31: EVG/COBI/FTC/TAF: extent and probability of added benefit

Research question	Therapeutic indication	ACT <sup>a</sup>	Sub-group	Extent and probability of added benefit
1	Treatment-naïve adults	<b>Efavirenz</b> in combination with 2 nucleoside/nucleotide analogues ( <b>tenofovir disoproxil plus emtricitabine</b> or abacavir plus lamivudine)		Hint of lesser benefit
2	Treatment-naïve adolescents <sup>b</sup>	Efavirenz in combination with abacavir and lamivudine		Added benefit not proven
3	Pretreated adults (without indication for a treatment switch)	Individual antiretroviral 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 side effects.	Men	Added benefit not proven
			Women	Hint of minor added benefit
	Pretreated adults (with indication for a treatment switch)			Added benefit not proven
4	Pretreated adolescents <sup>b</sup>			Added benefit not proven
<p>a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.</p> <p>b: 12 years of age and older and with a body weight of at least 35 kg.</p> <p>ACT: appropriate comparator therapy; COBI: cobicistat; EVG: elvitegravir; FTC: emtricitabine; G-BA: Federal Joint Committee; TAF: tenofovir alafenamide</p>				

There is a hint of lesser benefit of EVG/COBI/FTC/TAF in comparison with the ACT for **treatment-naïve adults** with HIV-1 infection. This deviates from the company's assessment, which derived proof of a minor added benefit for treatment-naïve patients.

There was a hint of a minor added benefit for **pretreated HIV-1 infected women (without indication for a treatment switch)**. An added benefit is not proven for pretreated HIV-1 infected **men (without indication for a treatment switch)**.

No data for the assessment of the added benefit were available for **pretreated patients with indication for a treatment switch**. Hence an added benefit of EVG/COBI/FTC/TAF in comparison with the ACT for this population is not proven. This deviates from the company's approach, which derived an indication of minor added benefit. The company neither distinguished between patients with and without indication for a treatment switch, nor considered the effect modification by sex.

Concurring with the results of the benefit assessment, the company derived no added benefit for **treatment-naïve or pretreated adolescents** (12 years of age and older and with a body weight of at least 35 kg).

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

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Please see full dossier assessment for full reference list.

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