IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Report – Commission No. A12-02

Rilpivirine/emtricitabine/tenofovir –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment ("Rilpivin/Emcitricitabin/Tenofovir – Nutzenbewertung gemäß § 35a SGB V" (Version 1.0; Status: 12.04.2012). 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.

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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:

- Christoph Stephan, J.W. Goethe University Hospital, Frankfurt, 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. Individual sections and conclusions in the dossier assessment therefore do not necessarily reflect his opinion.

IQWiG employees involved in the dossier assessment:[2]

- Sebastian Werner
- Elke Hausner
- Thomas Kaiser
- Stefan K. Lhachimi
- Yvonne-Beatrice Schüler
- Guido Skipka
- Sibylle Sturtz
- Min Zhou

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

Table of contents

List of tables

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
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)
NRTI	nucleoside reverse transcriptase inhibitor
RCT	randomized controlled trial
RIL/EMTRI/TENO.	rilpivirine/emtricitabine/tenofovir disoproxil
RNA	ribonucleic acid
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
STR	single tablet regime

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 undertake the benefit assessment of the fixed-dose combination rilpivirine/emtricitabine/tenofovir disoproxil[3] (RIL/EMTRI/TENO). 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 13.01.2012.

Research question

The aim of this report was to assess the added benefit of the fixed-dose combination RIL/EMTRI/TENO compared to the appropriate comparator therapy (ACT) (efavirenz in combination with emtricitabine/tenofovir) in the approved therapeutic indication (human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve adult patients with a viral load ≤ 100,000 HIV-1 RNA copies/ml).

The comparator therapy chosen by the company corresponded to the ACT previously specified by the G-BA.

Results

A total of 3 studies relevant for the assessment were identified (C204, C209 and C215). None of the 3 studies was conducted with the *fixed*-dose combination RIL/EMTRI/TENO; instead, in all 3 studies, rilpivirine was used in free combination with emtricitabine/tenofovir. These studies were considered relevant for the current research question, because the dosage of each active substance corresponded to that in the fixed-dose combination.

The Institute's assessment regarding the number of relevant studies deviated substantially from the company's procedure. The additional study included by the Institute (Study C204) is relevant for answering the research question. However, although this study fulfils the company's own inclusion criteria defined in its dossier, the company excluded it. Nevertheless, due to the low number of relevant patients, the Institute considers the possible influence of this study on the overall result of the benefit assessment as very minor.

In addition to the lack of consideration of the results of the C204 study in the benefit assessment, there was a serious deficiency in the company's dossier in that no subgroup analyses or investigations of potential effect modifiers were carried out. The dossier templates state that, where meaningful, as a minimum, the factors of gender, age and severity and stage

[3] For the sake of simplicity, in this document the drug name "tenofovir" is used instead of the prodrug name "tenofovir disoproxil".

of the disease should be investigated as a possible source of effect modification. However, such analyses were neither presented in the company's dossier nor was a reason given for the omission of these analyses. The examination of other documents showed that for the treatment comparison of rilpivirine and efavirenz (each in combination with a backbone therapy consisting of 2 nucleoside reverse transcriptase inhibitors (NRTIs)), there was proof of an effect modification by the characteristic "gender" for the outcome "viral load" (virologic response). These data prove a statistically significantly better virologic response under treatment with rilpivirine compared to efavirenz in men, but not in women. Knowledge of the effect modification caused by gender with regard to an outcome relevant to the assessment makes it essential to consider these subgroup results. No complete data for such an evaluation were available in the company's dossier.

In summary, the contents of the company's dossier are incomplete, in particular because relevant subgroup analyses required in the dossier templates were not presented by the company - without a reason given by the company for this omission. In addition, one relevant study was not included by the company in its assessment. However, it can be assumed with a high degree of probability that this study would not substantially affect the conclusions of the benefit assessment.

The company also investigated whether the administration of a complete antiretroviral combination treatment as a single tablet (single tablet regime [STR]) has an added benefit compared to the administration of the individual components (non-STR treatment). The analyses presented by the company were, however, basically not suitable for answering this research question because only the effect of a multi-tablet treatment regime "once daily" compared to a multi-tablet treatment regime "twice daily" was investigated.

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

Due to the incompleteness of the dossier contents, there is no proof of an added benefit for the fixed-dose combination RIL/EMTRI/TENO compared to the ACT. Hence there are also no patient groups for whom a therapeutically important added benefit can be derived.

The G-BA decides on the added benefit.

[4]. On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit of an intervention. 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 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 data not interpretable), see [2]. The extent of added benefit is graded into 6 categories: (1) major, (2) considerable, (3) minor, (4) non-quantifiable, (5) no added benefit, or (6) less benefit, see [3].

2.2 Research question

According to the Summary of Product Characteristics (SPC), the fixed-dose combination RIL/EMTRI/TENO is approved for the following therapeutic indication [1]:

- "…for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve adult patients with a viral load ≤ 100,000 HIV-1 RNA copies/ml".

The company designated efavirenz in combination with emtricitabine and tenofovir as ACT. It thereby followed the G-BA's specification, which named efavirenz in combination with emtricitabine/tenofovir or in combination with abacavir/lamivudine as ACT.

The assessment was carried out with respect to patient-relevant outcomes. Only direct comparative randomized, controlled trials (RCTs) were included in the assessment.

Further information about the research question can be found in Module 3, Section 3.1 and Module 4, 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

The study pool of the assessment was compiled from the following data:

- Studies completed by the company up to 25.11.2011 on the combination of RIL/EMTRI/TENO (study list of the company)
- Results of a search in trial registries for studies on the combination of RIL/EMTRI/TENO (last search on 30.08.2011, searches by the company)
- The Institute' own searches in trial registries for studies on the combination of RIL/EMTRI/TENO to check the company's search results up to 02.02.2012. The result of the check showed a deviation from the study pool presented in the company's dossier.

The study pool resulting from these steps differed substantially from that of the company. The company's study pool contained only 2 studies and is thus incomplete, because the company excluded an additional relevant Phase II study (C204). The Institute does not follow the company's reasoning for the exclusion of this study (see 2.7.2.3 of the full dossier assessment). Thus there are 3 relevant studies for the benefit assessment.

Further information about the inclusion criteria for studies in the present benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier and in Sections 2.7.2.1 and 2.7.2.3.1 of the full dossier assessment.

2.3.1 Studies included

The 3 studies listed in the following table were included in the benefit assessment.

Table 2: Study pool[5]

	Study category		
Study	**Study for approval of the drug to be assessed (yes/no)**	**Sponsored study[a] (yes/no)**	**Third-party study (yes/no)**
C204	yes	yes	no
C209 (ECHO)	yes	yes	no
C215 (THRIVE)	yes	yes	no
a: Study for which the company was sponsor, or in which the company was otherwise financially involved.			

Section 2.6 contains a list of data sources named by the company for the included studies.

None of the 3 studies was conducted with the *fixed*-dose combination RIL/EMTRI/TENO; instead, in all 3 studies, rilpivirine was used in free combination with emtricitabine/tenofovir. These studies were considered relevant for the current research question, because the dosage of each active substance corresponded to that in the fixed-dose combination.

The Institute's assessment regarding the number of relevant studies deviates substantially from the company's procedure. The additional study included by the Institute (Study C204) is relevant for answering the research question. However, although this study fulfils the company's own inclusion criteria defined in its dossier, the company excluded it. Nevertheless, due to the low number of relevant patients, the Institute considers the possible influence of this study on the overall result of the benefit assessment as very minor (see Section 2.7.2.3.2 of the full dossier assessment).

In addition to the lack of consideration of the results of the C204 study in the benefit assessment, there was a serious deficiency in the company's dossier in that no subgroup analyses or investigations of potential effect modifiers were carried out. According to the dossier templates, where meaningful, as a minimum the factors of gender, age and severity and stage of the disease should be investigated as a possible source of effect modification. However, such analyses were neither presented in the company's dossier nor was a reason given for the omission of these analyses (see Section 2.7.2.2 of the full dossier assessment).

To estimate the possible influence of the lack of subgroup analyses on the overall result of the benefit assessment, the Institute referred back to Module 4 of the dossier on rilpivirine (single drug) that it assessed in parallel [2]. For the treatment comparison of rilpivirine and efavirenz (each in combination with a backbone therapy consisting of 2 NRTIs), there was proof of an effect modification by the characteristic "gender" for the outcome "viral load" (virologic response) [2,3]. These data prove a statistically significantly better virologic response under treatment with rilpivirine compared to efavirenz in men, but not in women. Knowledge of the effect modification caused by gender with regard to an outcome relevant to the assessment

[5] Table numbering starts with "2" as numbering follows that in the full dossier assessment.

makes it essential to consider these subgroup results. No complete data for such an evaluation were available in the company's dossier.

In summary, the contents of the company's dossier are incomplete, in particular because the relevant subgroup analyses requested in the dossier documents were not presented by the company - without a reason given by the company for this omission. In addition, one relevant study was not included by the company in its assessment. However, it can be assumed with a high degree of probability that this study would not substantially affect the conclusions of the benefit assessment.

Due to the incompleteness of the dossier contents, there is no proof of added benefit for the fixed-dose combination RIL/EMTRI/TENO compared to the ACT.

Further information about the result of information retrieval and the resulting study pool can be found in Module 4, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier and in Section 2.7.2.3.2 of the full dossier assessment. Further information about the study design and study populations can be found in Module 4, Sections 4.3.1.2.1, 4.3.1.2.2 and 4.3.2.1.2 of the dossier. The information provided by the company on subgroup analyses can be found in Module 4, Sections 4.2.5.5 and 4.3.1.3.6 of the dossier and in Section 2.7.2.2 of the full dossier assessment.

2.4 Results concerning added benefit

Due to the incompleteness of the dossier contents, the data submitted by the company provide no proof of an added benefit for the fixed-dose combination RIL/EMTRI/TENO compared to the ACT.

The company also investigated whether the administration of a complete antiretroviral combination treatment as a single tablet (single tablet regime [STR]) has an added benefit compared to the administration of the individual components (non-STR treatment). The analyses presented by the company were, however, basically not suitable for answering this research question because only the effect of a multi-tablet treatment regime "once daily" compared to a multi-tablet treatment regime "twice daily" was investigated (see Section 2.7.2.4 of the full dossier assessment).

The result of the assessment by the Institute deviates from that by the company, which derived an added benefit for the fixed-dose combination RIL/EMTRI/TENO.

Further information about the choice of outcome, risk of bias at outcome level and outcome results can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier.

2.5 Extent and probability of added benefit

Due to the incompleteness of the dossier contents, there is no proof of an added benefit for the fixed-dose combination RIL/EMTRI/TENO compared to the ACT. Hence there are also no patient groups for whom a therapeutically important added benefit can be derived.

This deviates from the company's assessment, which derived an overall major added benefit.

Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier and in Section 2.7.2.5 of the full dossier assessment

2.6 List of included studies

C204

Tibotec. A phase IIb randomized, partially blinded, dose-finding trial of TMC278 in antiretroviral naive HIV-1 infected subjects: primary 48-week analysis; study TMC278-C204; clinical research report [unpublished]. 2007.

C209

Cohen C, Molina JM, Cahn P, Cloted B, Fourie J. Pooled week 48 efficacy and safety results from ECHO and THRIVE, two double-blind, randomised, phase III trials comparing TMC278 versus efavirenz in treatment-naïve, HIV-1-infected patients [Präsentationsfolien]. XVIII International AIDS Conference; 18.-23.07.2010; Wien, Österreich.

Cohen C, Moline JM, Chetchotisakd P, Lazzarin A, Rhame F, Stellbrink HJ et al. Pooled week 96 efficacy, resistance and safety results from the double-blind, randomised, phase III trials comparing rilpivirine (RPV, TMC278) versus efavirenz (EFV) in treatment-naïve, HIV-1-infected adults [online]. In: 6th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention; 17.-20.07.2011; Rom, Italien. [Accessed on: 27.03.2012]. URL: http://www.crine.org/templates/cri/pdfs/Poster-Rome-week-96-Final.pdf.

Hodder S, Arasteh K, De Wet J, Gathe J, Gold J, Kumar P. Effect of gender and race analyses on week 48 efficacy and safety findings in treatment-naïve, HIV-1-infected patients enrolled in ECHO and THRIVE [Poster]. 48th Annual Meeting of the Infectious Diseases Society of America; 21.-24.10.2010; Vancouver, Kanada.

Mills A, Antinori A, Clotet B, Fisher M, Fourie J, Herrera G. Neurologic and psychiatric safety profile of TMC278 compared with efavirenz in treatment-naïve, HIV-1-infected patients: pooled analysis from the randomized, double blind, phase III ECHO and THRIVE trials at 48 weeks [online]. In: 18th Conference on Retroviruses and Opportunistic Infections; 27.02.-02.03.2011; Boston, USA. [Accessed on: 27.03.2012]. URL: http://www.hivandhepatitis.com/2011_conference/croi2011/posters/mills.pdf.

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Molina JM, Cahn P, Grinsztejn B, Lazzarin A, Mills A, Saag M et al. Rilpivirine versus efavirenz with tenofovir and emtricitabine in treatment-naive adults infected with HIV-1 (ECHO): a phase 3 randomised double-blind active-controlled trial. Lancet 2011; 378(9787): 238-246.

Nelson M, Gazzard B, Walmsley S, Ruane P, Jayaweera D, Vanveggel S et al. Pooled week 48 safety and efficacy results from ECHO and THRIVE phase III trials comparing rilpivirine vs. efavirenz in treatment-naive HIV-1-infected patients receiving FTC/TDF [Poster]. 17th Annual Conference of the British HIV Association; 06.-08.04.2011; Bournemouth, Großbritannien.

Rimsky L, Vingerhoets J, Van Eygen V, Eron J, Cloted B, Vanveggel S. Genotypic and phenotypic characterization of HIV-1 isolates obtained from patients failing rilpivirine (RPV, TMC278) in the phase III studies ECHO and THRIVE: 48 week analysis [online]. In: 20th International Workshop on HIV & Hepatitis Virus Drug Resistance and Curative Strategies; 07.-11.06.2011; Los Cabos, Mexiko. [Accessed on: 27.03.2012]. URL: http://hivdb.stanford.edu/pages/pdf/RPV_IHDRW_2011_Poster_9.pdf.

Tibotec. A phase III, randomized, double-blind trial of TMC278 25 mg q.d. versus efavirenz 600 mg q.d. in combination with a fixed background regimen consisting of tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naïve HIV-1 infected subjects: study TMC278-TiDP6-C209; week 48 analysis report [unpublished] 2010.

C215

Cohen C, Molina JM, Cahn P, Cloted B, Fourie J. Pooled week 48 efficacy and safety results from ECHO and THRIVE, two double-blind, randomised, phase III trials comparing TMC278 versus efavirenz in treatment-naïve, HIV-1-infected patients [Präsentationsfolien]. XVIII International AIDS Conference; 18.-23.07.2010; Wien, Österreich.

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Rimsky L, Vingerhoets J, Van Eygen V, Eron J, Cloted B, Vanveggel S. Genotypic and phenotypic characterization of HIV-1 isolates obtained from patients failing rilpivirine (RPV, TMC278) in the phase III studies ECHO and THRIVE: 48 week analysis [online]. In: 20th International Workshop on HIV & Hepatitis Virus Drug Resistance and Curative Strategies; 07.-11.06.2011; Los Cabos, Mexiko. [Accessed on: 27.03.2012]. URL: http://hivdb.stanford.edu/pages/pdf/RPV_IHDRW_2011_Poster_9.pdf.

Tibotec. A phase III, randomized, double-blind trial of TMC278 25 mg q.d. versus efavirenz 600 mg q.d. in combination with a background regimen containing 2 nucleoside/nucleotide reverse transcriptase inhibitors in antiretroviral-naïve HIV-1 infected subjects: study TMC278-TiDP6-215; week 48 analysis report [unpublished]. 2010.

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Please see full dossier assessment for full reference list.

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