IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A16-30

Emtricitabine/ tenofovir alafenamide (HIV infection) –

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

Extract

[1] Translation of Sections 2.1 to 2.7 of the dossier assessment *Emtricitabin/Tenofoviralafenamid (HIV-Infektion) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.1; Status: 29 September 2016). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:

Institute for Quality and Efficiency in Health Care

Topic:

Emtricitabine/tenofovir alafenamide (HIV infection) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:

Federal Joint Committee

Commission awarded on:

13 May 2016

Internal Commission No.:

A16-30

Address of publisher:

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice:

- Mark Oette, Augustinerinnen Hospital, Cologne, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

IQWiG employees involved in the dossier assessment[2]:

- Stefan Kobza
- Lars Beckmann
- Susanne Haag
- Marco Knelangen
- Petra Kohlepp
- Sarah Mostardt
- Beate Wieseler
- Natalia Wolfram
- Min Zhou

Keywords: emtricitabine, tenofovir alafenamide, HIV infections, benefit assessment

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

Table of contents

List of tables[3]

Page

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
ATV	atazanavir
ATV/co	cobicistat-boosted atazanavir
ATV/r	ritonavir-boosted atazanavir
CD4	cluster of differentiation 4
CDC	Centers for Disease Control and Prevention
COBI	cobicistat
DRV	darunavir
DRV/r	ritonavir-boosted darunavir
DTG	dolutegravir
EFV	efavirenz
eGFR	estimated glomerular filtration rate
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
HLGT	High Level Group Term
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LPV/r	ritonavir-boosted lopinavir
MedDRA	Medical Dictionary for Regulatory Activities
MRC	maraviroc
NRTI	nucleoside reverse transcriptase inhibitor
PI/b	boosted protease inhibitor (boosted with ritonavir or cobicistat)
RAL	raltegravir
RCT	randomized controlled trial
RNA	ribonucleic acid
RPV	rilpivirine
RR	relative risk
SAE	serious adverse event

Abbreviation	Meaning
SF-36	Short Form (36) Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
SMQ	Standardized MedDRA Query
SPC	Summary of Product Characteristics
STB	Stribild (fixed combination of EVG/COBI/FTC/TDF)
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil
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 emtricitabine/tenofovir alafenamide (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 13 May 2016.

Research question

The aim of this report was to assess the added benefit of 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). FTC/TAF is used in combination with other antiretroviral drugs.

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 FTC/TAF

Research question	Therapeutic indication	ACT specified by the G-BA
1	Treatment-naive adults	NRTI backbone: tenofovir disoproxil plus emtricitabine or abacavir plus lamivudine In combination with NRTI backbone, third combination partners with the same active agent (efavirenz or rilpivirine or dolutegravir) were to be used with the same distribution across the study arms.
2	Treatment-naive adolescents[a]	Efavirenz in combination with abacavir plus 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[a]	
a: 12 years of age and older and with a body weight of at least 35 kg. ACT: appropriate comparator therapy; FTC: emtricitabine; G-BA: Federal Joint Committee; NRTI: nucleoside reverse transcriptase inhibitor; TAF: tenofovir alafenamide		

For research question 1 (treatment-naive adults), the company generally followed the ACT specified by the G-BA. The company also considered elvitegravir/cobicistat (EVG/COBI) in addition to the third combination partners specified by the G-BA. This expansion of the ACT was not followed because, in particular, the company did not prove the (at least) equivalence of EVG/COBI with one of the 3 third combination partners specified by the G-BA (efavirenz

[EFV] or rilpivirine or dolutegravir). The present assessment was conducted in comparison with the G-BA's ACT.

For research question 3 (pretreated adults), the company followed the G-BA's specification of the ACT. Within this research question, the company distinguished the following patient groups:

- For patients with indication for a treatment switch (for example 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 continuation of ongoing treatment.

This approach of the company was followed.

The company did not consider research questions 2 and 4 (treatment-naive or pretreated adolescents 12 years of age and older) in its dossier. This approach was not accepted. The present assessment was conducted in comparison with the G-BA's ACT.

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-naive adults

The company presented no relevant data for the assessment of the added benefit of FTC/TAF in comparison with the ACT for research question 1. This resulted in no hint of an added benefit of FTC/TAF in comparison with the ACT. An added benefit is therefore not proven.

Research question 3: pretreated adults

Study pool and study characteristics

The studies GS-US-292-0109 (hereinafter referred to as "292-0109") and GS-US-311-1089 (hereinafter referred to as "311-1089") were included in the benefit assessment.

Study 292-0109

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/tenofovir disoproxil (TDF) backbone therapy and a third combination partner were enrolled in the study. Possible third combination partners were EFV, EVG/COBI, and COBI-boosted or ritonavir-boosted atazanavir (ATV). Randomization was stratified by pretreatment (EVG/COBI/FTC/TDF, EFV/FTC/TDF or ATV/booster/FTC/TDF).

Only the stratum of the study in which only the backbone therapy (but not the third combination partner) was switched in the intervention arm in comparison with the comparator arm was relevant for the benefit assessment. Only the Stribild (STB) stratum was therefore used from the 292-0109 study. In this stratum, ongoing treatment (EVG/COBI/FTC/TDF) was continued in the comparator arm; in the intervention arm, only the nucleoside reverse transcriptase inhibitor (NRTI) backbone therapy was switched to FTC/TAF in comparison with ongoing treatment; the third combination partner (EVG/COBI) remained identical in comparison with ongoing treatment. In the STB stratum, a total of 306 patients were included in the intervention arm, and 153 patients in the comparator arm. The antiretroviral agents used 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, study 292-0109 could be used for the assessment of the added benefit in treatment-naive 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 adverse events (AEs)". It was not possible to assess the added benefit of FTC/TAF for pretreated adults with indication for a treatment switch on the basis of study 292-0109.

The planned treatment duration in the study was 96 weeks. However, at the time point of the benefit assessment, only results on the period of analysis of 48 weeks were available. These were used in the present assessment.

Study 311-1089

The 311-1089 study was an active-controlled randomized trial with patients with prior antiretroviral therapy. Virologically suppressed adults who had been pretreated with FTC/TDF and a third combination partner were included in the study. Regimens with boosted protease inhibitors (PI/b) (boosted with ritonavir: ATV/ritonavir, lopinavir/ritonavir or darunavir/ritonavir) or other regimens (EFV, rilpivirine, nevirapine, raltegravir, dolutegravir, or maraviroc) were used as third combination partners. Randomization was stratified by the previous third combination partner (PI/b regimen or other regimens). Administration of FTC/TAF or FTC/TDF was blinded for patient and outcome assessor.

Dosage for the NRTI backbone therapies (FTC/TAF and FTC/TDF) was in compliance with their approval. According to the Summary of Product Characteristics (SPC), the dosage of TAF in the intervention arm of the study depended on the drug class of the third combination partner: The dosage was 10 mg in combination with PI/b regimens; it was 25 mg in combination with other regimens.

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 311-1089. Hence, study 311-1089 could be used for the assessment of the added benefit in treatment-naive adults without indication for a treatment switch. A conclusive check whether the study also included a small proportion of patients with necessary treatment switch due to side effects was not possible on the basis of the documents presented by the company, however. Hence some uncertainty remained regarding this issue. This uncertainty had to be considered in the interpretation of the results on the outcome "discontinuation due to AEs". It was not possible to assess the added benefit of FTC/TAF for pretreated adults with indication for a treatment switch on the basis of study 311-1089.

The planned treatment duration in the study was 96 weeks. However, at the time point of the benefit assessment, only results on the period of analysis of 48 weeks were available. These were used in the present assessment.

Risk of bias

The risk of bias at study level was classed as low for both studies. The risk of bias for both studies was rated as low for the following outcomes: cluster of differentiation 4 (CD4) cell count; serious AEs (SAEs), severe AEs (grade 3-4), and bone fractures. The risk of bias was rated as high for study 292-0109 and as low for study 311-1089 for the following outcomes: acquired immunodeficiency syndrome (AIDS)-defining events, virologic response (snapshot), discontinuation due to AEs, and further specific AEs (nervous system disorders, psychiatric disorders, skin and subcutaneous tissue disorders, gastrointestinal disorders and renal and urinary disorders). The risk of bias for both studies was rated as high for the outcomes "health status" (European Quality of Life-5 Dimensions visual analogue scale [EQ-5D VAS]) and "health-related quality of life" (Short Form (36) Health Survey [SF-36]).

Results

Mortality

- All-cause mortality

The meta-analysis showed no statistically significant difference between the treatment groups for the outcome "all-cause mortality". For all-cause mortality, this resulted in no hint of an added benefit of 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 (Centers for Disease Control and Prevention [CDC] class C events); supplementary consideration of the surrogate outcomes "virologic response" and "CD4 cell count"

The meta-analysis showed no statistically significant difference between the treatment groups for the outcome "AIDS-defining events".

The meta-analysis also showed no statistically significant differences between the treatment groups for virologic response (snapshot) and the change in CD4 cell count.

Overall, there was therefore no hint of an added benefit of 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)

The meta-analysis showed no statistically significant difference between the treatment groups for the outcome "health status", measured with the EQ-5D VAS. For health status, this resulted in no hint of an added benefit of 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

The meta-analysis showed no statistically significant difference between the treatment groups for the outcome "physical sum score of the SF-36". For the physical sum score of the SF-36, this resulted in no hint of an added benefit of FTC/TAF in comparison with continuation of ongoing treatment; an added benefit is therefore not proven.

- SF-36 – mental sum score

For the mental sum score of the SF-36, there was heterogeneity between the studies without effects in the same direction ($p < 0.2$). Pooling both studies was therefore not meaningful for the mental sum score of the SF-36.

In the 311-1089 study, there was no statistically significant difference between the treatment groups. In the 292-0109 study, there was a statistically significant difference in favour of FTC/TAF. The standardized mean difference (SMD) in the form of Hedges' g was considered to check the relevance of the result. The 95% confidence interval was not completely above the irrelevance threshold of 0.2. It can therefore not be inferred that the effect is relevant.

For the mental sum score of the SF-36, overall there was no hint of an added benefit of FTC/TAF in comparison with continuation of ongoing treatment; an added benefit is therefore not proven.

Side effects

- Serious adverse events, severe adverse events (grade 3-4), psychiatric disorders, skin and subcutaneous tissue disorders, gastrointestinal disorders, renal and urinary disorders

The meta-analysis showed no statistically significant difference between the treatment groups for any of the following outcomes: SAEs, severe AEs (grade 3-4) 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 FTC/TAF in comparison with continuation of ongoing treatment for these outcomes; greater or lesser harm for these outcomes is therefore not proven.

- Discontinuation due to adverse events

The results for the outcome "discontinuation due to AEs" were interpreted separately for the studies 292-0109 and 311-1089. This was due to the fact that the result for the STB stratum of the 292-0109 study might have been influenced to a relevant degree by the inclusion of patients with indication for a treatment switch due to side effects. Consequently, the result of this study for the outcome "discontinuation due to AEs" was overall considered to be not interpretable with certainty.

A statistically significant difference in favour of FTC/TAF for the outcome "discontinuation due to AEs" was shown in the STB stratum of the 292-0109 study. Considering the rates of the patients in the total population of the study who had discontinued treatment (due to any cause), there was a tendency already after 4 weeks of treatment that fewer patients had discontinued treatment in the intervention arm than in the comparator arm (0.1% versus 1.0%, difference of 0.9 percentage points). In comparison, at week 48, the difference for the outcome "discontinuation due to AEs" between the treatment arms was only marginally higher in the total population with 1.6 percentage points. For this outcome, the statistical significance (relative risk [95% confidence interval]: 0.37 [0.16; 0.88]; p = 0.019) in the total population might be due to the treatment discontinuations (due to any cause) within the first 4 weeks of treatment. These early discontinuations were possibly caused by side effects of their ongoing treatment and the knowledge of the patients of continuation of this treatment. No corresponding data on the course of treatment discontinuations were available for the STB stratum. At week 48, however, fewer patients in the intervention arm than in the comparator arm had also discontinued treatment (2.3% versus 3.9%). Due to the missing information on the course of treatment discontinuations and the described situation in the total population, the result for the outcome "discontinuation due to AEs" for the STB stratum of the 292-0109 study was overall assessed as not being interpretable with sufficient certainty.

There was no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs" in the 311-1089 study. It was unclear also for this study, whether discontinuations due to AEs were caused by side effects of the continued treatment. The results showed no explicit indications of this, however. In contrast to the 292-0109 study there was therefore no important difference in the rate of treatment discontinuation (due to any cause) between both study arms in the first weeks after the start of treatment. It was therefore not assumed for the 311-1089 study that the result for the outcome "discontinuation due to AEs" might have been caused to an important extent by the possible inclusion of

patients with indication for a treatment switch due to side effects. In contrast to the 292-0109 study, the result of the 311-1089 study was therefore considered to be interpretable.

Overall, there was no hint of greater or lesser harm of FTC/TAF in comparison with continuation of ongoing treatment for the outcome "discontinuation due to AEs"; greater or lesser harm is therefore not proven.

- Nervous system disorders

The meta-analysis showed a statistically significant difference to the disadvantage of FTC/TAF for the outcome "nervous system disorders".

However, there was an indication of an effect modification by the characteristic "combination partner" for this outcome. For patients with a PI/b regimen as third combination partner, there was a hint of greater harm from FTC/TAF in comparison with continuation of ongoing treatment for the outcome "nervous system disorders". For patients with other regimens as third combination partner, there was proof of greater harm from FTC/TAF in comparison with continuation of ongoing treatment for the outcome "nervous system disorders".

It should be noted in the interpretation of these results that both subgroups not only differed in the substance class of the third combination partner, but that TAF was administered in a higher dosage (25 mg) in the subgroup "other regimens" than in the subgroup "PI/b regimen (10 mg). Hence it cannot be excluded that the effect modification could have (also) been caused by the dosage difference between the subgroups.

- Bone fractures

The results on the outcome "bone fractures" were not pooled in a meta-analysis because of different operationalizations (study 292-0109: High Level Group Term and Standardized Medical Dictionary for Regulatory Activities [MedDRA] Query; study 311-1089: Standardized MedDRA Query).

No statistically significant difference between the treatment groups was shown at the individual study level. This resulted in no hint of greater or lesser harm of FTC/TAF in comparison with continuation of ongoing treatment for the outcome "bone fractures"; greater or lesser harm is therefore not proven.

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

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

In the overall consideration, negative effects remained for pretreated adults without indication for a treatment switch. For the outcome "nervous system disorders", there is a hint of greater harm (extent: "minor") in patients receiving FTC/TAF in combination with a PI/b regimen, and proof of greater harm (extent: "considerable") in patients receiving FTC/TAF with other regimens.

In summary, there is a hint of lesser benefit of FTC/TAF in combination with a PI/b regimen in comparison with the ACT for pretreated HIV-1 infected adult patients without indication for a treatment switch. There is proof of lesser benefit of FTC/TAF in combination with other regimens in comparison with the ACT for pretreated HIV-1 infected adult patients without indication for a treatment switch.

No data were available for pretreated HIV-1 infected adult patients with indication for a treatment switch. There was no hint of an added benefit of FTC/TAF in comparison with the ACT for this patient population; an added benefit for these patients is not proven.

Research questions 2 and 4: treatment-naive and pretreated adolescents

The company presented no data for the assessment of the added benefit of FTC/TAF for research questions 2 and 4. This resulted in no hint of an added benefit of FTC/TAF in comparison with the ACT. An added benefit 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 FTC/TAF.

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

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

Research question	Therapeutic indication	ACT specified by the G-BA	Sub-group	Extent and probability of added benefit
1	Treatment-naive adults	NRTI backbone: tenofovir disoproxil plus emtricitabine or abacavir plus lamivudine In combination with NRTI backbone, third combination partners with the same active agent (efavirenz or rilpivirine or dolutegravir) were to be used with the same distribution across the study arms.	Added benefit not proven	
2	Treatment-naive adolescents[a]	Efavirenz in combination with abacavir plus 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.	PI/b regimen	Hint of lesser benefit
			Other regimens	Proof of lesser benefit
	Pretreated adults (with indication for a treatment switch)		Added benefit not proven	
4	Pretreated adolescents[a]		Added benefit not proven	

a: 12 years of age and older and with a body weight of at least 35 kg.
ACT: appropriate comparator therapy; FTC: emtricitabine; G-BA: Federal Joint Committee; NRTI: nucleoside reverse transcriptase inhibitor; PI/b: boosted protease inhibitor (boosted with ritonavir or cobicistat); TAF: tenofovir alafenamide

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 question

The aim of this report was to assess the added benefit of 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. FTC/TAF is used in combination with other antiretroviral drugs.

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 FTC/TAF

Research question	Therapeutic indication	ACT specified by the G-BA
1	Treatment-naive adults	NRTI backbone: tenofovir disoproxil plus emtricitabine or abacavir plus lamivudine In combination with NRTI backbone, third combination partners with the same active agent (efavirenz or rilpivirine or dolutegravir) were to be used with the same distribution across the study arms.
2	Treatment-naive adolescents[a]	Efavirenz in combination with abacavir plus 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[a]	
a: 12 years of age and older and with a body weight of at least 35 kg. ACT: appropriate comparator therapy; FTC: emtricitabine; G-BA: Federal Joint Committee; NRTI: nucleoside reverse transcriptase inhibitor; TAF: tenofovir alafenamide		

For research question 1 (treatment-naive adults), the company generally followed the ACT specified by the G-BA. The company also considered EVG/COBI in addition to the third combination partners specified by the G-BA. This expansion of the ACT was not followed because, in particular, the company did not prove the (at least) equivalence of EVG/COBI with one of the 3 third combination partners specified by the G-BA (EFV or rilpivirine [RPV] or dolutegravir [DTG]) (for detailed reasons, see Section 2.8.1 of the full dossier assessment). The present assessment was conducted in comparison with the G-BA's ACT.

For research question 3 (pretreated adults), the company followed the G-BA's specification of the ACT. Within this research question, the company distinguished the following patient groups:

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

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 company did not consider research questions 2 and 4 (treatment-naive or pretreated adolescents 12 years of age and older) in its dossier. The company justified this with low patient numbers and missing evidence relevant for the benefit assessment, among other reasons. This approach was not followed (see Sections 2.8.1 and 2.8.2.1 of the full dossier assessment). The present assessment was conducted in comparison with the G-BA's ACT.

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-naive adults

2.3.1 Information retrieval and study pool (research question 1)

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 FTC/TAF (status: 21 March 2016)
- bibliographical literature search on FTC/TAF (last search on 21 March 2016)
- search in trial registries for studies on FTC/TAF (last search on 21 March 2016)

To check the completeness of the study pool:

- search in trial registries for studies on FTC/TAF (last search on 1 June 2016)

The check of the completeness of the study pool produced no relevant RCTs on the comparison of FTC/TAF versus the ACT.

For the assessment of research question 1, the company included the studies GS-US-292-0102 [3], GS-US-292-0104 [4] and GS-US-292-0111 [4], which investigated a comparison of EVG/COBI/FTC/TAF versus EVG/COBI/FTC/TDF. Furthermore, it presented results of the study GS-US-299-0102 [5] on the comparison of darunavir (DRV)/COBI/FTC/TAF versus DRV/COBI/FTC/TDF as additional information. The company did not use this study for the derivation of the conclusions on the added benefit because, according to the company, the third combination partner DRV/COBI used in the study did not concur with the criteria of the ACT specified by the G-BA.

The assessment of the relevance of the studies used for the assessment of the added benefit by the company was not followed. The GS-US-299-0102 study was also not relevant for the benefit assessment. The ACT specified by the G-BA was not implemented in any of the studies presented by the company for research question 1 because the third combination partner (EVG/COBI or DRV/COBI deviated from the G-BA's specification (EFV or RPV or DTG) (see Section 2.8.1 of the full dossier assessment for detailed reasons).

2.3.2 Results on added benefit (research question 1)

The company presented no relevant data for the assessment of the added benefit of FTC/TAF in comparison with the ACT for research question 1. This resulted in no hint of an added benefit of FTC/TAF in comparison with the ACT. An added benefit is therefore not proven.

2.3.3 Extent and probability of added benefit (research question 1)

The company presented no suitable data for the assessment of the added benefit of FTC/TAF in treatment-naive adults. An added benefit of FTC/TAF in comparison with the ACT is therefore not proven for these patients.

This deviates from the company's assessment, which derived proof of considerable added benefit on the basis of the data presented by the company.

The G-BA decides on the added benefit.

2.3.4 List of included studies (research question 1)

Not applicable as no studies for research question 1 were included in the benefit assessment.

2.4 Research question 2: treatment-naive adolescents 12 years of age and older

2.4.1 Information retrieval and study pool (research question 2)

The company did not investigate research question 2 in the dossier. Hence it conducted no information retrieval for research question 2 and presented no data on this.

The Institute's check of completeness on the basis of the company's study list on FTC/TAF (status: 21 March 2016) and the search in trial registries on FTC/TAF (last search on 1 June 2016) identified no studies relevant for research question 2.

2.4.2 Results on added benefit (research question 2)

The company presented no data for the assessment of the added benefit of FTC/TAF for research question 2. This resulted in no hint of an added benefit of FTC/TAF in comparison with the ACT. An added benefit is therefore not proven.

2.4.3 Extent and probability of added benefit (research question 2)

The company presented no data for the assessment of the added benefit of FTC/TAF in treatment-naive adolescents 12 years of age and older. Hence an added benefit of FTC/TAF is not proven for these patients.

This concurs with the company's assessment who claimed no added benefit for these patients.

The G-BA decides on the added benefit.

2.4.4 List of included studies (research question 2)

Not applicable as no studies for research question 2 were included in the benefit assessment.

2.5 Research question 3: pretreated adults

2.5.1 Information retrieval and study pool (research question 3)

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 FTC/TAF (status: 21 March 2016)
- bibliographical literature search on FTC/TAF (last search on 21 March 2016)
- search in trial registries for studies on FTC/TAF (last search on 21 March 2016)

To check the completeness of the study pool:

- search in trial registries for studies on FTC/TAF (last search on 1 June 2016)

No additional relevant study was identified from the check.

2.5.1.1 Studies included (research question 3)

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

Table 5: Study pool – RCT, direct comparison: pretreated adults without indication for a treatment switch, FTC/TAF + third combination partner[a] vs. continuation of ongoing treatment (FTC/TDF + third combination partner[a])

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[b] (yes/no)	Third-party study (yes/no)
GS-US-292-0109 (292-0109)[c]	Yes	Yes	No
GS-US-311-1089 (311-1089)[c]	Yes	Yes	No
a: Different third combination partners that are continued in both arms. b: Study for which the company was sponsor. c: In the following tables, the study is referred to with this abbreviated form. FTC: emtricitabine; RCT: randomized controlled trial; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; vs.: versus			

The company used the studies 292-0109 und 311-1089 for the assessment of the added benefit of FTC/TAF for patients without medical indication for a treatment switch (for example 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 (for example due to virologic failure or side effects) was not possible on the basis of the studies 292-0109 and 311-1089. Hence no studies were available for these patients.

Section 2.5.4 contains a reference list for the studies included.

2.5.1.2 Study characteristics (research question 3)

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

Table 6: Characteristics of the studies included – RCT, direct comparison: pretreated adults without indication for a treatment switch, FTC/TAF + third combination partner[a] vs. continuation of ongoing treatment (FTC/TDF + third combination partner[a])

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
292-0109	RCT, open-label, parallel	HIV-1 infected adults[c, d] 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 an eGFR of ≥ 50 mL/min	EVG/COBI/FTC/TAF (N = 963) Continuation of ongoing treatment (N = 480) consisting of ▪ EVG/COBI/FTC/TDF (STB) or ▪ EFV/FTC/TDF[e] or ▪ ATV/co + FTC/TDF[e] or ▪ ATV/r + FTC/TDF[e] Relevant subpopulation thereof (STB stratum): EVG/COBI/FTC/TAF (n = 306) EVG/COBI/FTC/TDF (n = 153)	▪ Screening: 30 days prior to the start of treatment ▪ Planned treatment duration: 96 weeks[f] ▪ 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
311-1089	RCT, double-blind[g], parallel	HIV-1 infected adults[h, i] 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 an eGFR of ≥ 50 mL/min	FTC/TAF + third combination partner[j] (N = 334) Continuation of ongoing treatment consisting of FTC/TDF + third combination partner[j] (N = 334)	▪ Screening: 30 days prior to the start of treatment ▪ Planned treatment duration: 96 weeks[f] ▪ Follow-up: 30 days	78 centres in Belgium, Canada, France, Italy, United Kingdom, USA 5/2014–ongoing (Data cut-off at week 48: 8/2015)	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

(continued)

Table 6: Characteristics of the studies included – RCT, direct comparison: pretreated adults without indication for a treatment switch, FTC/TAF + third combination partner[a] vs. continuation of ongoing treatment (FTC/TDF + third combination partner[a]) (continued)

a: Different third combination partners that are continued in both arms.
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: Stratified by pretreatment (EVG/COBI/FTC/TDF or EFV/FTC/TDF or ATV/booster/FTC/TDF).
e: The arm is not relevant for the assessment and is not shown in the next tables.
f: Then all study participants have the possibility to receive unblinded EVG/COBI/FTC/TAF (study 292-0109) or FTC/TAF (study 311-1089) until the product is commercially available or until Gilead stops the research programme.
g: Blinding refers only to the backbone therapy (FTC/TAF or FTC/TDF). Administration of the third combination partner was unblinded.
h: Pretreatment with antiretroviral therapy consisting of FTC/TDF and one allowed third combination partner (ATV/r, LPV/r, DRV/r, EFV, RPV, NVP, RAL, DTG, or MRC) for ≥ 6 consecutive months before screening.
i: Stratified by the third combination partner (PI/b regimen/other regimens).
j: Continuation of the third combination partner from the ongoing treatment.

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; DRV/r: ritonavir-boosted darunavir; DTG: dolutegravir; EFV: efavirenz; eGFR: estimated glomerular filtration rate (according to Cockcroft-Gault equation); EVG: elvitegravir; FTC: emtricitabine; HIV-1: human immunodeficiency virus type 1; LPV/r: ritonavir-boosted lopinavir; MRC: maraviroc; n: relevant subpopulation; N: number of randomized patients; NVP: nevirapine; PI/b: boosted protease inhibitor (boosted with ritonavir or cobicistat); RAL: raltegravir; RCT: randomized controlled trial; RNA: ribonucleic acid; RPV: rilpivirine; STB: Stribild (fixed combination of EVG/COBI/FTC/TDF); TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; vs.: versus

Table 7: Characteristics of the interventions – RCT, direct comparison: pretreated adults without indication for a treatment switch, FTC/TAF + third combination partner[a] vs. continuation of ongoing treatment (FTC/TDF + third combination partner[a])

Study	Intervention	Comparison
292-0109 (STB stratum)	▪ EVG 150 mg/COBI 150 mg/ FTC 200 mg/TAF 10 mg (fixed combination) once daily orally with food	▪ EVG 150 mg/COBI 150 mg/ FTC 200 mg/TDF 300 mg[b] (fixed combination) once daily orally with food
	Pretreatment: EVG/COBI/FTC/TDF for ≥ 6 consecutive months preceding the final visit in an earlier study **Non-permitted concomitant medication:** drugs with high interaction potential (for example carbamazepine, HMG-CoA reductase inhibitors, St. John's Wort)	
311-1089	▪ FTC 200 mg/TAF 10 mg (fixed combination) + placebo for FTC/TDF + boosted third combination partner (ATV/r, LPV/r or DRV/r) or ▪ FTC 200 mg/TAF 25 mg (fixed combination) + placebo for FTC/TDF + unboosted third combination partner (EFV, RPV, NVP, RAL, DTG, or MRC) each once daily orally in the morning at about the same time of the day	▪ FTC 200 mg/TDF 300 mg[b] (fixed combination) + placebo for FTC/TAF + third combination partner (ATV/r, LPV/r, DRV/r, EFV, RPV, NVP, RAL, DTG, or MRC) once daily orally in the morning at about the same time of the day
	Pretreatment: treatment with FTC/TDF in combination with one allowed third combination partner (ATV/r, LPV/r, DRV/r, EFV, RPV, NVP, RAL, DTG, or MRC) for ≥ 6 consecutive months before screening **Non-permitted concomitant medication:** drugs with high interaction potential (for example carbamazepine, bisphosphonates, St. John's Wort)	

a: Different third combination partners that are continued in both arms.
b: Equivalent to 245 mg tenofovir disoproxil.

ATV/co: cobicistat-boosted atazanavir; ATV/r: ritonavir-boosted atazanavir; COBI. cobicistat; DRV/r: ritonavir-boosted darunavir; DTG: dolutegravir; EFV: efavirenz; EVG: elvitegravir; FTC: emtricitabine; HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme-A; LPV/r: ritonavir-boosted lopinavir; MRC: maraviroc; NVP: nevirapine; RAL: raltegravir; RCT: randomized controlled trial; RPV: rilpivirine; STB: Stribild (fixed combination of EVG/COBI/FTC/TDF); TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate; vs.: versus

Study 292-0109

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 combination partner were enrolled in the study. Possible third combination partners were EFV, EVG/COBI, and COBI-boosted atazanavir (ATV/co) or ritonavir-boosted atazanavir (ATV/r). Patients also had to have an estimated glomerular filtration rate (eGFR) of ≥ 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).

Since only the NRTI backbone therapy FTC/TAF was the drug combination under assessment, it was meaningful for the benefit assessment to have an identical third combination partner in the treatment arms to allow an unbiased result on the added benefit of FTC/TAF versus FTC/TDF. Hence only the stratum of the study in which only the backbone therapy (but not the third combination partner) was switched in the intervention arm in comparison with the comparator arm was relevant for the benefit assessment. Only the STB stratum was therefore used from the 292-0109 study. In this stratum, the ongoing treatment (EVG/COBI/FTC/TDF) was continued in the comparator arm; in the intervention arm, only the NRTI backbone therapy was switched to FTC/TAF in comparison with the ongoing treatment; the third combination partner (EVG/COBI) remained identical in comparison with the ongoing treatment. In the STB stratum, a total of 306 patients were included in the intervention arm, and 153 patients in the comparator arm.

Fixed combinations of EVG/COBI/FTC/TAF or EVG/COBI/FTC/TDF were used in the STB stratum of the 292-0109 study. The antiretroviral agents used were administered in compliance with their approval with food once daily orally [6,7]. According to the respective SPCs, no resistances to the agents or drug classes [6,7] used in the STB stratum were to be present. Yet there was no specification of 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).

The fact that the fixed combination of EVG/COBI/FTC/TAF (instead of the fixed combination FTC/TAF under assessment) was used in the intervention arm was not a problem for the inclusion of the study: The FTC/TAF component was used in the study in compliance with the SPC on FTC/TAF [8].

An evaluation regarding content of the investigated patient population showed that mostly patients without medically required indication for a treatment switch were enrolled in study 292-0109 (see Section 2.8.2.4.1 of the full dossier assessment). 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 FTC/TAF for pretreated adults with indication for a treatment switch on the basis of study 292-0109.

The planned treatment duration in the study was 96 weeks. However, at the time point of the benefit assessment, only results on the period of analysis of 48 weeks were available. These were used in the present assessment.

Study 311-1089

The 311-1089 study was an active-controlled randomized trial with patients with prior antiretroviral therapy. Virologically suppressed adults who had been pretreated with FTC/TDF and a third combination partner were included in the study. Boosted PI/b regimens (boosted with ritonavir: ATV/r, lopinavir/ritonavir [LPV/r] or DRV/ritonavir [DRV/r]) or other regimens (EFV, RPV, nevirapine [NPV], raltegravir [RAL], DTG, or maraviroc [MRC]) were used as third combination partners. Patients also had to have an eGFR of ≥ 50 mL/min.

A total of 668 patients were randomized in a ratio of 1:1 to the 2 study arms, 334 patients to the FTC/TAF arm, and 334 patients to the comparator arm (continuation of ongoing treatment). Randomization was stratified by the previous third combination partner (PI/b regimen or other regimens). Administration of FTC/TAF or FTC/TDF was blinded for patient and outcome assessor.

The antiretroviral agents used in the 311-1089 study were administered with food once daily orally. Dosage for the NRTI backbone therapies (FTC/TAF and FTC/TDF) was in compliance with their approval [8,9]. According to the SPC [8], the dosage of TAF in the intervention arm of the study depended on the drug class of the third combination partner: The dosage was 10 mg in combination with PI/b regimens; it was 25 mg in combination with other regimens.

No information on the dosage in the pretreatment and during the 311-1089 study was available for the third combination partner. Due to the randomization it could be assumed that the dosages did not differ substantially between the study arms. It could also not be inferred from the SPCs on FTC/TAF and FTC/TDF that the recommended dosages of the third combination partners mentioned above differed between the combination with FTC/TAF and FTC/TDF [8,9]. It could not be excluded, however, that too high or too low dosages of the third combination partner in combination with FTC/TAF and FTC/TDF could have different effects on the results: In its dossier, the company did not address a possible interaction between dosage of the third combination partner and the NRTI backbone therapy used (FTC/TAF or FTC/TDF). The potential influence was estimated to be minor, however, so that the suitability of the study was not questioned.

There was no specification of resistance testing or genotyping in study 311-1089. 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).

An evaluation regarding content of the investigated patient population showed that mostly patients without medically required indication for a treatment switch were enrolled in study 311-1089. A conclusive check whether the study also included a small proportion of patients with necessary treatment switch due to side effects was not possible on the basis of the documents presented by the company, however. Hence some uncertainty remained regarding this issue. 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 FTC/TAF for pretreated adults with indication for a treatment switch on the basis of study 311-1089.

The planned treatment duration in the study was 96 weeks. However, at the time point of the benefit assessment, only results on the period of analysis of 48 weeks were available. These were used in the present assessment.

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, direct comparison: pretreated adults without indication for a treatment switch, FTC/TAF + third combination partner[a] vs. continuation of ongoing treatment (FTC/TDF + third combination partner[a])

Study Group	N[b]	Age [years] mean (SD)	Sex [F/M] %	Ethnicity [Caucasian/ Asian/ Other[c]] %[d]	Third combination partner in the pretreatment[e] [ATV/r/DRV/r/LPV/r/DTG/ EFV/MRC/NVP/RAL/RPV] %[d]	Duration of pre-treatment	eGFR [mL/min] median (Q1; Q3)	Treat-ment discon-tinuation, week 48, n (%)	Study discon-tinuation, week 48, n (%)
292-0109									
EVG/COBI/FTC/TAF	306[f]	41 (10)	8/92	70/4/27[g]	EVG/COBI: 100	ND	103.2 (87.6; 120.2)	7 (2.3)	7 (2.3)
EVG/COBI/FTC/TDF	153[f]	42 (10)	8/92	69/3/27[g]	EVG/COBI: 100	ND	100.7 (85.0; 123.6)	6 (3.9)	4 (2.6)
311-1089									
FTC/TAF	333	47 (10)	14/86	73/2/25[g]	16/25/5/8/2/0/22/20/1	ND	99.4 (83.8; 120.3)	21 (6.3)	18 (5.4)
FTC/TDF	330	48 (10)	16/84	77/0/23[g]	15/25/6/7/2/2/20/22/2	ND	100.2 (83.8; 121.2)	21 (6.4)	14 (4.2)

a: Different third combination partners that are continued in both arms.
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.
c: This group includes blacks or patients of African or Afro-American origin, native Americans/native Alaskans, Hawaiians/Pacific Islanders, and others, as well as patients who provided no information.
d: Sum per group > or < 100% possible due to rounding.
e: Unless otherwise stated.
f: Number of patients in the relevant subpopulation: STB stratum.
g: Institute's calculation.

ATV/r: ritonavir-boosted atazanavir; COBI: cobicistat; DRV/r: ritonavir-boosted darunavir; DTG: dolutegravir; EFV: efavirenz; eGFR: estimated glomerular filtration rate (according to Cockcroft-Gault equation); EVG: elvitegravir; F: female; FTC: emtricitabine; LPV/r: ritonavir-boosted lopinavir; M: male; MRC: maraviroc; n: number of patients with event; N: number of patients included; ND: no data; NVP: nevirapine; Q: quartile; RAL: raltegravir; RCT: randomized controlled trial; RPV: rilpivirine; SD: standard deviation; STB: Stribild (fixed combination of EVG/COBI/FTC/TDF); TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; vs.: versus

Table 9: Characteristics of the study populations (disease severity at the start of the study) – RCT, direct comparison: pretreated adults without indication for a treatment switch, FTC/TAF + third combination partner[a] vs. continuation of ongoing treatment (FTC/TDF + third combination partner[a])

Study Group	N[b]	Viral load [log_{10} 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 (%)		
			< 50	≥ 50		< 350	≥ 350	Asymp-tomatic	Symp-tomatic	AIDS
292-0109										
EVG/COBI/FTC/TAF	306[c]	ND	302 (98.7)	4 (1.3)	693 (537; 849)	16 (5.2)[d]	290 (94.8)[d]	ND	ND	ND
EVG/COBI/FTC/TDF	153[c]	ND	152 (99.3)	1 (0.7)	673 (550; 849)	6 (4.0)[d]	147 (96.0)[d]	ND	ND	ND
311-1089										
FTC/TAF	333	ND	329 (98.8)	4 (1.2)	663 (505; 853)	26 (7.8)[d]	307 (92.2)[d]	277 (83.4)	21 (6.3)	34 (10.2)
FTC/TDF	330	ND	326 (98.8)	4 (1.2)	624 (477; 819)	34 (10.3)[d]	296 (89.7)[d]	270 (81.8)	29 (8.8)	31 (9.4)

a: Different third combination partners that are continued in both arms.
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.
c: Number of patients in the relevant subpopulation: STB stratum.
d: Institute's calculation.

AIDS: acquired immunodeficiency syndrome; CD4: cluster of differentiation 4; COBI: cobicistat; EVG: elvitegravir; FTC: emtricitabine; HIV-1: human immunodeficiency virus type 1; n: number of patients with event; N: number of patients included; ND: no data; Q: quartile; RCT: randomized controlled trial; RNA: ribonucleic acid; STB: Stribild (fixed combination of EVG/COBI/FTC/TDF); TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; vs.: versus

There were no important differences regarding the demographic characteristics “age”, “sex” and “ethnicity” between both treatment arms in the studies 292-0109 (STB stratum) and 311-1089 (total population). The mean age of the patients was 41 and 47 years. Markedly more men (about 92% and 85%) than women 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 (each about 69% to 77%).

The severity of the disease measured with the viral load and the median CD4 cell count was also balanced between the study arms: In both studies, almost all the patients in both treatment arms had a viral load of < 50 HIV ribonucleic acid (RNA) copies/mL according to the inclusion criteria (more than 98% in each case). The median CD4 cell count in the treatment arms was about 660 to 690 cells/µL.

According to the documents on the 311-1089 study, the proportion of patients with symptomatic HIV infection or AIDS at the start of the study was > 15% in each study arm at the start of the study. It remained unclear from the study documents whether symptomatic HIV infections or AIDS at the start of the study were also counted if they had occurred at a previous time point since the infection, but were no longer present at the start of the study. No information on HIV disease stage was available for the 292-0109 study.

Table 10 shows the risk of bias at study level.

Table 10: Risk of bias at study level – RCT, direct comparison: pretreated adults without indication for a treatment switch, FTC/TAF + third combination partner[a] vs. continuation of ongoing treatment (FTC/TDF + third combination partner[a])

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 (STB stratum)	Yes	Yes	No	No	Yes	Yes	Low
311-1089	Yes	Yes	Yes	Yes	Yes	Yes	Low

a: In combination with different third combination partners that are continued in both arms.
FTC: emtricitabine; RCT: randomized controlled trial; STB: Stribild (fixed combination of elvitegravir/cobicistat/FTC/TDF); TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; vs.: versus

The risk of bias at study level was assessed as low for both studies. This is in accordance with the assessment of the company.

Limitations resulting from the open-label study design of the 292-0109 study are described in Section 2.5.2.2 with the outcome-specific risk of bias.

2.5.2 Results on added benefit (research question 3)

2.5.2.1 Outcomes included (research question 3)

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
  - measured with the physical and mental sum score of the 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 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, direct comparison: pretreated adults without indication for a treatment switch, FTC/TAF + third combination partner[a] vs. continuation of ongoing treatment (FTC/TDF + third combination partner[a])

Study	Outcomes									
	All-cause mortality	AIDS-defining events (CDC class C events)	Virologic response (snapshot)[b]	CD4 cell count[b]	Health status (EQ-5D VAS)	Health-related quality of life (SF-36)	SAEs	Discontinuation due to AEs	Severe AEs (grade 3-4)[c]	Further specific AEs[d]
292-0109	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
311-1089	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a: Different third combination partners that are continued in both arms.
b: Virologic response and CD4 cell count as surrogate outcomes for the composite outcome "AIDS-defining illnesses/death" are presented as additional information.
c: Classification based on the "Gilead Sciences Grading Scale for Severity of Adverse Events and Laboratory Abnormalities".
d: 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 bone fractures (study 292-0109: HLGT and SMQ, study 311-1089: SMQ).
AE: adverse event; AIDS: acquired immunodeficiency syndrome; CD4: cluster of differentiation 4; CDC: Centers for Disease Control and Prevention; EQ-5D: European Quality of Life-5 Dimensions; FTC: emtricitabine; HLGT: High Level Group Term; MedDRA: Medical Dictionary for Regulatory Activities; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; SMQ: Standardized MedDRA Query; SOC: System Organ Class; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; VAS: visual analogue scale; vs.: versus

2.5.2.2 Risk of bias (research question 3)

Table 12 shows the risk of bias for the relevant outcomes.

Table 12: Risk of bias at study and outcome level – RCT, direct comparison: pretreated adults without indication for a treatment switch, FTC/TAF + third combination partner[a] vs. continuation of ongoing treatment (FTC/TDF + third combination partner[a])

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 adverse events (grade 3-4)	Bone fractures[b]	Further specific AEs[c]
292-0109 (STB stratum)	L	L	H[d]	H[e]	L	H[f, g]	H[h, i]	L	H[h]	L	L	H[h]
311-1089	L	L	L	L	L	H[g]	H[i]	L	L	L	L	L

a: Different third combination partners that are continued in both arms.
b: Consideration of the event "bone fractures" operationalized as HLGT and SMQ (study 292-0109) or SMQ (study 311-1089), in each case coded according to MedDRA.
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).
d: It was not clear from the study documents whether the rating of an AE as an AIDS-defining event was blinded or unblinded.
e: In the total population, differential proportions of patients with treatment discontinuation (for reasons other than death or AEs) with last measurement of < 50 HIV-1 RNA copies/mL with lack of blinding; no information on the STB stratum (see Section 2.8.2.2 of the full dossier assessment).
f: Patient-reported outcome in open-label study.
g: Proportion of missing values at the end of the study > 10%.
h: Due to lack of blinding in subjective recording of outcomes.
i: No information on the number of imputations of missing values and no information on the methodology used for this.

AE: adverse event; AIDS: acquired immunodeficiency syndrome; CD4: cluster of differentiation 4; CDC: Centers for Disease Control and Prevention; EQ-5D: European Quality of Life-5 Dimensions; FTC: emtricitabine; H: high; HIV-1: human immunodeficiency virus type 1; HLGT: High Level Group Term; L: low; MedDRA: Medical Dictionary for Regulatory Activities; RCT: randomized controlled trial; RNA: ribonucleic acid; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; SMQ: Standardized MedDRA Query; SOC: System Organ Class; STB: Stribild (fixed combination of elvitegravir/cobicistat/FTC/TDF): tenofovir alafenamide; TDF: tenofovir disoproxil; VAS: visual analogue scale; vs.: versus

The risk of bias for the outcome "all-cause mortality" was rated as low for both studies. For study 292-0109, 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.

For the outcome “AIDS-defining events”, which the company considered only as additional information under the outcome category of side effects, the risk of bias was rated as low for study 311-1089. It was rated as high for study 292-0109 because it was not clear from the corresponding study documents whether the rating of an AE as AIDS-defining event was blinded or unblinded.

The risk of bias for the outcome “virologic response” (snapshot) was rated as low for study 311-1089. Deviating from the company’s assessment, it was rated as high for study 292-0109. This was due to differential proportions of patients with treatment discontinuation (for reasons other than death or AEs) with a last measurement of < 50 HIV-1 RNA copies/mL in the total population, which caused substantial bias in the statistically significant result in the total population of the study (see Section 2.8.2.2 of the full dossier assessment). The corresponding data were not available for the relevant STB stratum of study 292-0109. Due to the situation in the total population of the study it could not be excluded, however, that the results for the STB stratum might also be biased.

Concurring with the company’s assessment, the risk of bias for the CD4 cell count was rated as low for both studies.

Concurring with the company’s assessment, the risk of bias of the patient-reported outcome “EQ-5D VAS” was rated as high for study 292-0109 because this was a patient-reported outcome in an open-label study. Deviating from the company’s assessment, a high risk of bias for the STB stratum of study 292-0109 and for study 311-1089 was due to a proportion of missing values of > 10% at the end of the study.

Concurring with the company’s assessment, the risk of bias of the outcome “SF-36” was rated as high for study 292-0109 because of a lack of blinding in subjective recording of outcomes. Deviating from the company’s assessment, a high risk of bias for the STB stratum of study 292-0109 and for study 311-1089 was additionally justified with the lack of information on the number of imputations for missing values and to the lack of information on the methodology used.

The risk of bias for the AE outcomes “SAEs”, “severe AEs (grade 3-4)”, and “bone fractures” was rated as low for both studies: Despite the open-label study design it was not assumed also for study 292-0109 that the recordings of the SAEs, severe AEs (grade 3-4), and bone fractures were influenced by subjective expectations. This deviates from the assessment of the company, which assumed a high risk of bias in these outcomes for study 292-0109 because of the open-label study design.

Concurring with the company’s assessment, the risk of bias of the outcomes “further specific AEs” and “discontinuation due to AEs” was rated as low for study 311-1089 and, due to lack of blinding in subjective recording of outcomes, as high for study 292-0109.

2.5.2.3 Results (research question 3)

The results on the comparison of FTC/TAF with continuation of ongoing treatment with FTC/TDF in pretreated adults with HIV-1 infection without indication for a treatment switch are summarized in Table 13 and Table 14. Where necessary, the data from the company's dossier were supplemented with the Institute's calculations.

Table 13: Results (mortality, morbidity [dichotomous data], side effects) – RCT, direct comparison: pretreated adults without indication for a treatment switch, FTC/TAF + third combination partner[a] vs. continuation of ongoing treatment (FTC/TDF + third combination partner[a])

Outcome category Outcome Study	FTC/TAF + third combination partner[a]		FTC/TDF + third combination partner[a]		FTC/TAF vs. FTC/TDF (+ third combination partner[a])
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Mortality					
All-cause mortality					
292-0109	306	2 (0.7)	153	0 (0)	2.51 [0.12; 51.92]; 0.552
311-1089	333	1 (0.3)	330	0 (0)	2.97 [0.12; 72.72]; 0.504
Total[b]					2.72 [0.30; 24.52]; 0.373
Morbidity					
AIDS-defining events (CDC class C)					
292-0109	306	5[c] (1.6[c])[d]	153	4 (2.6[c])[d]	0.63 [0.17; 2.29][c]; 0.512[e]
311-1089	333	6 (1.8[c])[d]	330	3 (0.9)	1.98 [0.50; 7.86][c]; 0.530[e]
Total[f]					1.09 [0.35; 3.37]; 0.885
Additional information: surrogate outcome "virologic response" (HIV-1 RNA < 50 copies/mL)					
Snapshot[g]					
292-0109	306	301 (98.4)	153	149 (97.4)	1.01 [0.98; 1.04]; 0.509
311-1089	333	314 (94.3)	330	307 (93.0)	1.01 [0.97; 1.05]; 0.504
Total[b]					1.01 [0.99; 1.04]; 0.353
Missing = failure[h]					
292-0109	306	ND	153	ND	ND
311-1089	333	319 (95.8)	330	314 (95.2)	1.01 [0.97; 1.04][c]; 0.753[e]
Total[b]					ND
Missing = excluded[h]					
292-0109	306	ND	153	ND	ND
311-1089	319	319 (100)	319	314 (98.4)	1.02 [1.00; 1.03][c]; 0.026[e]
Total[b]					ND
Side effects					
AEs (supplementary information)					
292-0109	306	263 (85.9)	153	129 (84.3)	–
311-1089	333	281 (84.4)	330	262 (79.4)	–
SAEs					
292-0109	306	18 (5.9)	153	10 (6.5)	0.90 [0.43; 1.90]; 0.783
311-1089	333	18 (5.4)	330	14 (4.2)	1.27 [0.64; 2.52]; 0.486
Total[b]					1.09 [0.66; 1.80]; 0.742

(continued)

Table 13: Results (mortality, morbidity [dichotomous data], side effects) – RCT, direct comparison: pretreated adults without indication for a treatment switch, FTC/TAF + third combination partner[a] vs. continuation of ongoing treatment (FTC/TDF + third combination partner[a]) (continued)

Outcome category Outcome Study	FTC/TAF + third combination partner[a]		FTC/TDF + third combination partner[a]		FTC/TAF vs. FTC/TDF (+ third combination partner[a])
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Severe AEs (grade 3-4)[i]					
292-0109	306	25 (8.2)	153	16 (10.5)	0.78 [0.43; 1.42]; 0.418
311-1089	333	17 (5.1)	330	12 (3.6)	1.40 [0.68; 2.89]; 0.358
Total[b]					1.01 [0.57; 1.79]; 0.975
Discontinuation due to AEs[j]					
292-0109	306	0 (0)	153	2 (1.3)	–[k]; 0.046[e]
311-1089	333	7 (2.1)	330	3 (0.9)	2.31 [0.60; 8.87]; 0.248[e]
Nervous system disorders					
292-0109	306	60 (19.6)	153	18 (11.8)	1.67 [1.02; 2.72]; 0.041
311-1089	333	58 (17.4)	330	40 (12.1)	1.44 [0.99; 2.09]; 0.057
Total[b]					1.52 [1.13; 2.04]; 0.006
Psychiatric disorders					
292-0109	306	46 (15.0)	153	33 (21.6)	0.70 [0.47; 1.04]; 0.079
311-1089	333	27 (8.1)	330	31 (9.4)	0.86 [0.53; 1.41]; 0.558
Total[b]					0.76 [0.56; 1.04]; 0.084
Skin and subcutaneous tissue disorders					
292-0109	306	45 (14.7)	153	27 (17.6)	0.83 [0.54; 1.29]; 0.412
311-1089	333	46 (13.8)	330	47 (14.2)	0.97 [0.67; 1.41]; 0.874
Total[b]					0.91 [0.68; 1.21]; 0.512
Gastrointestinal disorders					
292-0109	306	101 (33.0)	153	41 (26.8)	1.23 [0.91; 1.67]; 0.183
311-1089	333	90 (27.0)	330	90 (27.3)	0.99 [0.77; 1.27]; 0.943
Total[b]					1.08 [0.88; 1.34]; 0.451
Renal and urinary disorders					
292-0109	306	30 (9.8)	153	15 (9.8)	1.00 [0.56; 1.80]; > 0.999
311-1089	333	19 (5.7)	330	16 (4.8)	1.18 [0.62; 2.25]; 0.622
Total[b]					1.08 [0.70; 1.66]; 0.740
Bone fractures[l]					
292-0109	306	8 (2.6)	153	1 (0.7)	4.00 [0.50; 31.69]; 0.156[e]
311-1089	333	1 (0.3)	330	2 (0.6)	0.50 [0.05; 5.44]; 0.602[e]

(continued)

Table 13: Results (mortality, morbidity [dichotomous data], side effects) – RCT, direct comparison: pretreated adults without indication for a treatment switch, FTC/TAF + third combination partner[a] vs. continuation of ongoing treatment (FTC/TDF + third combination partner[a]) (continued)

a: Different third combination partners that are continued in both arms.
b: Calculated from meta-analysis.
c: Institute's calculation.
d: Deviating data from the company (see also Section 2.8.2.4.3 of the full dossier assessment): In Module 4 A, the company stated 3 events for the FTC/TAF arm of the STB stratum of study 292-0109, and 1 event for the FTC/TDF arm. For study 311-1089, it stated 5 events for the FTC/TAF arm, and (concurring with the information provided in the CSR) 3 events for the FTC/TDF arm.
e: Institute's calculation, unconditional exact test (CSZ method according to [11]).
f: Institute's calculation from meta-analysis.
g: 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].
h: 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 48 is relevant if several measurements are available within the analysis time window. There is no detailed description of the algorithms in the study documents.
i: Classification based on the "Gilead Sciences Grading Scale for Severity of Adverse Events and Laboratory Abnormalities".
j: It cannot be excluded that the events in the comparator arm of study 292-0109 were due to patients with indication for a treatment switch due to side effects at the start of the study (see text below and Section 2.8.2.4.1 of the full dossier assessment). The results in this study are therefore not interpretable. Hence no meta-analysis has been conducted for this outcome.
k: Effect estimate and 95% CI not meaningfully interpretable.
l: Since the operationalizations deviated between study 292-0109 (based on HLGT and SMQ) and study 311-1089 (based on SMQ), no meta-analysis is conducted for this outcome.

AE: adverse event; AIDS: acquired immunodeficiency syndrome; CDC: Centers for Disease Control and Prevention; CI: confidence interval; E: excluded; F: failure; FDA: Food and Drug Administration; FTC: emtricitabine; HIV-1: human immunodeficiency virus type 1, HLGT: High Level Group Term; M: missing; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; RNA: ribonucleic acid; RR: relative risk; SAE: serious adverse event; SMQ: Standardized Medical Dictionary for Regulatory Activities Query; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; vs.: versus

Table 14: Results (morbidity [continuous data], health related quality of life) – RCT, direct comparison: pretreated adults without indication for a treatment switch, FTC/TAF + third combination partner[a] vs. continuation of ongoing treatment (FTC/TDF + third combination partner[a])

Outcome category Outcome Study	FTC/TAF + third combination partner[a]			FTC/TDF + third combination partner[a]			FTC/TAF vs. FTC/TDF (+ third combination partner[a])
	N[b]	Baseline values mean (SD)	Change at end of study mean[c] (SD)	N[b]	Baseline values mean (SD)	Change at end of study mean[c] (SD)	MD [95% CI]; p-value
Morbidity							
Additional information: surrogate outcome "CD4 cell count/µL"							
292-0109	306	727 (281.2)	26 (178.1)	153	717 (252.9)	34 (169.3)	−8.00 [−41.43; 25.43]; 0.639
311-1089	333	691 (272.6)	13 (173.1)	330	667 (272.3)	19 (152.3)	−6.00 [−30.81; 18.81]; 0.636
Total[d]							−6.71 [−26.64; 13.21]; 0.509
Health status (EQ-5D VAS)[e]							
292-0109	276	86.7 (12.81)	0.4 (12.19)[f]	135	86.7 (12.29)	1.1 (14.46)[f]	−0.70 [−3.53; 2.13][f]; 0.628
311-1089	297	85.1 (12.30)	−1.5 (13.77)[f]	296	85.9 (13.48)	0.4 (11.62)[f]	−1.90 [−3.95; 0.15][f]; 0.069
Total[d]							−1.49 [−3.15; 0.17][f]; 0.079
Health-related quality of life							
SF-36							
Physical sum score[e]							
292-0109	288	55.0 (6.20)	−0.2 (6.07)[f]	144	54.9 (6.64)	0.4 (7.41)[f]	−0.60 [−2.00; 0.80][f]; 0.401
311-1089	315	52.2 (8.52)	−0.8 (7.11)[f]	311	52.6 (8.13)	0.0 (5.84)[f]	−0.80 [−1.82; 0.22][f]; 0.124
Total[d]							−0.73 [−1.55; 0.09]; 0.082
Mental sum score[e]							
292-0109	288	51.3 (9.06)	0.1 (8.69)[f]	144	51.8 (9.40)	−2.4 (8.94)[f]	2.50 [0.73; 4.27][f]; 0.006 Hedges' g: 0.28 [0.08; 0.49]
311-1089	315	50.7 (9.50)	−1.9 (9.58)[f]	311	51.2 (9.77)	−2.1 (9.57)[f]	0.20 [−1.30; 1.70][f]; 0.794
Total[d]							Heterogeneity: I^2 = 73.5%; p = 0.052

(continued)

Table 14: Results (morbidity [continuous data], health related quality of life) – RCT, direct comparison: pretreated adults without indication for a treatment switch, FTC/TAF + third combination partner[a] vs. continuation of ongoing treatment (FTC/TDF + third combination partner[a]) (continued)

a: Different third combination partners that are continued in both arms.
b: 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.
c: Unless stated otherwise, LOCF analysis of the ITT population.
d: Calculated from meta-analysis.
e: Higher values indicate better health status or better health-related quality of life.
f: Without imputation of missing values.

CD4: cluster of differentiation 4; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; 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; SF-36: Short Form (36) Health Survey; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; VAS: visual analogue scale; vs.: versus

At most proof, e.g. of an added benefit, could be derived from the meta-analysis of the study populations relevant for the benefit assessment (study 292-0109: STB stratum, study 311-1089: total population). This is in accordance with the assessment of the company.

Mortality

All-cause mortality

The meta-analysis showed no statistically significant difference between the treatment groups for the outcome “all-cause mortality”. For all-cause mortality, this resulted in no hint of an added benefit of FTC/TAF in comparison with continuation of ongoing treatment; an added benefit for the outcome “all-cause mortality” is therefore not proven.

This is in accordance with the assessment of the company.

Morbidity

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

The meta-analysis showed no statistically significant difference between the treatment groups for the outcome “AIDS-defining events” (the forest plot can be found in Appendix A of the full dossier assessment).

The meta-analysis showed no statistically significant difference between the treatment groups also for virologic response (snapshot). It is possible, however, that the result on virologic response was influenced by the algorithm used for the analysis (see Section 2.8.2.2 of the full dossier assessment). Additional consideration of further analyses was therefore meaningful to check the robustness of the result from the snapshot algorithm. Analyses using other algorithms (missing = failure and missing = excluded) were only available for study 311-1089. The results of these analyses (statistically significant result in favour of FTC/TAF

only for missing = excluded) did not raise doubts about the results of the primary analysis. A corresponding assessment was not possible for the STB stratum of study 292-0109 (and therefore possibly the meta-analysis) because the company presented no sensitivity analyses for the STB stratum.

The meta-analysis showed no statistically significant difference between the treatment arms for change in CD4 cell count.

Overall, there was therefore no hint of an added benefit of FTC/TAF in comparison with continuation of ongoing treatment for the outcome "AIDS-defining events"; an added benefit is therefore not proven.

The company's approach deviated insofar as it considered the outcomes "virologic response" and "CD4 cell count" separately from each other. The company also saw no statistically significant difference between the treatment arms for both outcomes.

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)

The meta-analysis showed no statistically significant difference between the treatment groups for the outcome "health status", measured with the EQ-5D VAS. For health status, this resulted in no hint of an added benefit of FTC/TAF in comparison with continuation of ongoing treatment; an added benefit is therefore not proven.

This is in accordance with the assessment of the company.

Health-related quality of life

SF-36 – physical sum score

The meta-analysis showed no statistically significant difference between the treatment groups for the outcome "physical sum score of the SF-36". For the physical sum score of the SF-36, this resulted in no hint of an added benefit of FTC/TAF in comparison with continuation of ongoing treatment; an added benefit is therefore not proven.

This is in accordance with the assessment of the company.

SF-36 – mental sum score

For the mental sum score of the SF-36, there was heterogeneity between the studies without effects in the same direction ($p < 0.2$). Pooling both studies was therefore not meaningful for the mental sum score of the SF-36.

In the 311-1089 study, there was no statistically significant difference between the treatment groups. In the 292-0109 study, there was a statistically significant difference in favour of FTC/TAF. The SMD in the form of Hedges' g was considered to check the relevance of the result [1]. The 95% confidence interval was not completely above the irrelevance threshold of 0.2. It can therefore not be inferred that the effect is relevant.

For the mental sum score of the SF-36, overall there was no hint of an added benefit of FTC/TAF in comparison with continuation of ongoing treatment; an added benefit is therefore not proven.

This deviates from the company's approach insofar as it did not discuss the mental sum score of the SF-36 at the individual study level in, from the company's point of view, statistically significant and unexplained heterogeneity. In the overall consideration, the company also derived no added benefit, however.

Side effects

Serious adverse events

The meta-analysis showed no statistically significant difference between the treatment groups for the outcome "SAEs". This resulted in no hint of greater or lesser harm of FTC/TAF in comparison with continuation of ongoing treatment for the outcome "SAEs"; greater or lesser harm is therefore not proven.

This is in accordance with the assessment of the company.

Severe adverse events (grade 3-4)

The meta-analysis showed no statistically significant difference between the treatment groups for the outcome "severe AEs (grade 3-4)". This resulted in no hint of greater or lesser harm of FTC/TAF in comparison with continuation of ongoing treatment for the outcome "severe AEs (grade 3-4)"; greater or lesser harm is therefore not proven.

This is in accordance with the assessment of the company.

Discontinuation due to adverse events

The results for the outcome "discontinuation due to AEs" were interpreted separately for the studies 292-0109 and 311-1089. This was due to the fact that the result for the STB stratum of the 292-0109 study might have been influenced to a relevant degree by the inclusion of patients with indication for a treatment switch due to side effects. Consequently, the result of this study for the outcome "discontinuation due to AEs" was overall considered to be not interpretable with certainty.

A statistically significant difference in favour of FTC/TAF for the outcome "discontinuation due to AEs" was shown in the STB stratum of the 292-0109 study. It is not excluded, however, that the statistically significant effect in discontinuation due to AEs was due to

patients who had experienced burdensome side effects under their ongoing treatment already before the start of the study (see Section 2.8.2.4.1 of the full dossier assessment). Considering the rates of the patients in the total population of study 292-0109 who had discontinued treatment (due to any cause), there was a tendency already after 4 weeks of treatment that fewer patients had discontinued treatment in the intervention arm than in the comparator arm (0.1% versus 1.0%, difference of 0.9 percentage points). In comparison, at week 48, the difference for the outcome "discontinuation due to AEs" between the treatment arms was only marginally higher in the total population with 1.6 percentage points. For this outcome, the statistical significance (relative risk [RR] [95% confidence interval]: 0.37 [0.16; 0.88]; p = 0.019) in the total population might be due to the treatment discontinuations (due to any cause) within the first 4 weeks of treatment. These early discontinuations were possibly caused by side effects of their ongoing treatment and the knowledge of the patients of continuation of this treatment. No corresponding data on the course of treatment discontinuations were available for the STB stratum. At week 48, however, fewer patients in the intervention arm than in the comparator arm had also discontinued treatment (2.3% versus 3.9%; see Table 8). As in the total population, this difference might have been caused to an important extent by early discontinuations following side effects of the ongoing treatment and the knowledge of the patients about the continuation of this treatment. This might also explain the statistically significant result in favour of the intervention for the outcome "discontinuation due to AEs". The result for this outcome for the STB stratum of study 292-0109 was therefore overall considered to be not interpretable with certainty.

There was no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs" in the 311-1089 study. It was unclear also for this study, whether discontinuations due to AEs were caused by side effects of the continued treatment. The results showed no explicit indications of this, however. In contrast to the 292-0109 study there was therefore no important difference in the rate of treatment discontinuation (due to any cause) between both study arms in the first weeks after the start of treatment. It was therefore not assumed for the 311-1089 study that the result for the outcome "discontinuation due to AEs" might have been caused to an important extent by the possible inclusion of patients with indication for a treatment switch due to side effects. In contrast to the 292-0109 study, the result of the 311-1089 study was therefore considered to be interpretable.

Overall, there was no hint of greater or lesser harm of FTC/TAF in comparison with continuation of ongoing treatment for the outcome "discontinuation due to AEs"; greater or lesser harm is therefore not proven.

Due to inconsistent results, the company considered the results for the outcome "discontinuation due to AEs" also at the individual study level. The company did not discuss the uncertainty of study 292-0109. Overall, the company also derived no greater or lesser harm from FTC/TAF, however.

Nervous system disorders

The meta-analysis showed a statistically significant difference to the disadvantage of FTC/TAF for the outcome "nervous system disorders".

However, there was an indication of an effect modification by the characteristic "combination partner" for this outcome (see Section 2.5.2.4). For patients with a PI/b regimen as third combination partner, there was a hint of greater harm from FTC/TAF in comparison with continuation of ongoing treatment for the outcome "nervous system disorders". This deviates from the assessment of the company insofar as it derived an indication of greater harm from FTC/TAF in comparison with continuation of ongoing treatment for this patient group. For patients with other regimens as third combination partner, there was proof of greater harm from FTC/TAF in comparison with continuation of ongoing treatment for the outcome "nervous system disorders". This is in accordance with the assessment of the company.

Psychiatric disorders

The meta-analysis showed no statistically significant difference between the treatment groups for the outcome "psychiatric disorders". This resulted in no hint of greater or lesser harm of FTC/TAF in comparison with continuation of ongoing treatment for the outcome "psychiatric disorders"; greater or lesser harm is therefore not proven.

This is in accordance with the assessment of the company.

Skin and subcutaneous tissue disorders

The meta-analysis showed 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 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 is in accordance with the assessment of the company.

Gastrointestinal disorders

The meta-analysis showed no statistically significant difference between the treatment groups for the outcome "gastrointestinal disorders". This resulted in no hint of greater or lesser harm of FTC/TAF in comparison with continuation of ongoing treatment for the outcome "gastrointestinal disorders"; greater or lesser harm is therefore not proven.

This is in accordance with the assessment of the company.

Renal and urinary disorders

The meta-analysis showed 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 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 deviates from the approach of the company, which did not consider the outcome "renal and urinary disorders" (operationalized as SOC) separately. Instead, the company listed renal and urinary disorders (SOC) as a component of the outcome "renal disorders" together with surrogate outcomes (see Section 2.8.2.9.4 of the full dossier assessment). Based on subgroup analyses on the surrogate outcomes, the company derived indications or proof of lesser harm from FTC/TAF for renal disorders.

Bone fractures

The results on the outcome "bone fractures" were not pooled in a meta-analysis because of different operationalizations (study 292-0109: High Level Group Term [HLGT] and Standardized MedDRA Query [SMQ]; study 311-1089: SMQ). The consideration of the events underlying the outcome in the total population of study 292-0109 showed that the result was mostly based on events within the HLGT analysis (analysis on the basis of SMQ: 10 patients with event; analysis on the basis of SMQ and HLGT: 28 patients with event). It was unclear how the results of study 311-1089 would change when adding the HLGT analysis.

No statistically significant difference between the treatment groups was shown at the individual study level. This resulted in no hint of greater or lesser harm of FTC/TAF in comparison with continuation of ongoing treatment for the outcome "bone fractures"; greater or lesser harm is therefore not proven.

This deviates from the approach of the company, which did not consider the outcome "bone fractures" separately. Instead, the company listed bone fractures as a component of the outcome "bone disorders" together with surrogate outcomes (see Section 2.8.2.9.4 of the full dossier assessment), for which it overall derived proof of lesser harm.

2.5.2.4 Subgroups and other effect modifiers (research question 3)

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

- age (< 50/≥ 50 years)
- sex (men/women)
- ethnicity (Caucasian/non-Caucasian)
- combination partner (PI/b regimen/other regimens)

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 arm 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 ≥ 0.05 and < 0.2 provides an indication of an effect modification.

The subgroup analyses on the direct comparison of FTC/TAF with continuation of ongoing treatment in pretreated adults with HIV-1 infection without indication for a treatment switch are summarized in Table 15. Where necessary, the data from the dossier were supplemented by the Institute's calculations.

Table 15: Subgroups (side effects) – RCT, direct comparison: pretreated adults without indication for a treatment switch, FTC/TAF + third combination partner[a] vs. continuation of ongoing treatment (FTC/TDF + third combination partner[a])

Outcome **Characteristic** **Study** **Subgroup**	**FTC/TAF + third combination partner[a]**		**FTC/TDF + third combination partner[a]**		**FTC/TAF vs. FTC/TDF (+ third combination partner[a])**	
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]**	**p-value**
Nervous system disorders						
Combination partner						
292-0109						
PI/b regimen	No patients in this subgroup					
Other regimens	306	60 (19.6)	153	18 (11.8)	1.67 [1.02; 2.72]	0.041
311-1089						
PI/b regimen	155	27 (17.4)	151	25 (16.6)	1.05 [0.64; 1.73]	0.841
Other regimens	178	31 (17.4)	179	15 (8.4)	2.08 [1.16; 3.71]	0.014
Total					Interaction:	0.082
PI/b regimen					1.05 [0.64; 1.73]	0.841
Other regimens					1.83 [1.26; 2.66]	0.002[b]

a: Different third combination partners that are continued in both arms.
b: Institute's calculation from meta-analysis.

CI: confidence interval; FTC: emtricitabine; n: number of patients with (at least one) event; N: number of analysed patients; PI/b: boosted protease inhibitor (boosted with ritonavir or cobicistat); RCT: randomized controlled trial; RR: relative risk; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; vs.: versus

Side effects

Nervous system disorders

The subgroup analysis on the outcome "nervous system disorders" showed an indication of an effect modification by the characteristic "combination partner". Since there was only an indication of an interaction, the result of the total study pool was considered in the interpretation of the results.

No statistically significant difference between the treatment groups was shown for patients with PI/b regimen as third combination partner. Due to the indication of an interaction with the same direction of the effect as in the total study pool, for which there was a statistically significant result (see Table 15), it was not assumed, however, that there was no effect in the subgroup. Compared with the total population, the certainty of results in the subgroup was downgraded, however. Since the result on the subgroup PI/b regimen only resulted from one study (311-1089) with a low risk of bias, there was a hint of greater harm from FTC/TAF in comparison with continuation of ongoing treatment for patients with PI/b regimen as third combination partner. This deviates from the assessment of the company insofar as it derived an indication of greater harm from FTC/TAF in comparison with continuation of ongoing treatment for this patient group.

A statistically significant difference to the disadvantage of FTC/TAF was shown for patients with other regimens as third combination partner (as in the total study pool). This resulted in proof of greater harm from FTC/TAF in comparison with continuation of ongoing treatment in patients with other regimens. This is in accordance with the assessment of the company.

It should be noted in the interpretation of the results of the subgroup analyses that both subgroups not only differed in the substance class of the third combination partner, but that TAF was administered in a higher dosage (25 mg) in the subgroup "other regimens" than in the subgroup "PI/b regimen" (10 mg) (see Table 7; both dosages are in compliance with the specifications of the SPC). Hence it cannot be excluded that the effect modification could have (also) been caused by the dosage difference between the subgroups.

2.5.3 Extent and probability of added benefit (research question 3)

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 (research question 3)

For the outcome "nervous system disorders", the data presented in Section 2.5.2 resulted in a hint of greater harm from FTC/TAF in comparison with continuation of ongoing treatment for patients with PI/b regimen, and in proof of greater harm for patients with other regimens as third combination partner. The outcome "nervous system disorders" was allocated to the category "non-serious/non-severe side effects" because it could be inferred from the clinical study reports that the majority of the events were classified as AEs, but not as SAEs. The extent of the respective harm at outcome level was estimated from these results (see Table 16).

Table 16: Extent of added benefit at outcome level: FTC/TAF + third combination partner[a] vs. continuation of ongoing treatment (FTC/TDF + third combination partner[a])

Outcome category **Outcome** **Effect modifier** **Subgroup**	**FTC/TAF vs. FTC/TDF (+ third combination partner[a])** **Proportion of events or mean** **Effect estimates [95% CI]; p-value** **Probability[b]**	**Derivation of extent[c]**
Mortality		
All-cause mortality	0.3 to 0.7% vs. 0.0%[d] RR: 2.72 [0.30; 24.52]; p = 0.373	Lesser benefit/added benefit not proven
Morbidity		
AIDS-defining events (CDC class C)	1.6 to 1.8% vs. 0.9 to 2.6%[d] RR: 1.09 [0.35; 3.37]; p = 0.885	Lesser benefit/added benefit not proven
Supplementary information:		
Virologic response (snapshot)	94.3 to 98.4% vs. 93.0 to 97.4%[d] RR: 1.02 [0.99; 1.05]; p = 0.194	
CD4 cell count	Mean (cells/µL): 13 to 26 vs. 19 to 34[d] MD: −6.71 [−26.64; 13.21]; p = 0.509	
Health status (EQ-5D VAS)	Mean: −1.5 to 0.4 vs. 0.4 to 1.1[d] MD: −1.49 [−3.15; 0.17]; p = 0.079	Lesser benefit/added benefit not proven
Health-related quality of life		
SF-36		
Physical sum score	Mean: −0.8 to −0.2 vs. 0.0 to 0.4[d] MD: −0.73 [−1.55; 0.09]; p = 0.082	Lesser benefit/added benefit not proven
Mental sum score	Heterogeneous results[e] No study showed a statistically significant and clinically relevant effect[f].	Lesser benefit/added benefit not proven
Side effects		
SAEs	5.4 to 5.9% vs. 4.2 to 6.5%[d] RR: 1.09 [0.66; 1.80]; p = 0.742	Greater/lesser harm not proven
Severe AEs (grade 3-4)	5.1 to 8.2% vs. 3.6 to 10.5%[d] RR: 1.01 [0.57; 1.79]; p = 0.975	Greater/lesser harm not proven
Discontinuation due to AEs[g]	2.1% vs. 0.9% RR: 2.31 [0.60; 8.87]; p = 0.248	Greater/lesser harm not proven

(continued)

Table 16: Extent of added benefit at outcome level: FTC/TAF + third combination partner[a] vs. continuation of ongoing treatment (FTC/TDF + third combination partner[a]) (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**FTC/TAF vs. FTC/TDF (+ third combination partner[a])** **Proportion of events or mean** **Effect estimates [95% CI]; p-value** **Probability[b]**	**Derivation of extent[c]**
Nervous system disorders Combination partner	17.4 to 19.6% vs. 11.8 to 12.1%[d] RR: 1.52 [1.13; 2.04] RR[h]: 0.66 [0.49; 0.88]; p = 0.006	
PI/b regimen[i]	17.4% vs. 16.6% RR: 1.05 [0.64; 1.73]; p = 0.841 probability: "hint"[j]	Outcome category: non-serious/non-severe side effects greater harm; extent[k]: "minor"
Other regimens	17.4 to 19.6% vs. 8.4 to 11.8%[d] RR: 1.83 [1.26; 2.66] RR[h]: 0.55 [0.38; 0.796]; p = 0.002 probability: "proof"[j]	Outcome category: non-serious/non-severe side effects $CI_u < 0.8$ greater harm; extent: "considerable"
Psychiatric disorders	8.1 to 15.0% vs. 9.4 to 21.6%[d] RR: 0.76 [0.56; 1.04]; p = 0.084	Greater/lesser harm not proven
Skin and subcutaneous tissue disorders	13.8 to 14.7% vs. 14.2 to 17.6%[d] RR: 0.91 [0.68; 1.21]; p = 0.512	Greater/lesser harm not proven
Gastrointestinal disorders	27.0 to 33.0% vs. 26.8 to 27.3%[d] RR: 1.08 [0.88; 1.34]; p = 0.451	Greater/lesser harm not proven
Renal and urinary disorders	5.7 to 9.8% vs. 4.8 to 9.8%[d] RR: 1.08 [0.70; 1.66]; p = 0.740	Greater/lesser harm not proven
Bone fractures[l]	STB stratum of study 292-0109: 2.6% vs. 0.7% RR: 4.00 [0.50; 31.69]; p = 0.156 Study 311-1089: 0.3% vs. 0.6% RR: 0.50 [0.05; 5.44]; p = 0.602	Greater/lesser harm not proven

(continued)

Table 16: Extent of added benefit at outcome level: FTC/TAF + third combination partner[a] vs. continuation of ongoing treatment (FTC/TDF + third combination partner[a]) (continued)

a: Different third combination partners that are continued in both arms. b: Probability provided if statistically significant and clinically relevant differences are present. c: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u. d: Minimum and maximum proportions of events or mean changes in each treatment arm in the included studies. e: No common effect estimate can be provided due to heterogeneous data. f: Added benefit assumed with upper and lower CI limits < –0.2 or > 0.2 for Hedges' g. g: Only the result of study 311-1089 is presented because the result of study 292-0109 is not interpretable. h: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit. i: Only results of study 311-1089 are available for this subgroup because no patient was treated with a PI/b regimen in the STB stratum of study 292-0109. j: Derivation of the probability under consideration of the result for the total study pool. k: Extent at most as high as in the total study pool. l: Due to different operationalizations between the studies, no meta-analysis is conducted so that the results are presented separately for each study. AE: adverse event; AIDS: acquired immunodeficiency syndrome; CD4: cluster of differentiation 4; CDC: Centers for Disease Control and Prevention; CI: confidence interval; CI_u: upper limit of confidence interval; EQ-5D: European Quality of Life-5 Dimensions; FTC: emtricitabine; MD: mean difference; mean: mean value (change at end of study); PI/b: boosted protease inhibitor (boosted with ritonavir or cobicistat); RR: relative risk; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; STB: Stribild (fixed combination of elvitegravir/cobicistat/FTC/TDF); TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; VAS: visual analogue scale; vs.: versus

2.5.3.2 Overall conclusion on the added benefit (research question 3)

Table 17 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 17: Positive and negative effects from the assessment of FTC/TAF + third combination partner[a] compared with continuation of ongoing treatment (FTC/TDF + third combination partner[a])

Positive effects	**Negative effects**
–	Non-serious/non-severe side effects ▪ Nervous system disorders: ▫ combination partner (PI/b regimen): hint of greater harm – extent: "minor" ▫ combination partner (other regimens): proof of greater harm – extent: "considerable"
a: Different third combination partners that are continued in both arms. FTC: emtricitabine; TAF: tenofovir alafenamide; PI/b: boosted protease inhibitor (boosted with ritonavir or cobicistat); TDF: tenofovir disoproxil	

In the overall consideration, negative effects remained for pretreated adults without indication for a treatment switch. For the outcome “nervous system disorders”, there is a hint of greater harm (extent: “minor”) in patients receiving FTC/TAF in combination with a PI/b regimen, and proof of greater harm (extent: “considerable”) in patients receiving FTC/TAF with other regimens.

In summary, there is a hint of lesser benefit of FTC/TAF in combination with a PI/b regimen in comparison with the ACT for pretreated HIV-1 infected adult patients without indication for a treatment switch. There is proof of lesser benefit of FTC/TAF in combination with other regimens in comparison with the ACT for pretreated HIV-1 infected adult patients without indication for a treatment switch.

No data were available for pretreated HIV-1 infected adult patients with indication for a treatment switch. There was no hint of an added benefit of 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 proof 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 (research question 3)

292-0109

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: 07.06.2016]. URL: 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; final week 48 final (all subjects) clinical study report [unpublished]. 2015.

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; Zusatzanalysen [unpublished]. 2016.

Gilead Sciences. Switching from a TDF-containing combination regimen to a TAF-containing fixed dose combination (FDC) in virologically-suppressed, HIV-1 positive participants: full text view [online]. In: ClinicalTrials.gov. 15.03.2016 [Accessed: 07.06.2016]. URL: https://ClinicalTrials.gov/show/NCT01815736.

Gilead Sciences. Switching from a TDF-containing combination regimen to a TAF-containing fixed dose combination (FDC) in virologically-suppressed, HIV-1 positive participants: study results [online]. In: ClinicalTrials.gov. 15.03.2016 [Accessed: 07.06.2016]. URL: https://clinicaltrials.gov/ct2/show/results/NCT01815736.

311-1089

Gilead Sciences. A phase 3, randomized, double-blind, switch study to evaluate F/TAF in HIV-1 positive subjects who are virologically suppressed on regimens containing FTC/TDF [online]. In: EU Clinical Trials Register. [Accessed: 07.06.2016]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-005138-39.

Gilead Sciences. A phase 3, randomized, double-blind, switch study to evaluate F/TAF in HIV-1 positive subjects who are virologically suppressed on regimens containing FTC/TDF: study GS-US-311-1089; interim week 48 clinical study report [unpublished]. 2015.

Gilead Sciences. A phase 3, randomized, double-blind, switch study to evaluate F/TAF in HIV-1 positive subjects who are virologically suppressed on regimens containing FTC/TDF: study GS-US-311-1089; Zusatzanalysen [unpublished]. 2015.

Gilead Sciences. Switch study to evaluate F/TAF in HIV-1 positive participants who are virologically suppressed on regimens containing FTC/TDF: full text view [online]. In: ClinicalTrials.gov. 29.02.2016 [Accessed: 07.06.2016]. URL: https://clinicaltrials.gov/ct2/show/study/NCT02121795.

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

2.6.1 Information retrieval and study pool (research question 4)

The company did not investigate research question 4 in the dossier. Hence it conducted no information retrieval for research question 4 and presented no data on this. For this reason, there is no information on the information retrieval and on the study pool for research question 4.

The Institute's check of completeness on the basis of the company's study list on FTC/TAF (status: 21 March 2016) and the search in trial registries on FTC/TAF (last search on 1 June 2016) identified no studies relevant for research question 4.

2.6.2 Results on added benefit (research question 4)

The company presented no data for the assessment of the added benefit of FTC/TAF for research question 4. This resulted in no hint of an added benefit of FTC/TAF in comparison with the ACT. An added benefit is therefore not proven.

2.6.3 Extent and probability of added benefit (research question 4)

The company presented no data for the assessment of the added benefit of FTC/TAF in pretreated adolescents 12 years of age and older. Hence an added benefit of FTC/TAF is not proven for these patients.

This concurs with the company's assessment who claimed no added benefit for these patients.

The G-BA decides on the added benefit.

2.6.4 List of included studies (research question 4)

Not applicable as no studies for research question 4 were included in the benefit assessment.

2.7 Extent and probability of added benefit – summary

The result of the assessment of the added benefit of FTC/TAF in comparison with the ACT is summarized in Table 18.

Table 18: FTC/TAF: extent and probability of added benefit

Research question	Therapeutic indication	ACT specified by the G-BA	Sub-group	Extent and probability of added benefit
1	Treatment-naive adults	NRTI backbone: tenofovir disoproxil plus emtricitabine or abacavir plus lamivudine In combination with NRTI backbone, third combination partners with the same active agent (efavirenz or rilpivirine or dolutegravir) were to be used with the same distribution across the study arms.	Added benefit not proven	
2	Treatment-naive adolescents[a]	Efavirenz in combination with abacavir plus 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.	PI/b regimen	Hint of lesser benefit
			Other regimens	Proof of lesser benefit
	Pretreated adults (with indication for a treatment switch)		Added benefit not proven	
4	Pretreated adolescents[a]		Added benefit not proven	

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

ACT: appropriate comparator therapy; FTC: emtricitabine; G-BA: Federal Joint Committee; NRTI: nucleoside reverse transcriptase inhibitor; PI/b: boosted protease inhibitor (boosted with ritonavir or cobicistat); TAF: tenofovir alafenamide

No data for the assessment of the added benefit of FTC/TAF in comparison with the ACT were available for treatment-naive adults with HIV-1 infection. Hence an added benefit of FTC/TAF in comparison with the ACT for this population is not proven. This deviates from the company's assessment, which claimed proof of a considerable added benefit. For its assessment, it used studies that, deviating from the ACT specified by the G-BA, compared FTC/TAF with FTC/TDF, each in combination with EVG/COBI.

There is a hint of lesser benefit of FTC/TAF for pretreated adults without indication for a treatment switch who are treated with FTC/TAF in combination with a PI/b regimen. There is proof of lesser benefit of FTC/TAF for pretreated adults without indication for a treatment switch who are treated with FTC/TAF in combination with another regimen. This deviates from the assessment of the company, which derived proof of a minor added benefit for

pretreated adults under inclusion of results on surrogate outcomes, the validity of which it did not prove (see Section 2.8.2.9.4 of the full dossier assessment). It did not distinguish between patients with and without indication for a treatment switch in its derivation.

No data for the assessment of the added benefit were available for pretreated adults with indication for a treatment switch. Hence an added benefit of FTC/TAF in comparison with the ACT for this population is not proven.

Concurring with the results of the benefit assessment, the company derived no added benefit for treatment-naive and 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.

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General Methods: version 4.2 [online]. 22.04.2015 [Accessed: 01.06.2016]. URL: https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-2.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58

3. 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.

4. 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.

5. Mills A, Crofoot G Jr, McDonald C, Shalit P, Flamm JA, Gathe J Jr et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate in the first protease inhibitor-based single-tablet regimen for initial HIV-1 therapy: a randomized phase 2 study. J Acquir Immune Defic Syndr 2015; 69(4): 439-445.

6. Gilead. Genvoya 150 mg / 150 mg / 200 mg / 10 mg Filmtabletten: Fachinformation [online]. 02.2016 [Accessed: 24.05.2016]. URL: http://www.fachinfo.de.

7. Gilead. Stribild 150 mg/150 mg/200 mg/245 mg Filmtabletten: Fachinformation [online]. 01.2016 [Accessed: 24.05.2016]. URL: http://www.fachinfo.de.

8. Gilead. Descovy Filmtabletten: Fachinformation [online]. 04.2016 [Accessed: 20.07.2016]. URL: http://www.fachinfo.de.

9. Gilead. Truvada 200 mg/245 mg Filmtabletten: Fachinformation [online]. 01.2016 [Accessed: 01.06.2016]. URL: http://www.fachinfo.de.

10. Robert Koch-Institut. HIV-Diagnosen und AIDS-Erkrankungen in Deutschland [online]. 06.07.2015 [Accessed: 19.07.2016]. (Epidemiologisches Bulletin; Volume 27/2015). URL: http://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2015/Ausgaben/27_15.pdf?__blob=publicationFile.

11. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574.

12. Food and Drug Administration. Guidance for industry: human immunodeficiency virus-1 infection; developing antiretroviral drugs for treatment [online]. 11.2015 [Accessed: 13.07.2016]. URL: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM355128.pdf.

13. Food and Drug Administration. Viread: statistical review and evaluation; clinical studies [online]. 18.07.2011 [Accessed: 13.07.2016]. URL: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM292365.pdf.

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a16-30-emtricitabine/tenofovir-alafenamide-benefit-assessment-according-to-35a-social-code-book-v.7453.html.