IQWiG Reports – Commission No. A16-58

# Emtricitabine/tenofovir alafenamide (HIV infection) –

## Addendum to Commission A16-30[1]

## Addendum

Commission: A16-58
Version: 1.0
Status: 10 October 2016

[1] Translation of addendum A16-58 *Emtricitabin/Tenofoviralafenamid (HIV-Infektion) – Addendum zum Auftrag A16-30* (Version 1.0; Status: 10 October 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) – Addendum to Commission A16-30

**Commissioning agency:**
Federal Joint Committee

**Commission awarded on:**
20 September 2016

**Internal Commission No.:**
A16-58

**Address of publisher:**
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**Keywords**: emtricitabine, tenofovir alafenamide, HIV infections, benefit assessment

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

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**List of abbreviations**

| Abbreviation | Meaning |
|---|---|
| AE | adverse event |
| AIDS | acquired immunodeficiency syndrome |
| FTC/TAF | emtricitabine/tenofovir alafenamide |
| FTC/TDF | emtricitabine/tenofovir disoproxil |
| G-BA | Gemeinsamer Bundesausschuss (Federal Joint Committee) |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care) |
| SGB | Sozialgesetzbuch (Social Code Book) |
| STB | Stribild (fixed combination of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil) |

# 1 Background

On 20 September 2016, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A16-30 (Emtricitabine/tenofovir alafenamide – Benefit assessment according to §35a Social Code Book (SGB) V [1]).

In its written comments to the dossier assessment [2], the pharmaceutical company (hereinafter referred to as "the company") presented supplementary information, which went beyond the information provided in the dossier on emtricitabine/tenofovir alafenamide [3], to prove the added benefit. These were the 96-week data of study GS-US-292-0109 [4,5] included by the company for the assessment of the added benefit in treatment-experienced adult patients (research question 3).

To be able to decide on the added benefit, the G-BA requires further analyses. The data submitted by the company were to be assessed under the research question whether there were changes regarding the assessment of patient-relevant outcomes in comparison with the 48-week data presented in the dossier. Additionally it was to be assessed whether the patients included were only patients without indication for a treatment switch.

The responsibility for the present assessment and the results of the assessment lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

# 2 Assessment of the data subsequently submitted (research question 3: treatment-experienced patients)

## 2.1 Patients without indication for a treatment switch in the Stribild stratum of study 292-0109

In its dossier, the company had presented a total of 2 randomized controlled trials for research question 3 (treatment-experienced patients without indication for a treatment switch): study 292-0109 (Stribild [STB] stratum) and study 311-1089. The presence of an indication for a treatment switch was checked for both studies in the dossier assessment. Some uncertainty remained whether patients with non-renal indication for a treatment switch had also possibly been included in the studies (see Section 2.8.2.4.1 of the dossier assessment [1]).

In its written comment, the company provided information for the STB stratum of study 292-0109 that a total of 2 patients in the STB stratum from the emtricitabine/tenofovir disoproxil (FTC/TDF) arm had discontinued treatment due to adverse events (AEs) in the course of the 292-0109 study. The time points of the treatment discontinuations were day 193 and 430. The company's dossier did not contain information on the course of the treatment discontinuations so that no conclusive assessment of the inclusion of the patients with non-renal indication for a treatment switch was possible.

Since treatment discontinuations occurred only late in the course of the treatment, it is now assumed that the patients in the STB stratum of the 292-0109 study had no indication for a treatment switch due to side effects. No new information on the indication for a treatment switch was available for study 311-1089.

## 2.2 Results of the Stribild stratum of study 292-0109 after 96 weeks of treatment

In principle, the consideration of long-term data is considered meaningful for the benefit assessment of the present chronic therapeutic indication. The results after week 96 were only available for study 292-0109, however. This study was an open-label study that (in contrast to the double-blind 311-1089 study) had a high risk of bias for several relevant outcomes (acquired immunodeficiency syndrome [AIDS]-defining events, virologic response, discontinuation due to AEs and specific AEs) (see Section 2.5.2.2 of the dossier assessment [1]). In addition, about 200 fewer patients were included in the relevant STB stratum of study 292-0109 than in study 311-1089 (459 versus 668). For these reasons, the results of the meta-analysis based on the 48-week data were considered to have a higher certainty of conclusions than the results from long-term data (after week 96) of study 292-0109.

Hereinafter, the results of study 292-0109 are presented as additional information (see Table 1 and Table 2). It is explained for which outcomes the results differed in comparison with the analysis of the 48-week data.

Table 1: Results (mortality, morbidity [dichotomous data], side effects) – RCT 292-0109, 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**<br>**Outcome**<br>**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]; 0.408[b] |
| **Morbidity** | | | | | |
| AIDS-defining events (CDC class C) | | | | | |
| 292-0109 | 306 | 6[c] (2.0[c])[d] | 153 | 5[c] (3.3[c])[d] | 0.60 [0.19; 1.93]; 0.448[b] |
| Additional information: surrogate outcome "virologic response" (HIV-1 RNA < 50 copies/mL) | | | | | |
| Snapshot[e] | | | | | |
| 292-0109 | 306 | 293 (95.8) | 153 | 142 (92.8) | 1.03 [0.98; 1.08]; 0.195[b] |
| *Missing = failure*[f] | | | | | |
| 292-0109 | 306 | ND | 153 | ND | ND |
| *Missing = excluded*[f] | | | | | |
| 292-0109 | 306 | ND | 153 | ND | ND |
| **Side effects** | | | | | |
| AEs (supplementary information) | | | | | |
| 292-0109 | 306 | 273 (89.2) | 153 | 135 (88.2) | – |
| SAEs | | | | | |
| 292-0109 | 306 | 23 (7.5) | 153 | 12 (7.8) | 0.96 [0.49; 1.87]; 0.941[b] |
| Severe AEs (grade 3-4)[g] | | | | | |
| 292-0109 | 306 | 31 (10.1) | 153 | 18 (11.8) | 0.86 [0.50; 1.49]; 0.624[b] |
| Discontinuation due to AEs | | | | | |
| 292-0109 | 306 | 0 (0) | 153 | 2 (1.3) | –[h]; 0.046[b] |
| Nervous system disorders[i] | | | | | |
| 292-0109 | 306 | 70 (22.8) | 153 | 21 (13.7) | 1.67 [1.07; 2.61]; 0.021[b] |
| Psychiatric disorders[i] | | | | | |
| 292-0109 | 306 | 48 (15.7) | 153 | 36 (23.5) | 0.67 [0.45; 0.98]; 0.042[b] |
| Skin and subcutaneous tissue disorders[i] | | | | | |
| 292-0109 | 306 | 54 (17.6) | 153 | 35 (22.8) | 0.77 [0.53; 1.13]; 0.195[b] |
| Gastrointestinal disorders[i] | | | | | |
| 292-0109 | 306 | 115 (37.5) | 153 | 49 (32.0) | 1.17 [0.89; 1.54]; 0.309[b] |
| Renal and urinary disorders[i] | | | | | |
| 292-0109 | 306 | 31 (10.1) | 153 | 20 (13.1) | 0.77 [0.46; 1.31]; 0.408[b] |

(continued)

Table 1: Results (mortality, morbidity [dichotomous data], side effects) – RCT 292-0109, 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<br>Outcome<br>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 |
| Bone fractures[j] | | | | | |
| 292-0109 | 306 | 10 (3.3) | 153 | 2 (1.3) | 2.50 [0.55; 11.27]; 0.239[b] |

a: EVG/COBI (concurs with the STB stratum of the study).
b: Institute's calculation, unconditional exact test (CSZ method according to [6]).
c: Institute's calculation.
d: Deviating data from the company: The company stated 3 events for the FTC/TAF arm of the STB stratum of study 292-0109, and 2 events for the FTC/TDF arm. In the CSR at week 48, 5 events were reported for the FTC/TAF arm and 4 events for the FTC/TDF arm. In the CSR at week 96, 2 patients in the FTC/TAF arm were no longer included as patients with an AIDS-defining event; at the same time, 1 additional patient with at least one AIDS-defining event was documented in comparison with week 48.
e: Calculated with FDA snapshot algorithm, primary analysis of the company. Time window for the analysis: day 294 to 377; if results from several samples are available within the time window, the last measurement is relevant [7].
f: Time window for the analysis: week 48 ± 6 weeks. Based on other approval processes in the therapeutic indication [8], 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. The company presented no results for the STB stratum.
g: Classification based on the "Gilead Sciences Grading Scale for Severity of Adverse Events and Laboratory Abnormalities".
h: Effect estimate and 95 % CI not meaningfully interpretable.
i: SOC.
j: HLGT and SMQ.

AE: adverse event; AIDS: acquired immunodeficiency syndrome; CDC: Centers for Disease Control and Prevention; CI: confidence interval; COBI: cobicistat; CSR: clinical study report; CSZ: convexity, symmetry, z score; EVG: elvitegravir; FDA: Food and Drug Administration; FTC: emtricitabine; HIV-1: human immunodeficiency virus type 1, HLGT: High Level Group Term; M = E: missing = excluded; M =F: missing = failure; 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; SOC: System Organ Class; STB: Stribild; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; vs.: versus

Table 2: Results (morbidity [continuous data], health related quality of life) – RCT 292-0109, 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**<br>**Outcome**<br>**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) | 52 (189.6) | 153 | 717 (252.9) | 38 (154.3) | 14.00 [-18.39; 46.69]; 0.397 |
| Health status (EQ-5D VAS)[d] | | | | | | | |
| 292-0109 | 279 | 86.7 (12.81) | 0.1 (12.53)[f] | 131 | 86.7 (12.29) | 0.6 (14.35)[f] | -0.50 [-3.36; 2.36][e]; 0.732 |
| **Health-related quality of life** | | | | | | | |
| SF-36 | | | | | | | |
| Physical sum score[d] | | | | | | | |
| 292-0109 | 286 | 55.0 (6.20) | -0.4 (6.00)[f] | 139 | 54.9 (6.64) | 0.5 (6.37)[f] | -0.90 [-2.17; 0.37][e]; 0.164 |
| Mental sum score[d] | | | | | | | |
| 292-0109 | 286 | 51.3 (9.06) | -1.1 (10.40)[f] | 139 | 51.8 (9.40) | -1.9 (9.16)[f] | 0.80 [-1.14; 2.74][e]; 0.420 |

a: EVG/COBI (concurs with the STB stratum of the study).
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: Higher values indicate better health status or better health-related quality of life.
e: Without imputation of missing values.

CD4: cluster of differentiation 4; CI: confidence interval; COBI: cobicistat; EQ-5D: European Quality of Life-5 Dimensions; EVG: elvitegravir; FTC: emtricitabine; ITT: intention to treat; LOCF: last observation carried forward; MD: mean difference; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SF-36: Short Form (36) Health Survey; STB: Stribild; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; VAS: visual analogue scale; vs.: versus

Concurring with the result of the analysis of the 48-week data, no statistically significant differences between the treatment groups were shown in the STB stratum of study 292-0109 after 96 weeks of treatment for all outcomes included in the benefit assessment except for discontinuation due to AEs, psychiatric disorders and nervous system disorders.

For the outcomes **"discontinuation due to AEs"** and **"psychiatric disorders"**, the analysis after 96 weeks showed a statistically significant difference in favour of emtricitabine/

tenofovir alafenamide (FTC/TAF). Due to the high risk of bias from the open-label study design, the result for these 2 outcomes was regarded as potentially highly biased however. The result for discontinuations due to AEs was based on discontinuations due to AEs that had already been included in the 48-week analysis (0 patients in the FTC/TAF arm versus 2 patients [1.3%] in the FTC/TDF arm). No advantage of FTC/TAF was derived from this result in the overall assessment with the not statistically significant effect of the 311-1089 study, which had a higher certainty of results at week 48. The difference for the outcome "psychiatric disorders" from the category "non-serious/non-severe side effects" was rated as no more than marginal. Overall, the results of the 292-0109 study after 96 weeks of treatment did not raise doubts about the result from the joint consideration and the meta-analysis of both studies after 48 weeks of treatment.

In addition, greater harm from FTC/TAF was derived in the meta-analysis for the outcome **"nervous system disorders"** in the benefit assessment. For the outcome, there was a hint of greater harm with the extent "minor" in patients receiving FTC/TAF in combination with a boosted protease inhibitor regimen, and proof of greater harm with the extent "considerable" in patients receiving FTC/TAF with other regimens. The result of the assessment was reflected in the results after week 96: The difference between the treatment groups was statistically significantly different to the disadvantage of FTC/TAF in the STB stratum of the study. These patients only received other regimens than protease inhibitor regimens. Conclusions for subgroups were therefore not meaningful on the basis of these results without consideration of study 311-1089.

### 2.3 Summary

It can be inferred from the information on the course of treatment discontinuations subsequently submitted by the company that only patients without indication for a treatment switch were included in the STB stratum of study 292-0109.

In the overall consideration, the assessment of the 96-week data of study 292-0109 resulted in no changes in comparison with the 48-week data presented in the dossier. The assessment of dossier assessment A16-30 on the added benefit of FTC/TAF for research question 3 was therefore not changed by the data subsequently submitted by the company.

**References**

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Emtricitabin/Tenofoviralafenamid (HIV-Infektion): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A16-30 [online]. 29.09.2016 [Accessed: 05.10.2016]. (IQWiG-Berichte; Volume 420). URL: https://www.iqwig.de/download/A16-30_Emtricitabin-Tenofoviralafenamid_Nutzenbewertung-35a-SGB-V_1-1.pdf.

2. Gilead Sciences. Stellungnahme zum IQWiG-Bericht Nr. 420: Emtricitabin/Tenofoviralafenamid (HIV-Infektion); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A16-30 [Soon available under https://www.g-ba.de/informationen/nutzenbewertung/233/#tab/beschluesse in the document "Zusammenfassende Dokumentation"].

3. Gilead Sciences. Emtricitabin/ Tenofoviralafenamid (Descovy): Dossier zur Nutzenbewertung gemäß § 35a SGB V; Modul 4A; in Kombination mit anderen antiretroviralen Arzneimitteln zur Behandlung von Erwachsenen und Jugendlichen (ab 12 Jahren und mit einem Körpergewicht von mindestens 35 kg), die mit dem Humanen Immundefizienzvirus Typ 1 (HIV-1) infiziert sind; medizinischer Nutzen und medizinischer Zusatznutzen, Patientengruppen mit therapeutisch bedeutsamem Zusatznutzen [online]. 15.05.2016 [Accessed: 23.09.2016]. URL: https://www.g-ba.de/downloads/92-975-1472/2016-05-15_Modul4A_Emtricitabin-Tenofoviralafenamid.pdf.

4. Gilead Sciences. Emtricitabin/ Tenofoviralafenamid (Descovy): Ergänzende Unterlagen zum Dossier Emtricitabin/ Tenofoviralafenamid (Descovy) im Rahmen der Stellungnahme (2016-05-15-D-228) gemäß 5. Kapitel § 19 Absatz 1 VerfO; in Kombination mit anderen antiretroviralen Arzneimitteln zur Behandlung von Erwachsenen und Jugendlichen (ab 12 Jahren und mit einem Körpergewicht von mindestens 35 kg), die mit dem Humanen Immundefizienzvirus Typ 1 (HIV-1) infiziert sind; Anhang A; 96-Wochen-Daten zu Studie GS-US-292-0109 (STB-Stratum) [unpublished]. 2016.

5. 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; tables and listings [unpublished]. 2016.

6. 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.

7. 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.

8. 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.