IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Addendum to Commission A12-02

Rilpivirine/emtricitabine/ tenofovir[1]

Extract

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Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
DAIDS	Division of Acquired Immune Deficiency Syndrome (Table for Grading the Severity of Adverse Events)
EMTRI/TENO	emtricitabine/tenofovir disoproxil
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	rilpivirine
RIL/EMTRI/TENO	rilpivirine/emtricitabine/tenofovir disoproxil
RNA	ribonucleic acid
SAE	serious adverse event
SF-36v2	Short Form (36) Health Survey, Version 2
SF-6D	Short Form (6) Domains Evaluation
SGB	Sozialgesetzbuch (Social Code Book)

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

On 13.01.2012, 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 fixed-dose combination containing the active substances rilpivirine/emtricitabine/tenofovir[3] (Commission Number A12-02). The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"), (Benefit assessment of IQWiG dated 12.04.2012). Within the framework of the Commenting Procedure, the company sent additional data to the G-BA on 07.05.2012. On 07.06.2012, the G-BA commissioned IQWiG to undertake a benefit assessment (corresponding to Section 2.5 of IQWiG benefit assessments [Extent and probability of added benefit]) of the existing data in the dossier and the data subsequently submitted by the company in the Commenting Procedure.

Research question

The aim of this report was to assess the added benefit of the fixed-dose combination rilpivirine/emtricitabine/tenofovir 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-naïve adult patients with a viral load of ≤ 100,000 HIV-1 RNA copies/ml).

Only randomized, controlled trials (RCTs) with a direct comparator were included in the assessment.

Results[4]

In total, 3 relevant studies (C204, C209 and C215) were available for the assessment. None of the studies was conducted with the fixed-dose combination rilpivirine/emtricitabine/tenofovir. Instead, in all 3 studies rilpivirine (RIL) was used in free combination with emtricitabine/tenofovir (EMTRI/TENO). These studies were considered relevant for the present research question, because the dosage of the single active substances corresponded to that in the fixed-dose combination. All 3 studies were randomized and active-controlled. A direct comparison on the basis of 3 RCTs was possible. Antiretroviral-naïve adult patients with confirmed HIV-1 infection and an HIV-1 plasma viral load at the start of the study of

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

[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 data not interpretable)., (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].

≥ 5000 RNA copies/ml were enrolled in all 3 studies. In 2 studies (C204, C215) other backbone therapies (consisting of 2 nucleoside reverse transcriptase inhibitors [NRTIs]) could be used as well as EMTRI/TENO. Data of the target population as defined by the research question were used from the relevant studies (patients with a viral load ≤ 100,000 HIV-1 RNA copies/ml, treated with the backbone therapy EMTRI/TENO).

The risk of bias of the 3 studies at study level was rated as low. If the study results were sufficiently homogeneous they were combined in a meta-analysis. On the basis of the available evidence (3 RCTs), in principle proof, e.g. of an added benefit, could be derived, unless outcome-specific aspects weakened the informative value.

The following results were found for the therapeutic indication investigated:

Mortality

An added benefit or greater harm from the fixed-dose combination RIL/EMTRI/TENO compared to efavirenz + EMTRI/TENO for this outcome is not proven. It should be considered that, due to study duration and the number of enrolled patients, the studies were not suitable for demonstrating differences between the treatments with regard to this outcome.

Morbidity

Viral load (virological response) as a surrogate outcome for the combined outcome "AIDS-defining diseases/death"

The Institute assessed the outcome "virological response" as sufficiently valid for use as a surrogate for a patient-relevant outcome that was not, however, recorded in the included studies (combined outcome "AIDS-defining diseases/death"). However, it must be considered that the viral load (virological response) is not clearly validated as surrogate. A correlation can only be demonstrated between an individual change in viral load and the risk of the combined outcome "AIDS-defining diseases/death" and no *clear* correlation has been found between the effects of the intervention on the surrogate and the patient-relevant outcome that the surrogate is supposed to replace [3-6]. Nevertheless, the fact that the Institute considers the surrogate to have "sufficient validity" is justified, particularly in view of the dramatic improvements in prognosis for HIV patients in terms of survival and outbreak of the disease, based on drug trials directed towards reducing the viral load (see also [7] for more detailed reasoning). The increased uncertainty is taken account of through the rating assigned to the extent of added benefit (rating of any added benefit as "non-quantifiable").

The meta-analysis showed no statistically significant difference between rilpivirine + EMTRI/TENO and efavirenz + EMTRI/TENO in terms of virological response. However, in subgroup analyses there was an indication of an effect modification ($p < 0.2$) for the characteristic "gender", so that a separate consideration of these subgroups was necessary. There was thus a statistically significant effect in favour of rilpivirine + EMTRI/TENO compared to efavirenz + EMTRI/TENO in men, but not in women. Overall, in men there is proof of added benefit of the fixed-dose combination RIL/EMTRI/TENO compared to the

ACT in terms of virological response. In contrast, an added benefit for women for this outcome is not proven.

Health-related quality of life

The result for health-related quality of life (recorded using SF-36v2) was not statistically significant. An added benefit in terms of the outcome "health-related quality of life" for the fixed-dose combination RIL/EMTRI/TENO compared to efavirenz + EMTRI/TENO is not proven.

Adverse events

The result for adverse events (AEs), serious AEs (SAEs) and psychiatric AEs was, in each case, not statistically significant. Although the result for adverse events affecting the skin showed a statistically significant difference in favour of rilpivirine + EMTRI/TENO, the effect size was too marginal. The results for study discontinuations due to AEs could not be combined in a meta-analysis because of heterogeneity ($p < 0.2$). No further investigation of heterogeneity was necessary in this case, because the individual results of all 3 studies were not statistically significant. Greater/lesser harm in relation to these 5 outcomes is not proven for the fixed-dose combination RIL/EMTRI/TENO compared to efavirenz + EMTRI/TENO.

The meta-analysis for the outcome "neurological AEs" showed a statistically significant effect in favour of rilpivirine + EMTRI/TENO compared to efavirenz + EMTRI/TENO. There is therefore an indication of lesser harm from the fixed-dose combination RIL/EMTRI/TENO compared to efavirenz + EMTRI/TENO in respect of this outcome.

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

The conclusions regarding added benefit are limited to a maximum treatment period of 48 weeks.

On the basis of the results presented, the extent and probability of the added benefit of the fixed-dose combination of rilpivirine, emtricitabine and tenofovir compared to efavirenz + emtricitabine and tenofovir are assessed as follows:

- For antiretroviral-naïve adult men with a viral load of ≤ 100,000 HIV-1 RNA copies/ml there remain 2 positive results of different certainty (one proof and one indication) in favour of the fixed-dose combination RIL/EMTRI/TENO. For the outcome "viral load (virological response)", the extent is "non-quantifiable"; for the outcome "neurological AEs", "considerable". In the overall assessment, the balancing of a considerable and a non-quantifiable added benefit is difficult, because it is unclear in which order of magnitude the non-quantifiable added benefit should be classified. However, in this case, because of the sufficient validity of the surrogate, it was possible to use the proof of an added benefit in the outcome "AIDS-defining diseases/death" as support for the certainty of results of the already positive overall conclusion. In summary, in men there is proof of

added benefit (extent: “considerable”) for the fixed-dose combination RIL/EMTRI/TENO compared to the ACT.

- For antiretroviral-naïve adult **women** with a viral load of ≤ 100,000 HIV-1 RNA copies/ml there remains a positive result in favour of the fixed-dose combination RIL/EMTRI/TENO with the extent “considerable” and the probability “indication” (neurological AEs). A decision on balancing of benefits and harms is not necessary. In summary, there is an indication (extent: “considerable”) of an added benefit for the fixed-dose combination RIL/EMTRI/TENO over the ACT.

The approach for deriving an overall conclusion concerning added benefit is a proposal from IQWiG. The decision regarding added benefit is made by the G-BA.

2.2 Research question

According to the Summary of Product Characteristics [8], the fixed-dose combination rilpivirine/emtricitabine/tenofovir is approved for the following therapeutic indication:

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

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

The assessment was carried out with respect to patient-relevant outcomes, with a surrogate outcome having to be used to assess the combined outcome "AIDS-defining diseases/death". Only RCTs with a direct comparator were included in the assessment.

2.3 Information retrieval and study pool

The study pool of this assessment corresponds to that already established by IQWiG in the benefit assessment of 12.04.2012 (Commission A12-02 [9,10]) and includes the studies C204, C209 (ECHO) and C215 (THRIVE).

Data of the target population as defined by the research question were used from the relevant studies (patients with a viral load ≤ 100,000 HIV-1 RNA copies/ml, who were treated with the backbone therapy emtricitabine/tenofovir). This population is hereinafter described as the "target population".

2.3.1 Included studies

The studies C204, C209 (ECHO) and C215 (THRIVE) listed in Table 1 were included in the benefit assessment.

Table 1: Study pool – RCTs with the drug to be assessed

	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	no[b]	yes
C209 (ECHO)	yes	no[b]	yes
C215 (THRIVE)	yes	no[b]	yes

a: Study for which the company was sponsor, or in which the company was otherwise financially involved.
b: Studies were conducted by the company's licensor.
RCT: randomized controlled trial

None of the 3 trials was carried out with the *fixed*-dose combination of rilpivirine, emtricitabine (EMTRI) and tenofovir (TENO). Instead, in all 3 studies rilpivirine was used in free combination with EMTRI/TENO. These studies were considered relevant for the current research question, because the dosage of the single active substances corresponded to that in the fixed-dose combination.

Accordingly, 3 RCTs with the drug to be assessed (rilpivirine + EMTRI/TENO) were submitted for the assessment in the approved therapeutic indication, from which data for a direct comparison with the ACT (efavirenz + EMTRI/TENO) could be used.

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

2.3.2 Study characteristics

Table 2 and Table 3 describe Studies C204, C209, C215 included in the benefit assessment.

Antiretroviral-naïve adult patients with confirmed HIV-1 infection and an HIV-1 plasma viral load at the start of the study of ≥ 5000 RNA copies/ml were enrolled in the 3 studies. In 2 studies, several backbone therapies were used (Study C215: emtricitabine/tenofovir, abacavir/lamivudine and zidovudine/lamivudine; Study C204: emtricitabine/tenofovir and zidovudine/lamivudine). Only a subpopulation of the 3 studies is relevant for this benefit assessment. This consists of patients with a viral load of ≤ 100,000 HIV-1 RNA copies/ml, who were treated with the backbone therapy emtricitabine/tenofovir.

Table 2: Characteristics of the included studies – RCT for the comparison rilpivirine + EMTRI/TENO versus efavirenz + EMTRI/TENO

Study	Study design	Population	Interventions (number of patients)	Duration of study	Location and period of study	Primary outcome; secondary outcomes[a]
C204	RCT, open-label[b], active-controlled	Antiretroviral-naïve adult HIV-1 infected patients	Study population: Rilpivirine 25 mg (N = 93) Rilpivirine 75 mg[c] (N = 95) Rilpivirine 150 mg[c] (N = 91) Efavirenz 600 mg (N = 89) each in combination with a backbone therapy consisting of EMTRI/TENO or ZIDO/LAMI of which target population[d]: Rilpivirine 25 mg + EMTRI/TENO (n = 10) Efavirenz 600 mg + EMTRI/TENO (n = 15)	Screening: 4 weeks Treatment: 96 weeks (interim analysis after 48 weeks) Follow-up: 4 weeks Open-label treatment: 144 weeks	14 countries in Africa, Asia, Europe, Latin America, USA Week 48, Treatment period 6/2005–10/2006 Week 96, Treatment period: 6/2005–10/2007	Primary: virological response Secondary: all-cause mortality, adverse events
C209	RCT, double-blind, double-dummy[e], parallel, active-controlled	Antiretroviral-naïve adult HIV-1 infected patients	Study population: Rilpivirine 25 mg (N = 346) Efavirenz 600 mg (N = 344) each in combination with the backbone therapy EMTRI/TENO of which target population[d]: Rilpivirine 25 mg + EMTRI/TENO (n = 181) Efavirenz 600 mg + EMTRI/TENO (n = 163)	Screening: 6 weeks Treatment: 96 weeks (interim analysis after 48 weeks) Follow-up: max. 6 weeks	20 countries in Africa, Asia, Australia, Europe, Canada, Latin America, USA Week 48, Treatment period: 4/2008–2/2010 Week 96, Treatment period: 4/2008–1/2011	Primary: virological response Secondary: all-cause mortality, health-related quality of life (SF-36v2), adverse events

(continued on next page)

Table 2: Characteristics of the included studies – RCT for the comparison rilpivirine + EMTRI/TENO versus efavirenz + EMTRI/TENO (continued)

Study	Study design	Population	Interventions (number of patients)	Duration of study	Location and period of study	Primary outcome; secondary outcomes[a]
C215	RCT, double-blind, double-dummy[e], parallel, active - controlled	Antiretroviral-naïve adult HIV-1 infected patients	Study population: Rilpivirine 25 mg (N = 340) Efavirenz 600 mg (N = 338) each in combination with a backbone therapy consisting of EMTRI/TENO or ZIDO/LAMI or ABA/LAMI of which target population[d]: Rilpivirine 25 mg + EMTRI/TENO (n = 107) Efavirenz 600 mg + EMTRI/TENO (n = 93)	Screening: 6 weeks Treatment: 96 weeks (interim analysis after 48 weeks) Follow-up: max. 6 weeks	21 countries in Africa, Asia, Australia, Europe, Canada, Latin America, USA Week 48, Treatment period: 5/2008–1/2010 Week 96, Treatment period: 4/2004–1/2011	Primary: virological response Secondary: all-cause mortality, health-related quality of life (SF-36v2), adverse events

a: Extracted primary outcome criteria contain information without consideration of relevance for this benefit assessment. Extracted secondary outcome criteria contain exclusively information on the relevant available outcomes for this benefit assessment.
b: Characterized as open-label study, because the patients were only blinded to the dosage used in the rilpivirine arms.
c: Treatment in this arm did not correspond to the German approval situation; it is therefore no longer shown in the subsequent tables.
d: Relevant population for the assessment: patients with a viral load at start of study ≤ 100,000 HIV-1 RNA copies/ml, treated with the backbone therapy EMTRI/TENO.
e: Due to the different dosage regimens of the drugs administered (rilpivirine: in the morning after a meal; efavirenz: fasting in the evening), blinding was maintained by an additional administration of placebo (double-dummy).
ABA: abacavir, EMTRI: emtricitabine, HIV-1: human immunodeficiency virus type 1, LAMI: lamivudine, n: number of patients in the target population, N: number of randomized patients, RCT: randomized controlled trial, SF-36v2: Short Form 36, Version 2, TENO: tenofovir, ZIDO: zidovudine

Table 3: Characteristics of the intervention/backbone therapy – RCT for the comparison rilpivirine versus efavirenz in patients with viral load ≤ 100,000 HIV-1 RNA copies/ml

Study **Study arm**	**Allocation to the backbone therapies[a]** **n (%)**		
	Tenofovir[b] 300 mg/day + emtricitabine 200 mg/day	Zidovudine 300 mg/day + lamivudine 300 mg/day	Abacavir 600 mg + lamivudine 300 mg/day[c]
C204			
Rilpivirine 25 mg/day	10 (16.4)	51 (83.6)	0
Efavirenz 600 mg/day	15 (26.8)	41 (73.2)	0
C209			
Rilpivirine 25 mg/day	181 (100.0)	0	0
Efavirenz 600 mg/day	163 (100.0)	0	0
C215			
Rilpivirine 25 mg/day	107 (57.2)	58 (31.0)	22 (11.8)
Efavirenz 600 mg/day	93 (55.7)	56 (33.5)	18 (10.8)

a: Depending on availability, standard treatment and approval in the respective country, backbone therapy was taken as fixed-dose combinations or as separate components.
b: Tenofovir disoproxil fumarate
c: With this combination of active substances, the daily dose is divided into 2 individual doses.
n: number of patients, RCT: randomized controlled trial

Studies C209 and C215 are Phase III approval studies. Study C204 is an open-label, phase-IIb dose-finding study. All 3 studies were multicentre studies, whose respective centres ranged from countries in Europe, Africa, America and Asia to Australia.

The treatment phase of the 3 studies lasted at least 96 weeks, but at the time of dossier submission, only the study reports at the analysis time of 48 weeks were available for studies C209 and C215. In order to ensure results were comparable, the 48-week data of the C204 study were therefore also used.

The relevant target population of patients with a viral load ≤ 100,000 HIV-1 RNA copies/ml under treatment with the backbone therapy EMTRI/TENO constitutes only a part of the study population (C204: approx. 14 %, C215: approx. 30 %, C209: approx. 50 %).

Table 4 shows the characteristics of these patients in the included studies for the characteristics of “age”, “gender”, “CD4 cell count” and “duration of HIV-1 infection”.

Table 4: Characteristics of the target population – RCT for the comparison rilpivirine + EMTRI/TENO versus efavirenz + EMTRI/TENO

Study Study arm	N	Age [years] median (min-max)	Gender f/m [%]	CD4 cell counts at start of study [cells/µl] median (min-max)	Duration of HIV-1 infection since diagnosis [years] median (min-max)
C204					
RIL + EMTRI/TENO	10	35.5 (24-47)	20/80	256.0 (64-445)	1.9 (0-16)
EFA + EMTRI/TENO	15	36.0 (23-46)	13/87	222.0 (79-451)	2.8 (0-16)
C209					
RIL + EMTRI/TENO	181	37.0 (20-74)	27/73	261.0 (7-888)	1.3 (0-22)
EFA + EMTRI/TENO	163	34.0 (19-58)	22/78	284.0 (18-757)	1.2 (0-22)
C215					
RIL + EMTRI/TENO	107	36.5 (20-62)	23/77	287.0 (5-744)	1.9 (0-20)
EFA + EMTRI/TENO	93	37.0 (19-53)	28/72	294.0 (21-857)	1.9 (0-14)

CD4: Cluster of Differentiation 4 Positive Cells, EFA: efavirenz, EMTRI/TENO: emtricitabine/tenofovir, f: female, HIV-1: human immunodeficiency virus type 1, m: male, N: number of patients in the target population, RCT: randomized controlled trial, RIL: rilpivirine

Table 5 shows the risk of bias at study level.

Table 5: Risk of bias at study level – RCT for the comparison rilpivirine + EMTRI/TENO versus efavirenz + EMTRI/TENO

			Blinding				
Study	Random sequence generation	Allocation concealment	Participants	Personnel	Selective reporting	Other sources of bias	Risk of bias at study level
C204[a]	yes	yes	no	no	no	no	low
C209	yes	yes	yes	yes	no	no	low
C215	yes	yes	yes	yes	no	no	low

a: The risk of bias at study level for Study C204 was estimated by the Institute, because this information was not submitted by the company.

Overall, the risk of bias at study level was rated as low for all 3 included studies. The lack of blinding in Study C204 did not cause a higher risk of bias at study level, but is taken into account in considering the risk of bias at outcome level.

2.4 Results concerning added benefit

2.4.1 Relevant outcomes

The following patient-relevant outcomes were considered in this assessment:

- Mortality
  - All-cause mortality
- Health-related quality of life
  - SF-36v2: using 2 sum scores for physical/mental health
- Adverse events
  - Overall rate of adverse events (AEs)
  - Overall rate of serious adverse events (SAEs)
  - Overall rate of adverse events that led to discontinuation (discontinuation due to AEs)
  - Adverse events affecting the skin (adverse skin events)
  - Neurological AEs
  - Psychiatric AEs

In addition, the following outcome is considered a sufficiently valid surrogate for the combined outcome "AIDS-defining diseases/death" in the benefit assessment (for detailed reasoning, see also [7]).

- Viral load (virological response)

This selection of patient-relevant outcomes and the definition of the respective outcomes corresponds to the benefit assessment A12-04 [7]. Details about these outcomes can be found in that assessment.

The selection of patient-relevant outcomes by the Institute partly deviates from that of the company, which used additional outcomes (e.g. virological failure [efficacy and resistance], CD4 cell count, health-related quality of life based on Short Form (6) Domains Evaluation (SF-6D), Division of Acquired Immune Deficiency Syndrome (DAIDS) Table for Grading the Severity of Adverse Events with severity grades 3 and 4, other adverse events such as neuropsychiatric events, rash, depression or sleep disorders) in its dossier (Module 4) and in the subsequently submitted data of the Commenting Procedure. The Institute considers that these outcomes are adequately covered by those already considered of mortality, morbidity, health-related quality of life, and adverse events.

2.4.2 Data availability and risk of bias

Table 6 shows the outcomes for which data were available from the studies included in the assessment.

Table 6: Matrix of outcomes – RCT for the comparison rilpivirine + EMTRI/TENO versus efavirenz + EMTRI/TENO

				Adverse events					
Study	**All-cause mortality**	**Viral load (virological response)[a]**	**Health-related quality of life (SF-36v2)**	**AEs**	**SAEs**	**Discontinuation due to AEs**	**Adverse skin events**	**Neurological AEs**	**Psychiatric AEs**
C204	yes	yes	no	yes	yes	yes	yes	yes	yes
C209	yes	yes	yes	yes	yes	yes	yes	yes	yes
C215	yes	yes	yes	yes	yes	yes	yes	yes	yes

a: The virological response represents the primary analysis of viral load measurements in the included studies and is considered in the benefit assessment as sufficiently valid surrogate for the combined outcome "AIDS-defining diseases/death".

AE: adverse event, EMTRI/TENO: emtricitabine/tenofovir, RCT: randomized controlled trial, SF-36v2: Short Form 36, Version 2, SAE: serious adverse event

Table 7 describes the risk of bias for these outcomes.

Table 7: Risk of bias at study and outcome levels – RCT for the comparison rilpivirine + EMTRI/TENO versus efavirenz + EMTRI/TENO

		Outcome level								
Study	**Study level**	**All-cause mortality**	**Viral load (virological response)[b]**	**Health-related quality of life (SF-36v2)**	**AEs**	**SAEs**	**Discontinuation due to AEs**	**Adverse skin events**	**Neurological AEs**	**Psychiatric AEs**
C204a	low	low	low	–[c]	low	low	low	high[e]	high[e]	low
C209	low	low	low	high[d]	low	low	low	high[e]	high[e]	low
C215	low	low	low	high[d]	low	low	low	high[e]	high[e]	low

a: The risk of bias at study level for Study C204 was estimated by the Institute, because this information was not submitted by the company.

b: The virological response represents the primary analysis of viral load measurements in the included studies and is considered in the benefit assessment as sufficiently valid surrogate for the combined outcome "AIDS-defining diseases/death".

c: Parameter was not recorded.

d: High proportion of patients not considered in the analysis (> 10 %).

e: No clear a-priori specification of the analysed preferred terms in the studies.

AE: adverse event, EMTRI/TENO: emtricitabine/tenofovir, RCT: randomized controlled trial, SF-36v2: Short Form 36, Version 2, SAE: serious adverse event

Except for the non-recorded data on health-related quality of life in Study C204, a good data availability for the approval population could be assumed for the relevant studies.

In Studies C209 and C215, as more than 10 % of patients to be included in the analysis were missing for the outcome "health-related quality of life", the risk of bias for this outcome was rated as high.

The risk of bias for the outcomes “adverse skin events” and “neurological AEs” was also rated as high because the choice of preferred terms from the MedDRA classification was not clearly specified a-priori.

A low risk of bias was present for all other outcomes included.

2.4.3 Results

Through the meta-analytical summary of the 3 studies it is, in principle, possible to derive proof, e.g. of an added benefit. The possible weakening by outcome-specific aspects is discussed separately below in the presentation of results on the individual outcomes.

Mortality

Table 8 summarizes the results on mortality for the comparison of rilpivirine + EMTRI/TENO and efavirenz + EMTRI/TENO.

Table 8: Results on all-cause mortality, rilpivirine + EMTRI/TENO versus efavirenz + EMTRI/TENO

Outcome Study	RIL + EMTRI/TENO		EFA + EMTRI/TENO		RIL + EMTRI/TENO vs. EFA + EMTRI/TENO	
	Total N	Patients with event n (%)	Total N	Patients with event n (%)	RR [95 % CI]	p-value
Mortality						
C204	10	0 (0)	15	0 (0)	not applicable[a]	
C209	181	0 (0)	163	0 (0)	not applicable[a]	
C215	107	0 (0)	93	n.k.[b]	not applicable[a]	
Meta-analysis					not applicable[a]	

a: Too low a proportion of patients with event
b: One patient died in the population with a viral load at the start of the study ≤ 100,000 HIV-1 RNA copies/ml. However, it is unclear from the information in the company’s dossier (Module 4) whether this patient was to be allocated to the target population (with backbone therapy EMTRI/TENO).
CI: confidence interval, EFA: efavirenz, EMTRI/TENO: emtricitabine/tenofovir, n.k.: not known, N: number of patients in the analysis, n: number of patients with event, RIL: rilpivirine, RR: relative risk, vs.: versus

No death occurred in the target population within the first 48 weeks in 2 of the studies used for the assessment. However, data from Study C215 did not enable any definitive conclusions about the ACT (EFA + EMTRI/TENO). In this study arm, one patient within the population

with the relevant viral load (≤ 100,000 HIV-1 RNA copies/ml) died. However, it is unclear from the information in the company's dossier (Module 4) whether this patient is to be allocated to the target population (with the backbone therapy EMTRI/TENO). In view of the low event rate, no statistical analysis of the outcome was carried out.

An added benefit or greater harm from rilpivirine + EMTRI/TENO compared to efavirenz + EMTRI/TENO for this outcome is not proven. It should be considered that, due to study duration and the number of enrolled patients, the studies were not suitable for demonstrating differences between the treatments with regard to this outcome.

Morbidity

Viral load (virological response)

Table 9 summarizes the results on viral load (virological response) for the comparison of rilpivirine + EMTRI/TENO and efavirenz + EMTRI/TENO.

Table 9: Results on viral load (virological response), rilpivirine + EMTRI/TENO versus efavirenz + EMTRI/TENO

Outcome Study	RIL + EMTRI/TENO		EFA + EMTRI/TENO		RIL + EMTRI/TENO vs. EFA + EMTRI/TENO
	Total N	Patients with event n (%)	Total N	Patients with event n (%)	RR [95 % CI] p-value[a]
Viral load (virological response)[b]					
C204	10	7 (70.0)[c]	15	13 (86.7)[c]	2.25 [0.45; 11.15]
C209	181	162 (89.5)	163	136 (83.4)	0.63 [0.37; 1.10]
C215	107	96 (89.7)	93	81 (87.1)	0.80 [0.37; 1.72]
Meta-analysis					0.76 [0.48; 1.21] p = 0.246

a: Institute's calculation: relative risk, confidence interval and p-value for non-responders (RIL + EMTRI/TENO vs. EFA + EMTRI/TENO).
b: Measured with the Roche Amplicor HIV-1 Monitor® Test Version 1.5 (C204, C209, C215) or using COBAS® TaqMan HIV-1 Test Version 1.0 (C209, C215).
c: Percentage: Institute's calculation.
CI: confidence interval, EFA: efavirenz, EMTRI/TENO: emtricitabine/tenofovir, N: number of patients in the analysis, n: number of patients with event, RIL: rilpivirine, RR: relative risk, vs.: versus

By itself, viral load defined via the virological response is not a patient-relevant outcome (see also [7] for a further discussion). Nevertheless, in the Institute's view, the prognostic value of viral load for subsequent diseases and death is such that adequate validity for viral load as a surrogate for the combined outcome "AIDS-defining diseases/death" could be assumed. Consideration of viral load via the virological response in the benefit assessment and the derivation of conclusions regarding added benefit are thus, in principle, possible.

Table 9 shows the effect estimators of the 3 relevant studies and the overall effect estimator of the meta-analysis on the comparison rilpivirine + EMTRI/TENO versus efavirenz + EMTRI/TENO for the outcome “viral load (virological response)”. The relative risks and 95 % confidence intervals were each calculated for the non-responders.

The proportions of patients in the three studies who showed virological response did not differ substantially between rilpivirine + EMTRI/TENO and efavirenz + EMTRI/TENO. The result of the meta-analysis was not statistically significant and there was no heterogeneity between the results of the individual studies (test with Q statistic: $p = 0.333$). However, in the subsequent course of the assessment, there was an indication of an effect modification through the characteristic "gender". Hence conclusions concerning added benefit must be drawn in terms of this outcome on the basis of these subgroups. The subgroup analyses with associated evidence maps can be found in Section 2.4.4.

Health-related quality of life

This outcome, recorded with the instrument SF-36v2, was only investigated in studies C209 and C215. This instrument is a generic (i.e. not disease-specific) self-assessment tool to determine the quality of life. The questionnaire items are aggregated into 8 scales, from which 2 sum scores (physical health/mental health) are formed. Higher values of the sum scores denote a high quality of life. This analysis of the results considered the mean change in sum scores compared to the start of the study (baseline).

Table 10 combines the results on health-related quality of life (measured using SF-36v2) for the comparison of rilpivirine + EMTRI/TENO and efavirenz + EMTRI/TENO.

Table 10: Results on health-related quality of life, rilpivirine + EMTRI/TENO versus efavirenz + EMTRI/TENO

Outcome Scale Study	RIL + EMTRI/TENO		EFA + EMTRI/TENO		RIL + EMTRI/TENO vs. EFA + EMTRI/TENO
	N	Change compared with baseline mean (SD)	N	Change compared with baseline mean (SD)	SMD [95 % CI] p-value
Health-related quality of life					
SF-36v2, mean sum score – physical health					
C209	128	1.3 (7.3)	114	1.1 (7.2)	0.20 [-1.63; 2.03]
C215	81	1.4 (5.6)	66	-0.4 (7.8)	1.80 [-0.44; 4.04]
Meta-analysis					0.86 [-0.68; 2.41] p = 0.273
SF-36v2, mean sum score – mental health					
C209	128	2.4 (10.7)	115	2.2 (11.0)	0.20 [-2.53; 2.93]
C215	81	2.9 (8.8)	67	1.8 (8.8)	1.10 [-1.75; 3.95]
Meta-analysis					0.63 [-1.34; 2.60] p = 0.530

CI: confidence interval, EFA: efavirenz, EMTRI/TENO: emtricitabine/tenofovir, N: number of analysed patients, RIL: rilpivirine, SD: standard deviation; SMD: standardized mean difference, SF-36v2: Short Form 36, Version 2, vs.: versus

The mean change in the two sum scores compared with the start of the study did not differ substantially between rilpivirine + EMTRI/TENO and efavirenz + EMTRI/TENO in the 2 studies. The result of the respective meta-analysis was not statistically significant for either sum score and there was no heterogeneity between the individual studies (test with Q statistic for physical health: $p = 0.279$ and mental health: $p = 0.655$).

In summary, in respect of health-related quality of life, an added benefit of rilpivirine + EMTRI/TENO compared to efavirenz + EMTRI/TENO is not proven.

Adverse events

Table 11 summarizes the results on adverse events for the comparison of rilpivirine + EMTRI/TENO and efavirenz + EMTRI/TENO.

Table 11: Results on adverse events, rilpivirine + EMTRI/TENO versus efavirenz + EMTRI/TENO

Outcome Study	RIL + EMTRI/TENO		EFA + EMTRI/TENO		RIL + EMTRI/TENO vs. EFA + EMTRI/TENO
	Total N	Patients with event n (%)	Total N	Patients with event n (%)	RR[a] [95 % CI] p-value
AEs					
C204	10	10 (100)[b]	15	15 (100)[b]	1.00 [0.69; 1.28][d]
C209	181	160 (88.4)	163	144 (88.3)	1.00 [0.93; 1.08]
C215	107	98 (91.6)	93	80 (86.0)	1.06 [0.96; 1.18]
Meta-analysis					1.02 [0.96; 1.08] p = 0.524
SAEs					
C204	10	2 (20.0)[b]	15	4 (26.7)[b]	0.75 [0.17; 3.35]
C209	181	10 (5.5)	163	16 (9.8)	0.56 [0.26; 1.20]
C215	107	6 (5.6)	93	5 (5.4)	1.04 [0.33; 3.31]
Meta-analysis					0.69 [0.38; 1.24] p = 0.212
Discontinuation due to AEs					
C204	10	2 (20.0)[b]	15	0 (0)[b]	7.27 [0.39; 137.26]
C209	181	5 (2.8)	163	12 (7.4)	0.38 [0.14; 1.04]
C215	107	6 (5.6)	93	5 (5.4)	1.04 [0.33; 3.31]
Meta-analysis					Heterogeneity: Chi^2 = 4.34, df = 2, p = 0.11, I^2 = 54 %
Adverse skin events (PT selection)[c]					
C204	10	3 (30.0)[b]	15	5 (33.3)[b]	0.90 [0.27; 2.95]
C209	181	26 (14.4)[b]	163	31 (19.0)[b]	0.76 [0.47; 1.22]
C215	107	8 (7.5)[b]	93	17 (18.3)[b]	0.41 [0.19; 0.90]
Meta-analysis					0.67 [0.45; 0.98] p = 0.039
Neurological AEs (PT selection)[c]					
C204	10	2 (20.0)[b]	15	7 (46.7)[b]	0.43 [0.11; 1.66]
C209	181	44 (24.3)[b]	163	72 (44.2)[b]	0.55 [0.40; 0.75]
C215	107	36 (33.6)[b]	93	50 (53.8)[b]	0.63 [0.45; 0.87]
Meta-analysis					0.58 [0.46; 0.72] p < 0.001
Psychiatric AEs (PT selection)[c]					
C204	10	3 (30.0)[b]	15	4 (26.7)[b]	1.13 [0.32; 3.99]
C209	181	41 (22.7)	163	54 (33.1)	0.68 [0.48; 0.97]
C215	107	27 (25.2)	93	24 (25.8)	0.98 [0.61; 1.57]
Meta-analysis					0.79 [0.60; 1.04] p = 0.087

(continued on next page)

Table 11: Results on adverse events, rilpivirine + EMTRI/TENO versus efavirenz + EMTRI/TENO (continued)

a: Institute's calculation: relative risk including confidence intervals and p-values (RIL + EMTRI/TENO vs. EFA + EMTRI/TENO).
b: Percentage: Institute's calculation
c: Due to lack of data for the target population, differentiation according to serious and non-serious adverse events was not possible for these outcomes.
d: Institute's calculation with exact method according to [11] implemented in StatXact Version 9.0
AE: adverse event, CI: confidence interval, EFA: efavirenz, EMTRI/TENO: emtricitabine/tenofovir, N: number of patients in the analysis, n: number of patients with event, PT: preferred term, RIL: rilpivirine, RR: relative risk, SAE: serious adverse event, vs.: versus

Overall rate of adverse events, serious adverse events and psychiatric adverse events

The proportions of patients with adverse events (AEs), serious adverse events (SAEs) and with psychiatric AEs did not differ substantially between rilpivirine + EMTRI/TENO and efavirenz + EMTRI/TENO in the 3 studies. The result of the respective meta-analysis was not statistically significant (Table 11) and there was no heterogeneity between the individual studies (test with Q statistic for AEs: $p = 0.664$, SAEs: $p = 0.677$ and psychiatric AEs: $p = 0.418$).

Lesser/greater harm from rilpivirine + EMTRI/TENO compared to efavirenz + EMTRI/TENO for these outcomes is not proven.

Overall rate of adverse events that led to discontinuation

Figure 1 shows the results of the 3 relevant studies on the comparison rilpivirine + EMTRI/TENO versus efavirenz + EMTRI/TENO for the outcome "discontinuation due to adverse events".

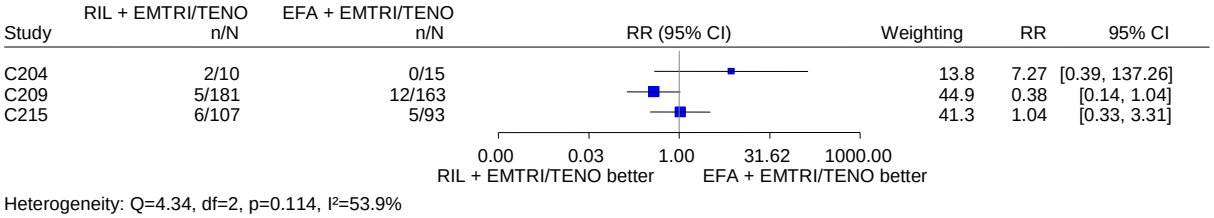

Figure 1: Meta-analysis, adverse events that led to discontinuation, rilpivirine + EMTRI/TENO versus efavirenz + EMTRI/TENO

Because of heterogeneity ($p < 0.2$) no overall effect estimator was illustrated in the meta-analysis. No further investigation of heterogeneity was necessary in this case, because the result of all 3 individual studies was not statistically significant.

Greater/lesser harm from rilpivirine + EMTRI/TENO compared to efavirenz + EMTRI/TENO for this outcome is not proven.

Adverse skin events

Figure 2 shows the results of the 3 relevant studies on the comparison rilpivirine + EMTRI/TENO versus efavirenz + EMTRI/TENO for the outcome “skin events”.

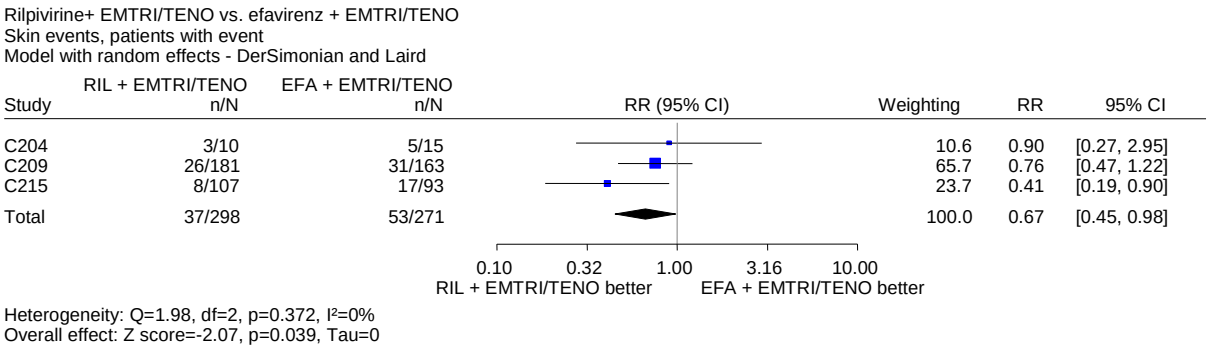

Figure 2: Meta-analysis, adverse skin events, rilpivirine + EMTRI/TENO versus efavirenz + EMTRI/TENO

Adverse skin events occurred more often in the patients treated with efavirenz + EMTRI/TENO than in those who received rilpivirine + EMTRI/TENO. The overall effect of the meta-analysis was statistically significant and there was no heterogeneity between the results of the individual studies. However, because of the marginal effect size (95 % confidence interval of the relative risk not fully below 0.9), there was no proof of lesser harm in favour of rilpivirine + EMTRI/TENO.

Greater/lesser harm from rilpivirine + EMTRI/TENO compared to efavirenz + EMTRI/TENO for this outcome is not proven.

Neurological adverse events

Figure 3 shows the results of the 3 relevant studies on the comparison rilpivirine + EMTRI/TENO versus efavirenz + EMTRI/TENO for the outcome “neurological AEs”.

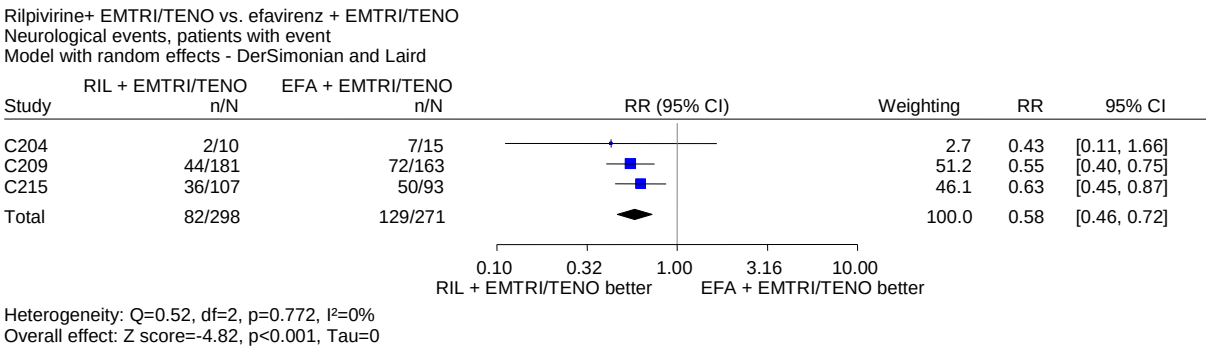

Figure 3: Meta-analysis, neurological adverse events, rilpivirine + EMTRI/TENO versus efavirenz + EMTRI/TENO

Neurological AEs occurred more often in the patients treated with efavirenz + EMTRI/TENO than in those who received rilpivirine + EMTRI/TENO. The overall effect of the meta-analysis was statistically significant and there was no heterogeneity between the results of the individual studies.

Since, due to the deficient definition, this outcome was rated as potentially having a high risk of bias (see Table 7 and [7] for more detailed reasoning), there is only an indication of a lesser harm from rilpivirine + EMTRI/TENO compared to efavirenz + EMTRI/TENO for the outcome “neurological AEs”.

2.4.4 Subgroup analyses

In order to analyse possible effect modifiers, the respective subgroups were investigated for potential effect modifications using the Q statistic for random effects. This was undertaken for the subgroup characteristics of “age” (< 55 years; ≥ 55 years) and “gender” presented by the company. The threshold values for age were pre-defined in the studies. Corresponding analyses were carried out by the company for the outcomes it rated as relevant in the target population. The one exception was the outcome “overall mortality”, for which no subgroup results were available.

Only results for subgroups and outcomes for which interactions between treatment effect and subgroup could be demonstrated, are presented below. The condition for proof of different subgroup effects was a statistically significant interaction ($p < 0.05$). A p-value between 0.05 and 0.2 provided an indication of interaction.

The subgroup analysis for the characteristic “gender” produced an indication of differing effects between men and women for virological response. For the outcome "neurological events", there was an indication of an effect modification by the characteristic "age". The results and conclusions concerning the subgroups and outcomes are shown below.

Gender and viral load (virological response)

Table 12 shows the results for virological response in the subgroups men/women for the comparison of rilpivirine + EMTRI/TENO and efavirenz + EMTRI/TENO.

Table 12: Subgroup results for virological response according to gender, rilpivirine + EMTRI/TENO versus efavirenz + EMTRI/TENO

Outcome Study Subgroup	RIL + EMTRI/TENO		EFA + EMTRI/TENO		RIL + EMTRI/TENO vs. EFA + EMTRI/TENO
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95 % CI][b] p-value[d]
Viral load (virological response)					
C204					
Men	8	7 (87.5)[c]	13	11 (84.6)[c]	0.81 [0.09; 7.58]
Women	2	0 (0)[c]	2	2 (100)[c]	5.00 [0.38; 66.01]
C209					
Men	132	122 (92.4)[c]	127	107 (84.3)[c]	0.48 [0.23; 0.99]
Women	49	40 (81.6)[c]	36	29 (80.6)[c]	0.94 [0.39; 2.30]
C215					
Men	82	74 (90.2)[c]	67	57 (85.1)[c]	0.65 [0.27; 1.56]
Women	25	22 (88.0)[c]	26	24 (92.3)[c]	1.56 [0.28; 8.56]
Meta-analysis					
Men					0.56 [0.33; 0.95]
Women					1.20 [0.57; 2.55]
Interaction test					p = 0.104

a: Number of patients in the analysis.
b: Institute's calculations. The relative risk and the confidence intervals were calculated on the basis of the non-responders.
c: Percentages: Institute's calculation.
d: Institute's calculations (interaction test). Q statistic with random effects.
CI: confidence interval, EFA: efavirenz, EMTRI/TENO: emtricitabine/tenofovir, N: number of patients analysed, n: number of patients with event; RIL: rilpivirine, RR: relative risk, vs.: versus

Figure 4 shows the corresponding subgroup analysis. In each case, the relative risks were calculated for the non-responders.

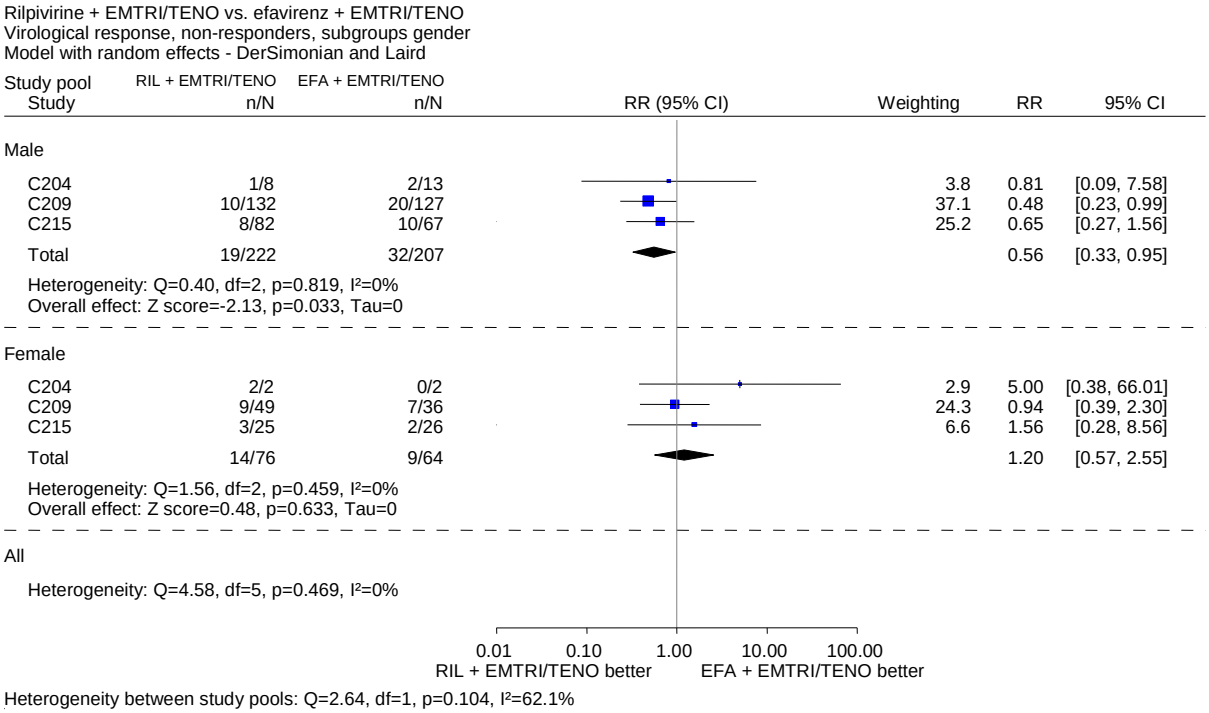

Figure 4: Meta-analysis, subgroup groups according to gender, viral load (virological response – non-responders), rilpivirine + EMTRI/TENO versus efavirenz + EMTRI/TENO, interaction test p = 0.104

For virological response, there was an indication (p = 0.104) of an effect modification through the characteristic “gender”.

In men, a virological response was achieved in a greater proportion of patients treated with rilpivirine + EMTRI/TENO than in those who received efavirenz + EMTRI/TENO. The result of the meta-analysis was statistically significant for the subgroup of men (p = 0.003) and there was no heterogeneity.

In women, there was no substantial difference in the proportions of patients with a virological response between rilpivirine + EMTRI/TENO and efavirenz + EMTRI/TENO. The result of the meta-analysis was not statistically significant for the subgroup of women and there was no heterogeneity.

Because of these results, overall conclusions on added benefit are drawn separately for men and women. However, in this case it should be noted that, due to the presence of an indication of effect modification, differing treatment effects for men and women are not unequivocally *proven*. The statistically significant effect for men, which differs from that of the total population in terms of the statistical significance (see Table 9), therefore shows increased uncertainty. This uncertainty would routinely be taken into account with the downgrading of the probability of added benefit for men (from “proof” to “indication”). However, based on the data presented in the benefit assessment on the single-agent product rilpivirine, which

clearly proved the differing treatment effects for men and women [7], this uncertainty is estimated as very low, so no downgrading is made in this case. This approach is largely justified because of the comparable sizes of the relative risks for the respective subgroups in the two benefit assessments (single-agent product: men = 0.50; women = 1.06; fixed-dose combination: men = 0.56; women = 1.20).

In summary, for men there is proof of added benefit of rilpivirine + EMTRI/TENO compared to efavirenz + EMTRI/TENO for the outcome "viral load (virological response)". In contrast, an added benefit is not proven for women.

Nevertheless, it should be considered that at outcome level, viral load (virological response) is not clearly validated as a surrogate and was assessed only as a surrogate with sufficient validity (for further discussion, see [7]). Account is taken below of this increased uncertainty by the rating of extent of the added benefit ("non-quantifiable").

Age and neurological adverse events

Figure 5 shows the meta-analysis of the 3 relevant studies on the comparison of rilpivirine + EMTRI/TENO and efavirenz + EMTRI/TENO for the outcome "neurological AEs" subdivided according to age categories (</≥ 55 years).

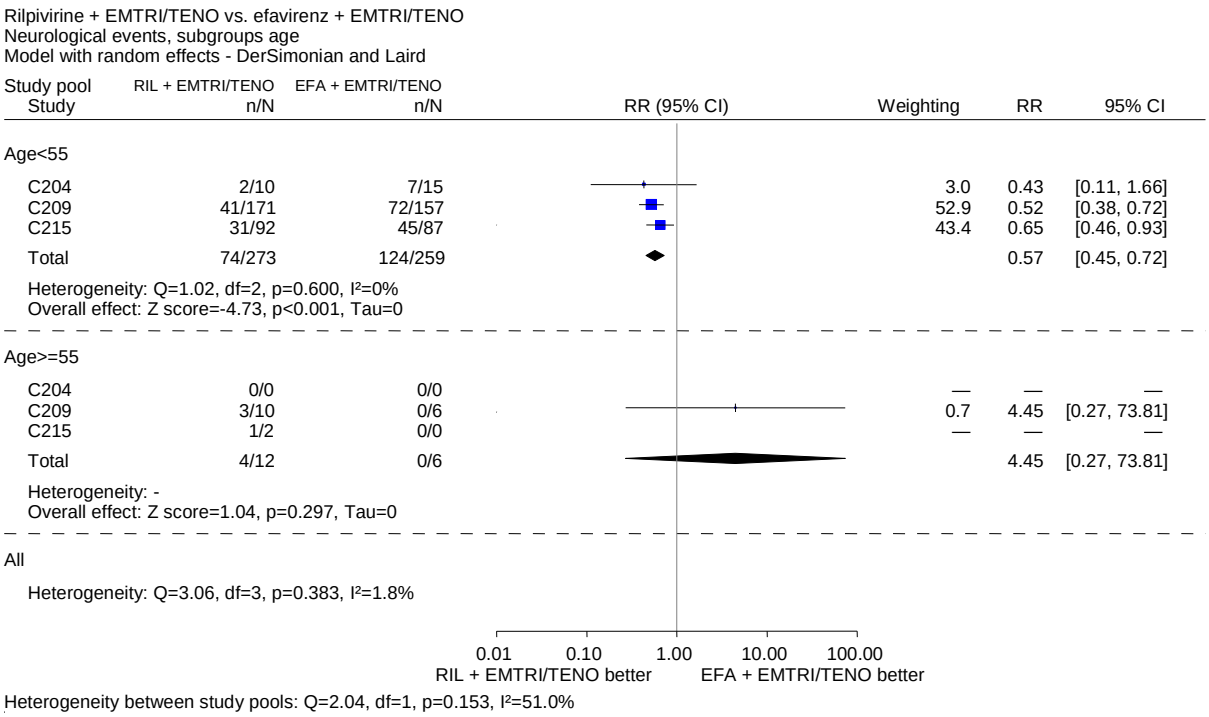

Figure 5: Meta-analysis, subgroups according to age (< / ≥ 55 years), neurological adverse events, rilpivirine + EMTRI/TENO versus efavirenz + EMTRI/TENO, interaction test p = 0.153

For the outcome "neurological AEs", there was an indication (p = 0.153) of an effect modification by the characteristic "age". In patients < 55 years, there were statistically significantly fewer neurological events under treatment with rilpivirine + EMTRI/TENO than under treatment with efavirenz + EMTRI/TENO. This effect was not seen in the group of patients ≥ 55 years.

However, no reliable result can be deduced from these data because the indicated interaction is possibly based solely on the markedly different sample sizes (532 patients < 55 years, 18 patients ≥ 55 years), so the confidence interval for patients over 55 completely covers that for patients under 55.

This indication of effect modification does not lead to separate overall conclusions on added benefit for patients < 55 / ≥ 55 years.

2.5 Extent and probability of added benefit

The derivation of the extent and probability of added benefit for antiretroviral-naïve adult patients infected with the HIV-1 virus and a viral load of ≤ 100,000 HIV-1 RNA copies/ml at outcome level is shown below. Account is taken of the different outcome categories and effect sizes. The methods used are explained in Appendix A of Benefit Assessment A11-02 [2].

The approach for deriving an overall conclusion concerning added benefit based on the aggregation of conclusions derived at outcome level is a proposal from IQWiG. The decision regarding added benefit is made by the G-BA.

2.5.1 Evaluation of added benefit at outcome level

The data presented in Section 2.4 produced proof of added benefit for the outcome "viral load" (virological response) for **men**. Viral load represents a sufficiently valid surrogate for the combined outcome "AIDS-defining diseases/death" that was rated as severe/serious symptoms.

In addition, there was an indication of lesser harm with respect to neurological adverse events (overall effect for both **men and women**).

The extent of the respective added benefit at outcome level was estimated from these results (see Table 13).

Table 13: Extent of added benefit at outcome level: rilpivirine + EMTRI/TENO versus efavirenz + EMTRI/TENO

		Effect estimator [95 % CI]/ proportion of events rilpivirine + EMTRI/TENO versus efavirenz + EMTRI/TENO/ p-value/probability[a]	**Derivation of extent[b]**
Mortality			
All-cause mortality		Not applicable[c]	Lesser benefit/added benefit not proven.
Morbidity			
AIDS-defining diseases/death considered via the surrogate viral load (virological response)[d]	**Men**[e]	Non-quantifiable. Probability: proof	Outcome category: serious/severe symptoms/late complications Added benefit, extent: "non-quantifiable".
	Women[e]	Result not statistically significant.	Outcome category: serious/severe symptoms/late complications Lesser benefit/added benefit not proven.
Health-related quality of life			
SF-36v2 physical health mental health		 Result not statistically significant. SMD 0.86 [-0.68; 2.41] p = 0.273 Result not statistically significant. SMD 0.63 [-1.34; 2.60] p = 0.530	Added benefit / greater harm not proven.
Adverse events			
AEs (overall rate)		RR 1.02 [0.96; 1.08] 89.9 % vs. 88.2 % p = 0.524	Greater/lesser harm not proven.
SAEs (overall rate)		RR 0.69 [0.38; 1.24] 6.0 % vs. 9.2 % p = 0.212	Greater/lesser harm not proven.
Discontinuation due to AEs (overall rate)		A summarizing analysis of patients who discontinued due to AEs could not be undertaken because the heterogeneity between the studies was too high. Greater or lesser harm cannot be derived.	Greater/lesser harm not proven.
Adverse skin events		RR 0.67 [0.45; 0.98] 12.4 % vs. 19.6 % p = 0.039	Outcome category: non-serious/non-severe adverse events $CI_o \geq 0.9$ Greater/lesser harm not proven[f]

(continued on next page)

Table 13: Extent of added benefit at outcome level: rilpivirine + EMTRI/TENO versus efavirenz + EMTRI/TENO (continued)

	Effect estimator [95 % CI]/ proportion of events rilpivirine + EMTRI/TENO versus efavirenz + EMTRI/TENO/ p-value/probability[a]	**Derivation of extent[b]**
Neurological AEs	RR 0.58 [0.46; 0.72] 40.6 vs. 80.7 % p = 0.001 Probability: indication	Outcome category: non-serious/non-severe adverse events $CI_o < 0.8$ Lesser harm, extent "considerable"
Psychiatric AEs	RR 0.79 [0.60; 1.04] 32.3 vs. 80.7 % p = 0.087	Greater/lesser harm not proven.
a: Probability, if statistically significant differences are present. b: Estimations of effect size made according to outcome category with different limits based on upper limit of confidence interval (CI_o) of the observed effect (see [2]). c: Too small a proportion of patients with event . d: Virological response was assessed as sufficiently valid as a surrogate for a patient-relevant outcome (combined outcome from AIDS-defining diseases/death) in order to be considered in the benefit assessment (for detailed reasoning, see [7]). e: Division of population due to an indication of effect modification through the characteristic "gender". f: Because upper limit of confidence interval is not below the threshold of 0.9. AE: adverse event, CI_o: upper limit of confidence interval, EMTRI/TENO: emtricitabine/tenofovir, RR: relative risk, SF-36v2: Short Form 36, Version 2, SMD: standardized mean difference, SAE: serious adverse event, vs.: versus		

2.5.2 Overall conclusion on added benefit

The summary of results that determine the overall conclusion on added benefit is shown in Table 14 and Table 15, divided according to the relevant subgroups.

The conclusions regarding added benefit are limited to a maximum treatment period of 48 weeks.

Table 14: Men: positive and negative effects from the assessment of rilpivirine + EMTRI/TENO compared to efavirenz + EMTRI/TENO

Positive effects	**Negative effects**
Proof of added benefit – extent: "non-quantifiable" (serious/severe symptoms/late complications considered via the viral load [virological response])	-
Indication of lesser harm - extent: "considerable" (non-serious/non-severe symptoms/late complications: neurological adverse events)	-

In the overall assessment, there remain 2 positive results of differing certainty of results (one proof and one indication) in favour of rilpivirine + EMTRI/TENO for the group of men. For the outcome “viral load (virological response)” the extent is “non-quantifiable”, for the outcome “neurological adverse events”, the extent is “considerable”.

In the overall assessment, the balancing of a considerable and a non-quantifiable added benefit is difficult, because it is unclear in which order of magnitude the non-quantifiable added benefit should be classified. In this case, because of the sufficient validity of the surrogate, it was, however, possible to use the proof of an added benefit in the outcome “AIDS-defining diseases/death” as support for the certainty of results of the already positive overall conclusion.

In summary, for antiretroviral-naïve adult **men** with an HIV-1 infection and a viral load of ≤ 100,000 HIV-1 RNA copies/ml, there is proof of an added benefit (extent: “considerable”) of rilpivirine + EMTRI/TENO compared to efavirenz + EMTRI/TENO.

Table 15: Women: positive and negative effects from the assessment of rilpivirine + EMTRI/TENO compared to efavirenz + EMTRI/TENO

Positive effects	**Negative effects**
Indication of lesser harm - extent: "considerable" (non-serious/non-severe symptoms/late complications: neurological adverse events)	-

In the overall assessment, for the group of women there remains one positive result in favour of rilpivirine + EMTRI/TENO with the extent "considerable" and the probability "indication" (neurological adverse events). A decision on balancing of benefits and harms is not necessary.

In summary, for antiretroviral-naïve adult **women** with an HIV-1 infection and a viral load of ≤ 100,000 HIV-1 RNA copies/ml, there is an indication of an added benefit (extent: “considerable”) of rilpivirine + EMTRI/TENO compared to efavirenz + EMTRI/TENO.

2.5.3 Extent and probability of added benefit – summary

The result of the benefit assessment of the fixed-dose combination rilpivirine/emtricitabine/tenofovir compared to the ACT is shown in Table 16 below.

Table 16: Summary – rilpivirine/emtricitabine/tenofovir: extent and probability of the added benefit

	Population	**ACT**	**Extent and probability of added benefit**
1	Antiretroviral-naïve adult **men** with a viral load ≤ 100,000 HIV-1 RNA copies/ml	Efavirenz + emtricitabine/tenofovir	Proof of added benefit (extent "considerable") of rilpivirine/emtricitabine/tenofovir
2	Antiretroviral-naïve adult **women** with a viral load ≤ 100,000 HIV-1 RNA copies/ml	Efavirenz + emtricitabine/tenofovir	Indication of added benefit (extent "considerable") of rilpivirine/emtricitabine/tenofovir
ACT: appropriate comparator therapy, HIV: human immunodeficiency virus			

The approach for deriving an overall conclusion concerning added benefit is a proposal from IQWiG. The decision regarding added benefit is made by the G-BA.

2.6 List of included studies

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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.

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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; Rome, Italy. [accessed: 27.03.2012]. URL: http://www.crine.org/templates/cri/pdfs/Poster-Rome-week-96-Final.pdf.

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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, United Kingdom.

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, Mexico. [accessed: 27.03.2012]. URL: http://hivdb.stanford.edu/pages/pdf/RPV_IHDRW_2011_Poster_9.pdf.

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Please see addendum for full reference list.

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