

IQWiG Reports – Commission No. A14-03

**Rilpivirine/emtricitabine/
tenofovir (new therapeutic
indication) –
Benefit assessment according
to §35a Social Code Book V¹**

Extract

¹ Translation of Sections 2.1 to 2.6 of the dossier assessment *Rilpivirin/Emtricitabin/Tenofovir (neues Anwendungsgebiet) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 March 2014). 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:

Rilpivirine/emtricitabine/tenofovir (new therapeutic indication) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:

Federal Joint Committee

Commission awarded on:

2 January 2014

Internal Commission No.:

A14-03

Address of publisher:

Institute for Quality and Efficiency in Health Care
Im Mediapark 8 (KölnTurm)
50670 Cologne
Germany

Tel.: +49 (0)221 – 35685-0

Fax: +49 (0)221 – 35685-1

E-Mail: berichte@iqwig.de

Internet: www.iqwig.de

Medical and scientific advice:

- Ingo Niemetz, practice, Kassel, 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 assessment²:

- Teresa Schade
- Katharina Biester
- Dorothea Gechter
- Thomas Kaiser
- Florina Kerekes
- Stefan K. Lhachimi
- Katrin Pieper
- Christoph Schürmann
- Min Zhou

Keywords: emtricitabine, rilpivirine, tenofovir disoproxil, HIV infections, benefit assessment

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

Table of contents

	Page
List of tables	iv
List of abbreviations.....	v
2 Benefit assessment	1
2.1 Executive summary of the benefit assessment.....	1
2.2 Research question	4
2.3 Information retrieval and study pool.....	5
2.3.1 Information retrieval.....	5
2.3.2 Description of the GS-US-264-0106 study	5
2.4 Results on added benefit.....	8
2.5 Extent and probability of added benefit	9
2.6 List of included studies	9
References for English extract	10

List of tables³

	Page
Table 2: RPV/FTC/TDF: extent and probability of added benefit.....	3
Table 3: Characteristics of the study included by the company – RCT, direct comparison: RPV/FTC/TDF vs. SBR	6
Table 4: RPV/FTC/TDF: extent and probability of added benefit.....	9

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
eGFR	estimated glomerular filtration rate
FTC	emtricitabine
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HIV-1	human immunodeficiency virus type 1
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
PI/r	ritonavir-boosted protease inhibitor
RCT	randomized controlled trial
RNA	ribonucleic acid
RPV	rilpivirine
SBR	stayed on baseline regimen
SGB	Sozialgesetzbuch (Social Code Book)
TDF	tenofovir disoproxil fumarate
TI	therapeutic indication

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/rilpivirine/tenofovir disoproxil. 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 2 January 2014.

Research question

The aim of the present report was to assess the added benefit of the drug combination rilpivirine/emtricitabine/tenofovir disoproxil (hereinafter referred to as RPV/FTC/TDF) for the new therapeutic indication of RPV/FTC/TDF approved in November 2013 in comparison with the appropriate comparator therapy (ACT). The assessment referred to adults infected with human immunodeficiency virus type 1 (HIV-1) without known mutations associated with resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, tenofovir or emtricitabine, and with a viral load $\leq 100\,000$ HIV-1 ribonucleic acid (RNA) copies/mL who have received previous antiretroviral treatment.

The G-BA specified the following ACT:

- 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 adverse events (AEs). The respective approval of the drugs was to be considered.

The company named individual antiretroviral therapy as ACT with the respective approval of the drugs to be considered. The company considered the individuality of the therapy when it specified the ACT. However, the fact that treatment switching may be advisable for certain reasons (particularly treatment failure or AEs) – as described in detail in the G-BA’s ACT – was not explicitly mentioned in the company’s ACT. The ACT specified by the G-BA was therefore used for the present dossier assessment.

The assessment was to be conducted based on patient-relevant outcomes and on randomized controlled trials (RCTs). Only studies with a minimum duration of 48 weeks (patients with previous antiretroviral treatment with several treatment options after treatment failure) or 2 years (patients with previous antiretroviral treatment who respond to their current treatment) were to be included.

Results

The study pool of the company for proving the added benefit of RPV/FTC/TDF contained the RCT GS-US-264-0106. This study was a multinational, randomized, open-label phase 3 study

for the expansion of the approval of RPV/FTC/TDF. The study compared RPV/FTC/TDF as single-tablet regimen after switching from an antiretroviral treatment regimen (consisting of 1 ritonavir-boosted protease inhibitor [PI/r] and 2 nucleoside reverse transcriptase inhibitors [NRTIs]) with continuation of this ongoing treatment (stayed on baseline regimen [SBR]). The total study duration was 48 weeks, however, the randomized controlled study phase already ended after week 24.

The study presented by the company was unsuitable for assessing the added benefit of RPV/FTC/TDF versus the ACT. The ACT specified by the G-BA was not implemented in the study, and the study duration with a randomized controlled phase of 24 weeks was too short.

No implementation of ACT

The patients in the control group, the SBR arm, stayed on their baseline therapy (1 PI/r and 2 NRTIs) in the GS-US-264-0106 study. It was not possible for the patients to adapt or switch their treatment regimen during the randomized controlled study phase, although the majority of patients had wanted to switch treatments before the start of the study. For example, 10.7% of the patients in the SBR arm reported current AEs and 21.4% concerns about the longterm AEs of their current treatment as reason for their study participation. This highlights that an adaption or a switch of antiretroviral therapy should have been at least offered in the study to reflect the ACT. The ACT mentions these aspects in particular, among other ones, to characterize an individual antiretroviral therapy: "(...) under consideration of the reason for the treatment switch, particularly (...) due to adverse events." In the GS-US-264-0106 study, however, the patients' wish to switch treatments was ignored in the randomized controlled study phase.

Overall, the ACT was not implemented in the GS-US-264-0106 study.

Study duration insufficient

The randomized controlled first phase of the GS-US-264-0106 study lasted 24 weeks and was therefore not sufficiently long. A minimum study duration of 48 weeks (patients with previous antiretroviral treatment with several treatment options after treatment failure) or 2 years (patients with previous antiretroviral treatment who respond to their current treatment) was considered necessary for the present research question. This is explained in detail in Section 2.7.2.1 of the full dossier assessment.

Extent and probability of added benefit, patient groups with therapeutically important added benefit⁴

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

Table 2: RPV/FTC/TDF: extent and probability of added benefit

Therapeutic indication	ACT	Extent and probability of added benefit
Treatment of adults infected with HIV-1 without known mutations associated with resistance to the NNRTI class, tenofovir or emtricitabine, and with a viral load $\leq 100\,000$ HIV-1 RNA copies/mL who have received previous antiretroviral treatment	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 AEs The respective approval of the drugs was to be considered.	Added benefit not proven
ACT: appropriate comparator therapy; AE: adverse event; HIV-1: human immunodeficiency virus type 1; NNRTI: non-nucleoside reverse transcriptase inhibitor; RNA: ribonucleic acid; RPV/FTC/TDF: rilpivirine/emtricitabine/tenofovir disoproxil		

The G-BA decides on the added benefit.

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), see [1]. The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit), see [2].

2.2 Research question

The aim of the present report was to assess the added benefit of the drug combination RPV/FTC/TDF for the new therapeutic indication of RPV/FTC/TDF approved in November 2013 in comparison with the ACT. The assessment referred to adults infected with HIV-1 without known mutations associated with resistance to the NNRTI class, tenofovir or emtricitabine, and with a viral load $\leq 100\,000$ HIV-1 RNA copies/mL who have received previous antiretroviral treatment.

The G-BA specified the following ACT:

- 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 AEs. The respective approval of the drugs was to be considered.

The company named individual antiretroviral therapy as ACT with the respective approval of the drugs to be considered. The company considered the individuality of the therapy when it specified the ACT. However, the fact that treatment switching may be advisable for certain reasons (particularly treatment failure or AEs) – as described in detail in the G-BA's ACT – was not explicitly mentioned in the company's ACT. The ACT specified by the G-BA was therefore used for the present dossier assessment.

The assessment was to be conducted based on patient-relevant outcomes and on RCTs. Only studies with a minimum duration of 48 weeks (patients with previous antiretroviral treatment with several treatment options after treatment failure) or 2 years (patients with previous antiretroviral treatment who respond to their current treatment) were to be included.

Further information about the research question can be found in Module 3A, Section 3.1, and Module 4A, Section 4.2.1, of the dossier, and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

2.3 Information retrieval and study pool

2.3.1 Information retrieval

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 RPV/FTC/TDF (studies completed up to 31 October 2013)
- bibliographical literature search on RPV/FTC/TDF (last search on 8 November 2013)
- search in trial registries for studies on RPV/FTC/TDF (last search on 4 November 2013)

One study in the relevant therapeutic indication was identified from the steps of information retrieval mentioned (GS-US-264-0106 [3]). This study was unsuitable for assessing the added benefit of RPV/FTC/TDF versus the ACT specified by the G-BA. The reason for this was that the G-BA's ACT was not implemented in the study. Moreover, the study duration with a randomized controlled phase of 24 weeks was too short. The GS-US-264-0106 study is described and the reasons for exclusion are explained in detail in the following Section 2.3.2.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4A, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment. Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4A, Section 4.3.1.1 of the dossier and in Sections 2.7.2.3.1 and 2.7.2.3.2 of the full dossier assessment.

2.3.2 Description of the GS-US-264-0106 study

Table 3 describes the study characteristics of the GS-US-264-0106 study.

Table 3: Characteristics of the study included by the company – RCT, direct comparison: RPV/FTC/TDF vs. SBR

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes ^a
GS-US-264-0106	RCT, open-label, active-controlled, parallel, multicentre	<p>Virologically suppressed^b HIV-1 infected adults with previous antiretroviral therapy</p> <ul style="list-style-type: none"> ▪ no prior virologic failure ▪ on their first or second antiretroviral therapy ▪ therapy with 1 PI/r and 2 NRTIs at study inclusion ▪ no previous use of NNRTIs ▪ adequate renal function (eGFR ≥ 70 mL/min) 	<p>1) RPV/FTC/TDF (25 mg/200 mg/245 mg^c): once daily at approximately the same time with a meal (N = 321)</p> <p>2) SBR: continuation of current treatment consisting of 1 PI/r and 2 NRTIs (N = 161)</p> <p>thereof with mutations associated with resistance against NNRTI^d:</p> <p>1) RPV/FTC/TDF: n = 65/317 (20.5%)</p> <p>2) SBR: n = 25/159 (15.7%)</p>	<p>Screening: 30 days</p> <p>Treatment: 48 weeks:</p> <ul style="list-style-type: none"> ▪ controlled phase up to week 24 ▪ uncontrolled phase (weeks 25-48): patients in the SBR arm switched to RPV/FTC/TDF <p>follow-up: 30 days^e</p>	<p>110 study centres in Austria, Belgium, Canada, France, Germany, Italy, Puerto Rico, Spain, United Kingdom, and United States</p> <p>Treatment period: 11/2010 – 08/2012</p>	<p><u>Primary outcome:</u> virologic response at week 24 (< 50 HIV-1 RNA copies/mL)</p> <p><u>secondary outcomes:</u> mortality, AIDS-defining events, symptoms, change in CD4 cell count, AEs</p>

a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes contain exclusively information on relevant available outcomes for this benefit assessment.

b: < 50 HIV-1 RNA copies/mL at the time point of screening and 6 months prior to screening.

c: 300 mg tenofovir disoproxil fumarate cited in the study, corresponding to 245 mg tenofovir disoproxil.

d: In relation to the analysis of the full analysis set, which included all patients who had received the study drug at least once. A detailed overview of the mutations associated with resistance against NNRTI from historical genotype determination of resistances can be found in Table 8, Appendix A of the full dossier assessment.

e. Continued treatment of the patients until the study drug becomes commercially available in their country.

AE: adverse event; AIDS: acquired immunodeficiency syndrome; CD4: cluster of differentiation 4; eGFR: estimated glomerular filtration rate; HIV-1: human immunodeficiency virus type 1; N: number of randomized patients; n: number of patients; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; PI/r: ritonavir-boosted protease inhibitor; RCT: randomized controlled trial; RNA: ribonucleic acid; RPV/FTC/TDF: rilpivirine/emtricitabine/tenofovir disoproxil; SBR: stayed on baseline regimen; vs.: versus

The GS-US-264-0106 study [3] was a multinational, randomized, open-label phase 3 study for the expansion of the approval of RPV/FTC/TDF. The study compared RPV/FTC/TDF as single-tablet regimen after switching from an antiretroviral treatment regimen (consisting of 1 PI/r and 2 NRTIs) with continuation of this ongoing treatment (SBR).

HIV-infected adult patients who were virologically suppressed at the time point of screening and in the previous 6 months and who had no history of virologic failure were included in the study. Moreover, the patients had to be on their first or second antiretroviral therapy, and their current treatment regimen had to consist of 1 PI/r and 2 NRTIs for ≥ 6 months. Previous use of any drugs from the NNRTI class was not allowed. Adequate renal function (defined as estimated glomerular filtration rate [eGFR] of at least 70 mL/min) was an inclusion criterion.

Only patients who had a determination of their genotype conducted prior to starting initial antiretroviral therapy were included in the GS-US-264-0106 study. Furthermore, patients were not allowed to have a known resistance to any of the drugs used in the study at an earlier time point (according to the inclusion criterion: including, but not limited to the reverse transcriptase resistance mutations K65R, K101E/P, E138G/K/R/Q, Y181C/I/V, M184V/I or H221Y).

A total of 482 patients were randomized to RPV/FTC/TDF (N = 321) and SBR (N = 161). The 2:1 randomization was stratified by TDF use (as individual substance or in fixed combination with FTC) and ritonavir-boosted lopinavir.

Patients in the RPV/FTC/TDF arm took the drug combination once daily with a meal at approximately the same time, according to the approval (25 mg/200 mg/245 mg). Patients in the SBR arm stayed on their previous antiretroviral treatment regimen. After the end of the randomized controlled study phase, they also had the option to switch treatment.

The total study duration was 48 weeks plus 30 days follow-up, however, the randomized controlled study phase already ended after week 24.

No implementation of ACT

The ACT was an 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 AEs. The respective approval of the drugs was to be considered.

The ACT was not implemented in the GS-US-264-0106 study.

The patients in the control group, the SBR arm, stayed on their baseline therapy in the study. This therapy consisted of a combination of 1 PI/r and 2 NRTIs. It was not possible for the patients to adapt or switch their treatment regimen during the randomized controlled study phase, although the majority of patients had wanted to switch treatments before the start of the study. For example, 10.7% of the patients in the SBR arm reported current AEs and 21.4%

concerns about the longterm AEs of their current treatment as reason for their study participation (8.5% and 13.9% in the RPV/FTC/TDF arm). An overview of the reasons given by the patients is provided in Appendix A (Table 9) of the full dossier assessment. This highlights that an adaption or a switch of antiretroviral therapy should have been at least offered in the study to reflect the ACT. The ACT mentions these aspects in particular, among other ones, to characterize an individual antiretroviral therapy: “(...) under consideration of the reason for the treatment switch, particularly (...) due to adverse events.” Moreover, the company itself described in Module 4A, Section 4.4.2, that it was not acceptable to continue the regimen of a patient who is indicated for a treatment switch. The explanations given above are also not outbalanced by the company’s claim in its reporting of results on AEs (Module 4A, Section 4.3.1.3.1.5) that patients with relevant intolerance already switched treatment long before the study started. The data presented above show that a considerable proportion of patients in the control group had current AEs or were worried about longterm AEs.

In a different section of Module 4A (at the end of Section 4.4.2), the company explained that an antiretroviral therapy consisting of 2 NRTIs in combination with PI/r was a therapeutic option within the G-BA’s ACT “individual antiretroviral therapy”. The company also described there that it was generally out of question that it is impossible to conduct a multinational multicentre RCT that would allow to compare the drug to be assessed with all kinds of individual treatments because of the vast number of possible treatment options within an individual antiretroviral therapy.

Such a study, as described by the company above, was not required in the present dossier assessment. However, in an individual antiretroviral therapy, as characterized by the ACT, the option of adapting or switching the current treatment regimen must exist, and an adaption or switch must be possible. In the GS-US-264-0106 study, however, this patients’ wish to switch treatments was ignored in the randomized controlled study phase.

Study duration insufficient

The randomized controlled first phase of the GS-US-264-0106 study lasted 24 weeks and was therefore not sufficiently long. A minimum study duration of 48 weeks (patients with previous antiretroviral treatment with several treatment options after treatment failure) or 2 years (patients with previous antiretroviral treatment who respond to their current treatment) was considered necessary for the present research question. This is explained in detail in Section 2.7.2.1 of the full dossier assessment.

Further information about the study design and the study populations can be found in Module 4A, Section 4.3.1.2.1 of the dossier, and in Section 2.7.2.3.2 of the full dossier assessment.

2.4 Results on added benefit

In its dossier, the company presented no suitable studies for the assessment of the added benefit of RPV/FTC/TDF versus the ACT specified by the G-BA. Since no relevant data for

the benefit assessment were presented, there is no proof of added benefit of RPV/FTC/TDF in comparison with the ACT specified by the G-BA.

This result deviates from that of the company, which derived an added benefit from the study it included.

Further information about the results on added benefit can be found in Module 4A, Section 4.3.1.3 of the dossier, and in Section 2.7.2.4 of the full dossier assessment.

2.5 Extent and probability of added benefit

The result of the assessment of the added benefit of RPV/FTC/TDF in comparison with the ACT is shown in Table 4.

Table 4: RPV/FTC/TDF: extent and probability of added benefit

Therapeutic indication	ACT	Extent and probability of added benefit
Treatment of adults infected with HIV-1 without known mutations associated with resistance to the NNRTI class, tenofovir or emtricitabine, and with a viral load \leq 100 000 HIV-1 RNA copies/mL who have received previous antiretroviral treatment	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 AEs The respective approval of the drugs was to be considered.	Added benefit not proven
ACT: appropriate comparator therapy; AE: adverse event; HIV-1: human immunodeficiency virus type 1; NNRTI: non-nucleoside reverse transcriptase inhibitor; RNA: ribonucleic acid; RPV/FTC/TDF: rilpivirine/emtricitabine/tenofovir disoproxil		

This assessment deviates from that of the company, which derived a hint of a non-quantifiable added benefit for RPV/FTC/TDF.

The G-BA decides on the added benefit.

2.6 List of included studies

The information usually provided here is not applicable as the study included by the company was unsuitable for the assessment of the added benefit of RPV/FTC/TDF versus the ACT specified by the G-BA for the reasons stated above.

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 4.1 [online]. 28 November 2013 [accessed: 7 February 2014]. URL: https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-1.pdf.
2. Institute for Quality and Efficiency in Health Care. Ticagrelor: benefit assessment according to §35a Social Code Book V; extract; commission no. A11-02 [online]. 29 September 2011 [accessed: 5 May 2012]. URL: https://www.iqwig.de/download/A11-02_Extract_of_dossier_assessment_Ticagrelor.pdf.
3. Gilead Sciences. A phase 3 randomized, open-label study to evaluate switching from regimens consisting of a ritonavir-boosted protease inhibitor and two nucleoside reverse transcriptase inhibitors to emtricitabine/rilpivirine/tenofovir disoproxil fumarate (FTC/RPV/TDF) fixed-dose regimen in virologically-suppressed, HIV-1 infected patients: study GS-US-264-0106; week 48 clinical study report [unpublished]. 2012.

The full report (German version) is published under

https://www.iqwig.de/de/projekte_ergebnisse/projekte/arzneimittelbewertung/a14_03_wirkstoffkombination_rilpivirin_emtricitabin_und_tenofovirdisoproxil_neues_anwendungsgebiet_nutzenbewertung_gemaess_35a_sgb_v_dossierbewertung.5372.html.