IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Rilpivirine –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment (”Rilpvirin – Nutzenbewertung gemäß § 35a SGB V” (Version 1.0; Status: 12.04.2012). In the present extract, references to Sections 2.7 onwards relate to the full version of the assessment report (hereinafter called the “full dossier assessment”). 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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[3] Table numbers start with “2” as numbering follows that of the full dossier assessment.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AIDS	acquired immune deficiency syndrome
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)
MedDRA	Medical Dictionary for Regulatory Activities
NRTI	nucleoside reverse transcriptase inhibitor
RCT	randomized controlled trial
RNA	ribonucleic acid
SAE	serious adverse event
SF-36v2	Short Form 36, Version 2
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

On 16.01.2012, 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 drug rilpivirine. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company").

Research question

The aim of this report is to assess the added benefit of rilpivirine compared to efavirenz as appropriate comparator therapy (ACT) 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" [1]. The assessment was carried out in comparison with efavirenz as ACT with respect to patient-relevant outcomes. This deviates from the specification of the G-BA, because the latter designates efavirenz in combination with two nucleoside reverse transcriptase inhibitors (NRTIs; tenofovir/emtricitabine or abacavir/lamivudine) as ACT. However, in the Institute's view, it is not necessary to specify the particular backbone therapy of efavirenz for this assessment. The resulting wider consideration of backbone therapies does not contravene the approval status of rilpivirine [1]. Only randomized controlled trials (RCTs) with a direct comparator were included in the assessment.

Results

A total of 3 relevant studies were available. The study TMC278-C204 (in brief: C204) was an open-label Phase IIb RCT, whereas the two studies TMC278-C209 (in brief: C209) and TMC278-C215 (in brief: C215) were double-blind Phase III RCTs. In all 3 studies, the ACT efavirenz in the approved dosage (600 mg) served as active comparator, so a direct comparison on the basis of 3 RCTs was possible. All 3 studies specified the use of a combination of 2 NRTIs as backbone therapy. The risk of bias of the 3 studies at study level was rated as low. If homogeneity was adequate, the studies 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 results for the therapeutic indication investigated were as follows:

Mortality

An added benefit or greater harm from rilpivirine for this outcome is not proven. In this context, 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"

In the Institute's view, the outcome "virological response" was sufficiently valid for use as a surrogate for a patient-relevant outcome (combined outcome "AIDS-defining diseases/death") that was, however, not actually recorded in the studies included in the assessment. Nevertheless, it must be considered that the viral load (virological response) is not clearly validated as a 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" [4-7]; no clear correlation has been found between effects of the intervention on the surrogate and the patient-relevant outcome that the surrogate is supposed to replace. 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 progression of the disease, based on clinical drug trials directed towards reducing the viral load (see Section 2.7.2.9.4 of the full dossier assessment for further reasoning). The increased uncertainty is taken account of by the rating assigned to the extent of the added benefit (rating of any added benefit as "non-quantifiable").

Consideration of the meta-analysis of the entire approval population for the outcome "virological response" showed a statistically significant difference in favour of rilpivirine. In subgroup analyses, there was proof of an effect modification ($p < 0.05$) for the characteristic "gender", so that separate consideration of these subgroups was necessary. The result in men was statistically significantly in favour of rilpivirine, but not in women. Overall, there is proof of an added benefit for men in terms of virological response in the approval population. On the other hand, an added benefit of rilpivirine for women 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 of rilpivirine with respect to this outcome is not proven.

Adverse events

The result for adverse events (AEs), serious adverse events and psychiatric events was, in each case, not statistically significant. Because of heterogeneity ($p < 0.2$), the results for treatment discontinuations due to AEs were not combined in a meta-analysis. No further investigation of heterogeneity was necessary in this case, because the result of all 3 individual studies was not statistically significant. Results for the outcome "skin events" also showed high heterogeneity ($p < 0.2$) between the 3 studies, so that a statistical pooling of the study results did not appear reasonable. The meta-analysis showed a statistically significant effect in favour of rilpivirine for the outcome "neurological events". There is therefore an indication of lesser harm (extent: "considerable") from rilpivirine compared to efavirenz in relation to the outcome "neurological events".

Additional comment by IQWiG

The benefit assessment relates solely to results at the time of the 48-week analysis, because not all the analyses after 96 weeks were available. Since the duration of treatment in the therapeutic indication is long-term in nature, consideration of results at the later analysis time after 96 weeks is basically meaningful. The results available for this time for the approval population were considered in addition.

Unlike the analysis after 48 weeks, results on the outcome "AIDS-defining diseases/death" (considered via the surrogate viral load [virological response]) after 96 weeks show no statistically significant difference. However, there are no data from subgroup analyses for the characteristic "gender" for the time of 96 weeks. It is therefore unclear whether the deviating result for men and women applies to the same extent.

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

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 agent rilpivirine are assessed as follows:

- For antiretroviral-naïve adult **men** with a viral load of ≤ 100,000 HIV-1 RNA copies/ml there are 2 positive results of different certainty of results (one proof and one indication) in favour of rilpivirine. For the outcome "viral load (virological response)", the extent is "non-quantifiable", for the outcome "neurological events (AE)", "considerable". In the global 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, it was, however, possible - because of the sufficient validity of the surrogate - 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 an added benefit (extent: "considerable") of rilpivirine over efavirenz.

[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].

- For antiretroviral-naïve adult **women** and a viral load of ≤ 100,000 HIV-1 RNA copies/ml there is a positive result in favour of rilpivirine with the extent "considerable" and the probability "indication" (neurological events, AE). A decision on balancing of benefits and harms is not necessary. In summary, there is an indication of an added benefit (extent: "considerable") of rilpivirine over efavirenz.

These overall conclusions concerning added benefit are based on the aggregation of the extents of added benefit derived at outcome level.

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

Additional information about the added benefit on use of the ACT specified by the G-BA

In most cases in the 3 relevant studies, only the backbone therapies specified by the G-BA as ACT were used (in approx. 75% of patients). From the analyses of potential effect modifiers, no different conclusions regarding added benefit arose for the different backbone therapies.

Overall, it is therefore not to be assumed that the results of this benefit assessment would differ substantially if the ACT were to be restricted to the backbone therapies specified by the G-BA.

2.2 Research question

The benefit assessment of rilpivirine was carried out according to the following therapeutic indication stated in the Summary of Product Characteristics (SPC) [1]:

Rilpivirine in combination with other antiretroviral drugs is indicated for "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 designates efavirenz in combination with two NRTIs (tenofovir/emtricitabine or abacavir/lamivudine or zidovudine/lamivudine) as ACT for the benefit assessment of rilpivirine. It thus deviates from the specification of the G-BA, because, when designating the ACT, the G-BA restricted its choice of backbone therapies to 2 particular combinations (tenofovir/emtricitabine or abacavir/lamivudine). Although the company states that the backbone therapy not specified by the G-BA (zidovudine/lamivudine) is to be shown merely as an addition, it nonetheless draws conclusions about added benefit based on study results that include this combination.

The Institute concurs with the specification of the G-BA for the ACT in respect of efavirenz. On the other hand, this benefit assessment does not follow the restriction of backbone therapy by the G-BA to 2 specific combinations of 2 NRTIs or the restriction to 3 particular combinations by the company. In the Institute's view, it is not necessary to specify the

backbone therapy of efavirenz for this assessment (see Section 2.7.1 of the full dossier assessment). Regardless of this, in the concluding assessment it is presented whether and what different conclusions arise from the use of the ACT designated by the G-BA or the specification of the backbone therapy for efavirenz. Detailed information on the ACTs of the G-BA and of the company is given in Table 2.

Table 2: Overview of the ACT chosen by the G-BA and the company, together with the interpretation of IQWiG

Components of the ACT	**G-BA**	**Company**	**Interpretation of IQWiG**
NNRTI	Efavirenz	Efavirenz	Efavirenz
Backbone therapy	Tenofovir/emtricitabine, abacavir/lamivudine	Tenofovir/emtricitabine, abacavir/lamivudine, zidovudine/lamivudine	No restriction to certain drug combinations
ACT: active comparator therapy, G-BA: Gemeinsamer Bundesausschuss (Federal Joint Committee), IQWiG: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care), NNRTI: non-nucleoside reverse transcriptase inhibitor			

The assessment is carried out with respect to patient-relevant outcomes, 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.

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 on rilpivirine completed by the company up to 09.01.2012 (study list of the company).
- Results of a search in trial registries for studies on rilpivirine (last search 29.08.2011 and 17.11.2011, searches by the company).
- The Institute’s own searches for studies on rilpivirine in trial registries (search date: 02.02.2012) and subsequent check of the contents of the company’s information retrieval using the inclusion criteria specified by the Institute to check the company’s search results. The check produced no deviations from the study pool presented in the company’s dossier.

The resulting study pool for the direct comparison with efavirenz corresponded to that of the company.

The data from the relevant studies of the target population defined in the SPC (patients with a viral load ≤ 100,000 HIV-1 RNA copies/ml) were used for the assessment. This population is described as the "approval population" below.

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 of the full dossier assessment.

2.3.1 Included studies

The studies C204, C209 and C215 listed in Table 3 were included in the benefit assessment. In accordance with the research question, studies that compared rilpivirine with efavirenz, each in combination with other antiretroviral drugs, were considered.

Table 3: Study pool – RCTs with the drug to be assessed

Study	Study category		
	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	yes	yes	no
C215	yes	yes	no

a: Study for which the company was sponsor, or in which the company was otherwise financially involved.
RCT: randomized controlled trial

The study pool for the benefit assessment of rilpivirine corresponded to that of the company. Three RCTs with the drug to be assessed were submitted for the assessment of rilpivirine in the approved therapeutic indication, from which data for a direct comparison with the ACT efavirenz could be used.

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

Further information about the result of information retrieval and the resulting study pool can be found in Module 4, Section 4.3.1.1 of the dossier and in Section 2.7.2.3.1 of the full dossier assessment.

2.3.2 Study characteristics

Table 4 and Table 5 describe the studies C204, C209 and C215 included in the benefit assessment.

Antiretroviral-naïve adult patients with confirmed HIV-1 infection and a HIV-1 plasma viral load at the start of the study of ≥ 5000 copies/ml were enrolled in the 3 studies. However, only one subpopulation of each of the studies is relevant for the benefit assessment. This is the

population of patients with a viral load of ≤ 100,000 HIV-1 RNA copies/ml (approval population [1]).

Table 4: Characteristics of the included studies – RCT for the comparison rilpivirine vs. efavirenz

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) Of which approval population[d]: Rilpivirine 25 mg (n = 61) Efavirenz 600 mg (n = 58[e])	Screening: 4 weeks Treatment: 96 weeks (interim analysis after 48 weeks[f]) Follow-up: 4 weeks Open-label treatment: 144 weeks	14 countries in Asia, Europe, Latin America, Africa, USA 48 weeks, treatment period: 6/2005–10/2006 96 weeks, treatment period: 6/2005–10/2007	Primary: virological response Secondary: all-cause mortality, adverse events
C209	RCT, double-blind, double-dummy[g], parallel, active controlled	Antiretroviral-naïve adult HIV-1 infected patients	Study population Rilpivirine 25 mg (N = 346) Efavirenz 600 mg (N = 344) Of which approval population[d]: Rilpivirine 25 mg (n = 181) Efavirenz 600 mg (n = 163)	Screening: 6 weeks Treatment: 96 weeks (interim analysis after 48 weeks[f]) Follow-up: max. 6 weeks	20 countries in Australia, Asia, Europe, Canada, Latin America, Africa, USA 48 weeks, treatment period: 4/2008–2/2010 96 weeks, treatment period: 4/2008–1/2011	Primary: virological response Secondary: all-cause mortality, health-related quality of life (SF-36v2), adverse events
C215	RCT, double-blind, double-dummy[g], parallel, active controlled	Antiretroviral-naïve adult HIV-1 infected patients	Study population Rilpivirine 25 mg (N = 340) Efavirenz 600 mg (N = 338) Of which approval population[d]: Rilpivirine 25 mg (n = 187) Efavirenz 600 mg (n = 167)	Screening: 6 weeks Treatment: 96 weeks (interim analysis after 48 weeks[f]) Follow-up: max. 6 weeks	21 countries in Australia, Asia, Europe, Canada, Latin America, Africa, USA 48 weeks, treatment period: 5/2008–1/2010 96 weeks, treatment period: 4/2004–1/2011	Primary: virological response Secondary: all-cause mortality, health-related quality of life (SF-36v2), adverse events

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Table 4: Characteristics of the included studies – RCT for the comparison rilpivirine vs. efavirenz (continued)

a: Extracted primary outcome criteria contain information with no 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 blinded only to the dosage used in the rilpivirine arm.
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 the start of the study ≤ 100,000 HIV-1 RNA copies/ml.
e: In Study C204, the number of randomized patients in the efavirenz arm (58) differed from the number treated and hence included in the assessment (56).
f: The 48-week data were the basis of this benefit assessment, because the study reports for Studies C209 and C215 inclusive of all appendices were not yet available at the time the dossier was submitted. Section 2.7.2.4.3 of the full dossier assessment contains further information about the time of analysis for the benefit assessment.
g: 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).

HIV-1: human immunodeficiency virus type 1, n = number of patients in the approval population, N = number of randomized patients, RCT: randomized controlled trial, SF-36v2: Short Form 36, Version 2

Table 5: Backbone therapies – RCT for the comparison rilpivirine vs. efavirenz

Population Study Study arm	**Allocation to the backbone therapies[a] n (%)**		
	Tenofovir 300 mg/day + emtricitabine 200 mg/day	**Zidovudine 300 mg/day + lamivudine 300 mg/day**	**Abacavir 600 mg + lamivudine 300 mg/day[b]**
Approval population[c]			
C204			
Rilpivirine	10 (16.4)	51 (83.6)	0
Efavirenz	15 (26.8)	41 (73.2)	0
C209			
Rilpivirine	181 (100.0)	0	0
Efavirenz	163 (100.0)	0	0
C215			
Rilpivirine	107 (57.2)	58 (31.0)	22 (11,8)
Efavirenz	93 (55.7)	56 (33.5)	18 (10.8)
Study population			
C204			
Rilpivirine	22 (23.9)	70 (76.1)	0
Efavirenz	22 (25.0)	66 (75.0)	0
C209			
Rilpivirine	346 (100.0)	0	0
Efavirenz	344 (100.0)	0	0
C215			
Rilpivirine	202 (59.4)	102 (30.0)	36 (10.6)
Efavirenz	201 (59.5)	103 (30.5)	34 (10.1)

a: Depending on availability, standard treatment and approval in the respective country, backbone therapy was taken as fixed combinations or as separate components.
b: The daily dose with this combination of drugs was divided into two single doses.
c: Relevant population for the assessment (patients with viral load at baseline ≤ 100,000 HIV-1 RNA copies/ml); proportions self-calculated.
n: number of patients, RCT: randomized controlled trial

Studies C209 and C215 are the company's Phase III approval studies. C204 study is an open-label, Phase IIb RCT (dose-finding study) by the company.

The treatment phase of the 3 studies was at least 96 weeks. At the time of dossier submission, study reports for the analysis after 96 weeks for Studies C209 and C215 were not available in their final and complete form (including all appendices). In particular, hardly any data were available for the approval population of interest at the time of the 96-week analysis. Hence the 48-week data (pre-specified interim analysis) were used for the present benefit assessment. In order to ensure results were comparable, the 48-week data of the C204 study were therefore also used. As additional information, the results on those outcomes for which data were

available for the approval population at 96 weeks are shown in Appendix A of the full dossier assessment.

All 3 studies were multicentre studies, whose respective centres ranged from countries in Europe, Africa, America and Asia to Australia.

In all 3 studies, rilpivirine and also efavirenz were given orally once daily in accordance with the approval [1, 8]. Because rilpivirine is best taken in the morning along with a meal, whereas the preferred administration of efavirenz is on an empty stomach in the evening, in order to maintain blinding, the additional administration of a placebo (*double-dummy*) was necessary in Studies C209 and C215. According to their approval status, both rilpivirine and efavirenz must be combined with other antiretroviral drugs. This requirement was met in the three studies included in the assessment by the use of a backbone therapy, always consisting of a combination of 2 NRTIs. Three different backbone therapies were possible (tenofovir/emtricitabine, abacavir/lamivudine, zidovudine/lamivudine) in the relevant studies. However the proportion of patients allocated to the various backbone therapies in these 3 relevant studies differed substantially (see Table 5). The 3 backbone therapies are distributed over the 3 studies as shown below:

- Approx. 70% of patients received tenofovir/emtricitabine.
- Approx. 5% of patients received abacavir/lamivudine.
- Approx. 25% of patients received zidovudine/lamivudine.

The backbone therapy was selected by the investigator on an individual patient basis and depended on the approval status in the respective country, the standard treatment and tolerability. The study protocols of all studies specified that the backbone therapy had to be kept constant. However, this could be changed in the case of intolerance to the backbone therapy. The estimation of the possible influence of the different backbone therapies is the subject of the benefit assessment.

Table 6 shows the characteristics of the patients in the included studies.

Table 6: Characteristics of the approval population and the study population – RCT for the comparison rilpivirine vs. efavirenz

Population Study Study arm **N**	**n (%)**[a]	**Age [years] mean (SD)**	**Gender f/m [%]**[b]	**CD4 cell counts (cells/µl) at start of study n (%)**				**Duration of HIV-1 infection since diagnosis [years] mean (SD)**	**Ethnicity**		**Study discontinuations up to and including Week 48 n (%)**
				< 50	50 ≤ x < 200	200 ≤ x < 350	≥ 350		**White**	**Non-white**[c]	
Approval population											
C204											
Rilpivirine	61 (66)	n.k.	34 / 66	n.k.	n.k.	n.k.	n.k.	n.k.	n.k.	n.k.	n.k.
Efavirenz	56 (63)	n.k.	29 / 71	n.k.	n.k.	n.k.	n.k.	n.k.	n.k.	n.k.	n.k.
C209											
Rilpivirine	181 (52)	n.k.	27 / 73	n.k.	n.k.	n.k.	n.k.	n.k.	n.k.	n.k.	n.k.
Efavirenz	163 (47)	n.k.	22 / 78	n.k.	n.k.	n.k.	n.k.	n.k.	n.k.	n.k.	n.k.
C215											
Rilpivirine	187 (55)	n.k.	32 / 68	n.k.	n.k.	n.k.	n.k.	n.k.	n.k.	n.k.	n.k.
Efavirenz	167 (49)	n.k.	33 / 67	n.k.	n.k.	n.k.	n.k.	n.k.	n.k.	n.k.	n.k.
Study population											
C204											
Rilpivirine	93	37 (9)	30 / 70	n.k.[d]	n.k.[d]	n.k.[d]	n.k.[d]	2.7 (3.8)	44[e]	47[e]	15 (16.1)
Efavirenz	89	35 (8)	33 / 67	n.k.[d]	n.k.[d]	n.k.[d]	n.k.[d]	2.9 (3.7)	47[e]	44[e]	16 (18.0)
C209											
Rilpivirine	346	37 (10)	23 / 77	15 (4.3)	110 (31.8)	154 (44.5)	67 (19.4)	2.7 (3.6)	62	38	50 (14.5)
Efavirenz	344	37 (10)	20 / 80	19 (5.5)	84 (24.4)	162 (47.1)	79 (23.0)	2.5 (3.5)	60	40	56 (16.3)
C215											
Rilpivirine	340	36 (9)	27 / 73	19 (5.6)	84 (24.8)	159 (46.9)	77 (22.7)	2.9 (3.9)	61	39	44 (12.9)
Efavirenz	338	36 (9)	28 / 72	17 (5.0)	91 (26.9)	145 (42.9)	85 (25.1)	2.5 (3.4)	60	40	56 (16.6)

(continued on next page)

Table 6: Characteristics of the approval population and the study population – RCT for the comparison rilpivirine vs. efavirenz (continued)

a: Percentage of the approval population in the study population.
b: The proportion of each gender in the approval population was calculated from the dossier itself.
c: This group is composed of Afro-American, Asiatic and other ethnicities, as well as patients where local legislation did not permit the question.
d: In Study C204, characteristics of the study population in terms of CD4 cell counts were only available for other threshold values.
e: In Studies C209 and C215, Hispanic/non-Hispanic origin was recorded differently ("ethnicity") than in Study C204 ("race"). Due to lack of comparability, this characteristic is not included in the table, which is why the proportions of ethnic origin for Study C204 do not add up to 100%.

HIV-1: human immunodeficiency virus type 1, f: female, m: male, N: number of patients in the study population, n: number of patients in the approval population/patients with event, n.k.: not known, RCT: randomized controlled trial, SD: standard deviation

Depending on the study, the relevant approval population of patients with a viral load ≤ 100,000 HIV-1 RNA copies/ml represented approx. 50 to 65% of the study population. The company did not characterize this population in the dossier, so only data on gender and on the respective backbone therapy could be derived from the subgroup analyses presented by the company. The data on the study population are therefore also shown in Table 6.

The risk of bias at study level is shown in Table 7.

Table 7: Risk of bias at study level – RCT for the comparison rilpivirine vs. efavirenz

Study	Adequate randomization sequence generation	Allocation concealment	Blinding		Selective outcome reporting	Other sources of bias	Risk of bias at study level
			Patient	Treating persons			
C204	yes	yes	no	no	no	no	low
C209	yes	yes	yes	yes	no	no	low
C215	yes	yes	yes	yes	no	no	low
RCT: randomized controlled trial							

Overall, the risk of bias at study level was rated as low for all 3 included studies. This concurs with the company's assessment. The lack of blinding in Study C204 did not lead to a deviating assessment of the risk of bias at study level, but is taken into account when considering the risk of bias at outcome level.

Further information about study design, study populations and the risk of bias at study level can be found in Module 4, Sections 4.3.1.2.1 and 4.3.1.2.2 of the dossier and in Sections 2.7.2.2, 2.7.2.4.1 and 2.7.2.4.2 of the full dossier assessment.

2.4 Results concerning added benefit

2.4.1 Relevant outcomes

This assessment covers the following patient-relevant outcomes (for more detailed reasoning, see Section 2.7.2.4.3 of the full dossier 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)
- Skin events
- Neurological events
- Psychiatric events

In addition, the following outcome is considered as a sufficiently valid surrogate for the combined outcome "AIDS-defining diseases/death" in the benefit assessment (for detailed description see Section 2.7.2.9.4 of the full dossier assessment).

- Viral load (virological response)

The Institute chose partly different patient-relevant outcomes to those of the company, which included further outcomes in Module 4 of its dossier (e.g. virological failure [efficacy and resistance]). The Institute considers these two outcomes as adequately covered by the outcome "virological response". In the choice of other adverse events, the Institute does not agree with that of the company, insofar as it does not consider neuropsychiatric events and skin rashes separately, because they are already covered under skin events as a whole and under neurological events and psychiatric events (see Section 2.7.2.4.3 of the full dossier assessment for reasons for the choice of outcomes by the Institute). In addition, the Institute rated the outcome "all-cause mortality" as patient-relevant and included it in the benefit assessment.

2.4.2 Data availability and risk of bias

Table 8 shows the outcomes for which data were available from the studies included in the assessment.

Table 8: Matrix of outcomes – RCT for the comparison rilpivirine vs. efavirenz

				Adverse events					
Study	**All-cause mortality**	**Viral load (virological response)[a]**	**Health-related quality of life (SF-36v2)**	**AEs**	**SAEs**	**Discontinuation due to AEs**	**Skin events**	**Neurological events**	**Psychiatric events**
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 a sufficiently valid surrogate for the combined outcome "AIDS-defining diseases/death".
AE: adverse event, RCT: randomized controlled trial, SF-36v2: Short Form 36, Version 2, SAE: serious adverse event

Table 9 provides the risk of bias for these outcomes.

Table 9: Risk of bias at study and outcome levels. RCT for the comparison rilpivirine vs. efavirenz

		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**	**Skin events**	**Neurological events**	**Psychiatric events**
C204	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 assessment of the risk of bias of the outcome was undertaken by the Institute, because the outcome was considered in addition to the outcomes included 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 a 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, 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 availability of data for the approval population could be assumed for the relevant studies.

The outcome "health-related quality of life" was missing from the analysis for more than 10% of patients to be included in Studies C209 and C215, so the risk of bias for this outcome was rated as high – in contrast to the company's assessment.

The risk of bias for skin events and neurological events was also rated as high because the choice of *preferred terms* from the Medical Dictionary for Regulatory Activities (MedDRA) classification was not clearly specified a-priori. This deviates from the company's assessment, which rates the risk of bias as low for these outcomes. The outcome "all-cause mortality" added by the Institute was assessed as having a low risk of bias.

A low risk of bias was present for all other outcomes included. This concurs with the company's assessment.

Further information about the choice of outcome and risk of bias at outcome level can be found in Module 4, Sections 4.3.1.2.2 and 4.3.1.3 of the dossier and in Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.

2.4.3 Results

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

Mortality

Table 10 summarizes the results on all-cause mortality for the comparison of rilpivirine and efavirenz.

Table 10: Results on all-cause mortality, rilpivirine vs. efavirenz

	Rilpivirine		Efavirenz		Rilpivirine vs. efavirenz	
	Total N	Events n (%)	Total N	Events n (%)	RR [95% CI]	p-value
Mortality						
C204	61	0 (0)	56	0 (0)	not applicable[a]	
C209	181	0 (0)	163	0 (0)	not applicable[a]	
C215	187	0 (0)	167	1 (0.6)	not applicable[a]	
Meta-analysis					not applicable[a]	

a: Too low a proportion of patients with event.
CI: confidence interval, N: number of patients in the analysis, n: number of patients with event, RR: relative risk

In the 3 studies used for the assessment, only 1 death occurred in the approval population within the first 48 weeks. No statistical analysis of this low event rate was carried out. An added benefit or greater harm from rilpivirine compared with efavirenz for this outcome is not proven. It should be considered that, due to the 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 11 summarizes the results on viral load (virological response) for the comparison of rilpivirine and efavirenz.

Table 11: Results on viral load (virological response), rilpivirine vs. efavirenz

	Rilpivirine		Efavirenz		Rilpivirine vs. efavirenz
	Total N	**Events n (%)**	**Total N**	**Events n (%)**	**RR [95% CI] p-value**
Viral load (virological response)[a]					
C204	61	51 (83.6)	56	46 (82.1)	0.92 [0.41; 2.04]
C209	181	162 (89.5)	163	136 (83.4)	0.63 [0.37; 1.10]
C215	187	170 (90.9)	167	140 (83.8)	0.56 [0.32; 0.99]
Meta-analysis					0.65 [0.46; 0.93] p = 0.017

a: 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).
b: Institute's calculation: relative risk, confidence interval and p-value for non-responders (rilpivirine vs. efavirenz).
CI: confidence interval, N: number of patients in the analysis, n: number of patients with event, RR: relative risk

By itself, viral load defined via the virological response is not a patient-relevant outcome. This concurs with the company's assessment. In its assessment, the company uses viral load (based on the analysis of virological response) as a surrogate for the combined outcome "AIDS-defining diseases/death". An examination of the studies with which the company wishes to demonstrate validity of the surrogate [4-7], does not allow derivation of formal surrogate validity (see Section 2.7.2.9.4 of the full dossier assessment for detailed reasoning). Nevertheless, in the Institute's view the prognostic value of viral load for subsequent diseases and death is such that sufficient 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.

Figure 1 shows the meta-analysis of the 3 relevant studies for the comparison of rilpivirine vs. efavirenz for the outcome "viral load" (virological response). In each case, the relative risks were calculated for the non-responders.

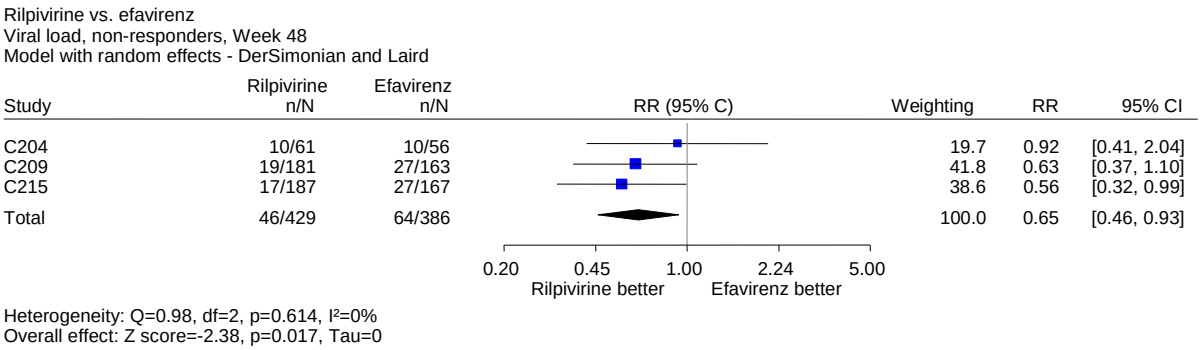


Figure 1: Meta-analysis, viral load (virological response, non-responders), rilpivirine vs. efavirenz

A statistically significantly higher proportion of patients of the approval population treated with rilpivirine achieved a virological response compared to those treated with efavirenz. However, in the subsequent course of the assessment, proof was produced 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 the related evidence can be found in Section 2.4.4.

Health-related quality of life

This outcome was only investigated in Studies C209 and C215 using the instrument SF-36v2. The latter is a general (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. High values of the sum scores denote a high quality of life.

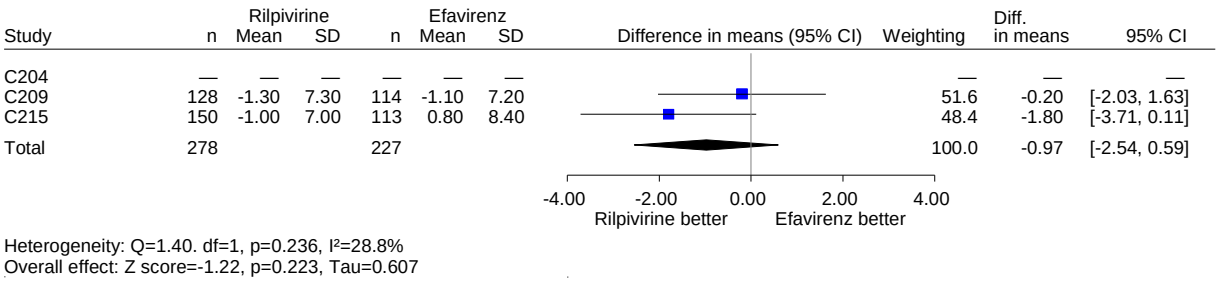
Table 12 summarizes the results on health-related quality of life (measured using SF-36v2) for the comparison of rilpivirine and efavirenz.

Table 12: Results on health-related quality of life, rilpivirine vs. efavirenz

Outcome	Rilpivirine				Efavirenz				Rilpivirine vs. efavirenz
Study	N[a]	Values at start of study Mean (SD)	N[b]	Change at end of study Mean (SD)	N[a]	Values at start of study Mean (SD)	N[b]	Change at end of study Mean (SD)	Difference in means[c] [95% CI], p-value
Health-related quality of life									
SF-36v2, average sum score "physical health"									
C209	158	53.7 (7.9)	128	1.3 (7.3)	149	53.6 (6.8)	114	1.1 (7.2)	–0.20 [–2.03; 1.63]
C215	179	52.7 (7.3)	150	1.0 (7.0)	153	52.9 (7.2)	113	-0.8 (8.4)	–1,80 [–3.71; 0.11]
Meta-analysis									–0.97 [–2.54; 0.59] p = 0.22
SF-36v2, average sum score "mental health"									
C209	158	47.4 (11.6)	128	2.4 (10.7)	150	46.1 (11.3)	115	2.2 (11.0)	–0.20 [–2.93; 2.53]
C215	179	46.1 (11.3)	150	3.5 (9.4)	154	46.7 (12.1)	114	1.2 (10.5)	–2.30 [–4.74; 0.14]
Meta-analysis									–1.34 [–3.39; 0.71] p = 0.20

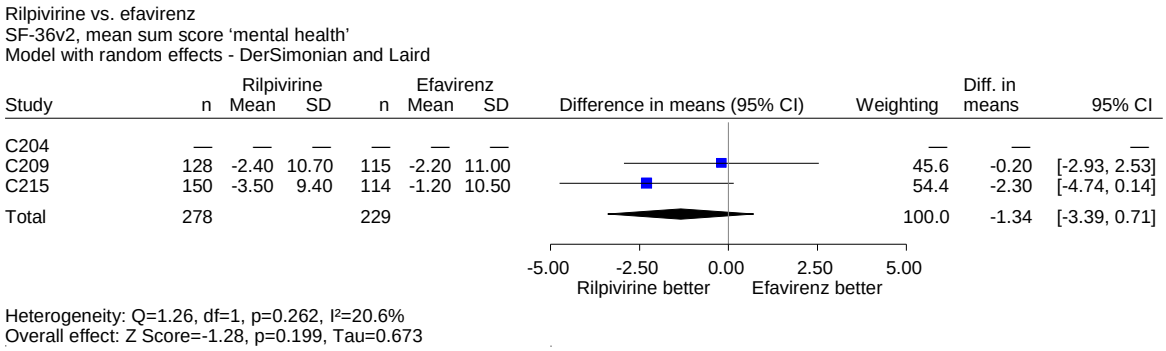
a: Number of patients for whom data were available at the start of the study.
b: Number of patients for whom data were available for the 48-week time of analysis.
c: Negative differences correspond to a difference in favour of rilpivirine.
CI: confidence interval; N: number of analysed patients; SD: standard deviation, SF-36v2: Short Form 36, Version 2

Figure 2 and Figure 3 show the meta-analyses of the two studies in which the quality of life was recorded using the SF-36v2 tool. In each case, the mean change in sum scores "physical health" and "mental health" is shown.



The signs of the mean values per group were reversed to enable a uniform presentation of the direction of effects.

Figure 2: Meta-analysis, mean change in sum score "physical health", rilpivirine vs. efavirenz



The signs of the mean values per group were reversed to enable a uniform presentation of the direction of effects

Figure 3: Meta-analysis, mean change in sum score "mental health", rilpivirine vs. efavirenz

The two sum scores to illustrate physical and mental health did not differ substantially at Week 48 from the results at the start of the studies. The result was not statistically significant either in the individual studies or in the meta-analyses and there was no heterogeneity between the individual studies.

In summary, an added benefit of rilpivirine compared to efavirenz in respect of health-related quality of life is not proven. This concurs with the company's assessment.

Adverse events

Table 13 summarizes the results on adverse events for the comparison of rilpivirine and efavirenz.

Table 13: Results on adverse events, rilpivirine vs. efavirenz

	Rilpivirine		**Efavirenz**		**Rilpivirine vs. efavirenz**
	Total N	**Events n (%)**	**Total N**	**Events n (%)**	**RR[a] [95% CI] p-value**
AEs					
C204	61	55 (90.2)	56	50 (89,3)	1.01 [0.89; 1.14]
C209	181	160 (88,4)	163	144 (88,3)	1.00 [0.93; 1.08]
C215	187	169 (90.4)	167	147 (88,0)	1.03 [0.95; 1.10]
Meta-analysis					1.01 [0.97; 1.06] p = 0.587

(continued on next page)

Table 13: Results on adverse events, rilpivirine vs. efavirenz (continuation)

	Rilpivirine		Efavirenz		Rilpivirine vs. efavirenz
	Total N	Events n (%)	Total N	Events n (%)	RR[a] [95% CI] p-value
SAE					
C204	61	7 (11.5)	56	7 (12.5)	0.92 [0.34; 2.45]
C209	181	10 (5.5)	163	16 (9.8)	0.56 [0.26; 1.20]
C215	187	10 (5.3)	167	7 (4.2)	1.28 [0.50; 3.28]
Meta-analysis					0.81 [0.49; 1.35] p = 0.423
Discontinuation due to AEs					
C204	61	6 (9.8)	56	2 (3.6)	2.75 [0.58; 13.09]
C209	181	5 (2.8)	163	12 (7.4)	0.38 [0.14; 1.04]
C215	187	10 (5.3)	167	9 (5.4)	0.99 [0.41; 2.38]
Meta-analysis	Heterogeneity: Q = 4.75, df = 2, p = 0.093, I^2 = 57.9%				
Skin events[b]					
C204	61	8 (13.1)	56	12 (21.4)	0.61 [0.27; 1,39]
C209	181	26 (14.4)	163	31 (19.0)	0.76 [0.47; 1,22]
C215	187	10 (5.3)	167	30 (18.0)	0.30 [0.15; 0.59]
Meta-analysis	Heterogeneity: Q = 4.89, df = 2, p = 0.087, I^2 = 59.1%				
Neurological events[b]					
C204	61	14 (23.0)	56	22 (39.3)	0.58 [0.36; 1.03]
C209	181	44 (24.3)	163	72 (44.2)	0.55 [0.40; 0.75]
C215	187	59 (31.6)	167	85 (50.9)	0.62 [0.48; 0.80]
Meta-analysis					0.59 [0.49; 0.71] p < 0.001
Psychiatric events[b]					
C204	61	8 (13.1)	56	8 (14.3)	0.92 [0.37; 2.28]
C209	181	41 (22.7)	163	54 (33.1)	0.68 [0.48; 0.97]
C215	187	46 (24.6)	167	38 (22.8)	1.08 [0.74; 1.57]
Meta-analysis					0.86 [0.62; 1.20] p = 0.370

a: Institute's calculation: relative risk including confidence intervals and p-values (rilpivirine vs. efavirenz).
b: Due to lack of data for the approval population, a differentiation according to serious and non-serious events for this outcome was not possible.

AE: adverse event, CI: confidence interval, N: number of patients in the analysis, n: number of patients with event, RR: relative risk, SAE: serious adverse event

Overall rate of adverse events

Figure 4 shows the meta-analysis of the 3 relevant studies on the comparison of rilpivirine vs. efavirenz for the outcome "adverse events" (overall rate).

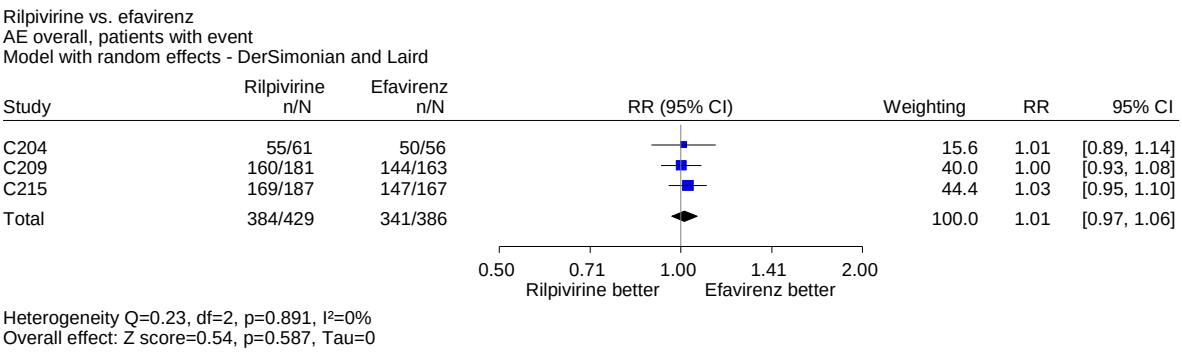


Figure 4: Meta-analysis, overall rate of adverse events, rilpivirine vs. efavirenz

The proportions of patients with adverse events (overall rate) in the 3 studies did not differ substantially between rilpivirine and efavirenz. The result of the meta-analysis was not statistically significant and there was no heterogeneity between the individual studies.

Lesser/greater harm of rilpivirine for this outcome is not proven. This concurs with the company's assessment.

Overall rate of serious adverse events

Figure 5 shows the meta-analysis of the 3 relevant studies on the comparison of rilpivirine vs. efavirenz for the outcome "serious adverse events" (overall rate).

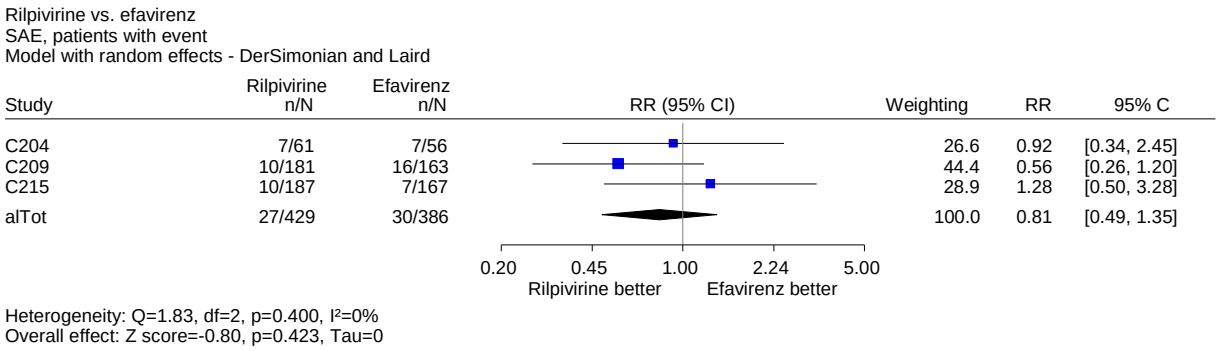


Figure 5: Meta-analysis, serious adverse events, rilpivirine vs. efavirenz

The proportions of patients with serious adverse events in the 3 studies did not differ substantially between rilpivirine and efavirenz. The result of the meta-analysis was not statistically significant and there was no heterogeneity between the individual studies.

Greater/lesser harm from rilpivirine compared to efavirenz for this outcome is not proven. This concurs with the company's assessment.

Overall rate of adverse events that led to discontinuation

Figure 6 shows the results of the 3 relevant studies on the comparison of rilpivirine vs. efavirenz for the outcome "discontinuation due to adverse events" (overall rate).

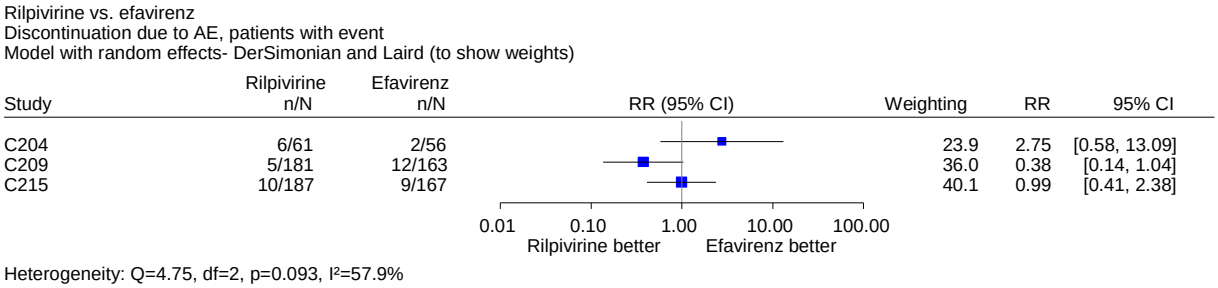


Figure 6: Meta-analysis, adverse events that led to discontinuation, rilpivirine vs. efavirenz

The proportions of patients with discontinuation due to adverse events in the 3 studies did not differ substantially between rilpivirine and efavirenz. Because of heterogeneity ($p < 0.2$) the results were not summarized by meta-analysis and therefore no overall effect estimator was illustrated. 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 compared to efavirenz for this outcome is not proven. This concurs with the company's assessment.

Skin events

Figure 7 shows the results of the 3 relevant studies on the comparison of rilpivirine vs. efavirenz for the outcome "skin events".

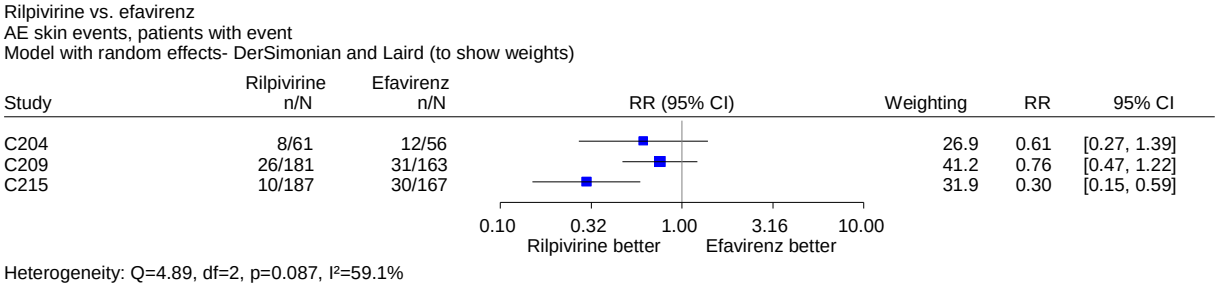


Figure 7: Meta-analysis, skin events, rilpivirine vs. efavirenz

Because of heterogeneity ($p < 0.2$), the results on the outcome "skin events" were not summarized by meta-analysis. Based on the results of the individual studies, in the C215

study, there was a statistically significant result in favour of rilpivirine. In Studies C204 and C209, although the estimators were in favour of rilpivirine in terms of the avoidance of skin events, the results were not statistically significant in either case. A separate meta-analysis of these two studies, which have a weighting in the meta-analysis of approx. 70%, does not lead to a statistically significant result. In particular, it is inexplicable why the two studies C209 and C215 of very similar design show this high heterogeneity. Lesser harm from rilpivirine compared to efavirenz cannot be derived from these data. This concurs with the company's assessment.

Neurological events

Figure 8 shows the meta-analysis of the 3 relevant studies on the comparison of rilpivirine vs. efavirenz for the outcome "neurological events".

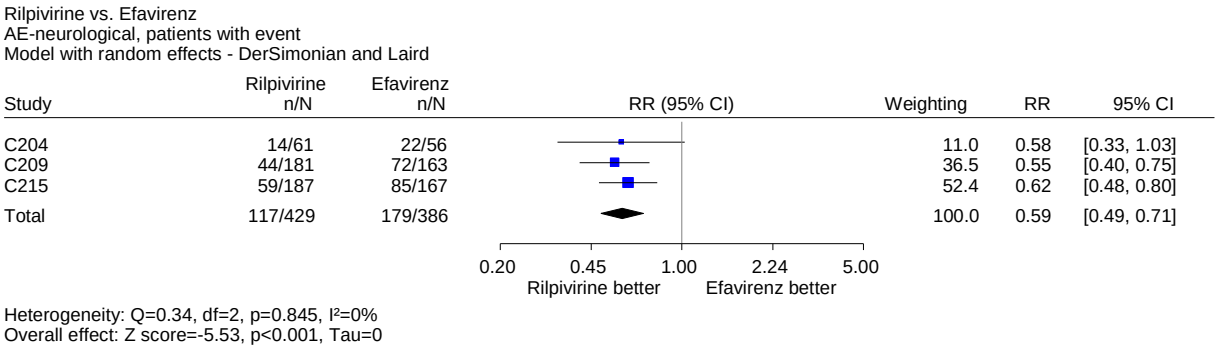


Figure 8: Meta-analysis, neurological events, rilpivirine vs. efavirenz

Neurological events occurred more frequently in the patients treated with efavirenz than in those who received rilpivirine. The overall effect of the meta-analysis was statistically significant, and there was no heterogeneity between the results of the individual studies.

Since this outcome, because of the unclear definition, has a potentially high risk of bias (see Section 2.7.2.4.3 of the full dossier assessment for more detailed reasoning), there is merely an indication of lesser harm from rilpivirine compared to efavirenz for the outcome "neurological events". This deviates from the company's assessment, which derived proof of an added benefit of rilpivirine in respect of this outcome.

Psychiatric events

Figure 9 shows the meta-analysis of the 3 relevant studies on the comparison of rilpivirine vs. efavirenz for the outcome "psychiatric events".

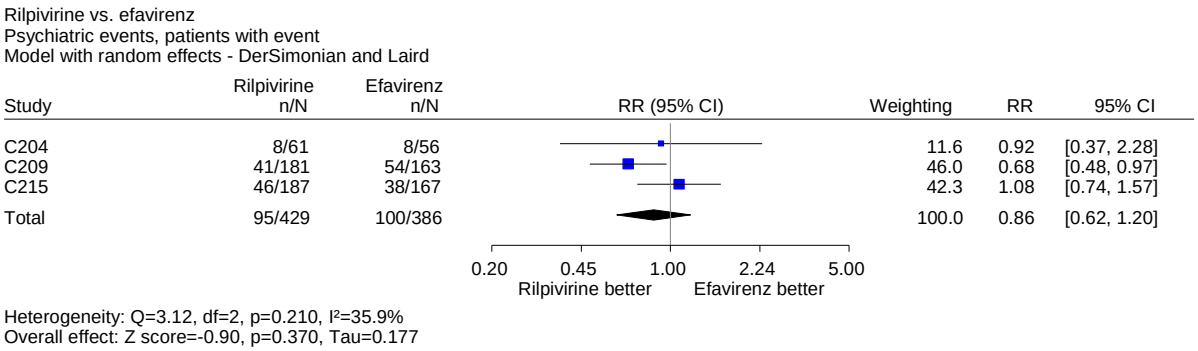


Figure 9: Meta-analysis, psychiatric events, rilpivirine vs. efavirenz

The proportions of patients with psychiatric events did not differ substantially between rilpivirine and efavirenz. The overall effect of the meta-analysis was not statistically significant and there was no important heterogeneity.

Greater/lesser harm from rilpivirine compared to efavirenz for this outcome is not proven. This concurs with the company's assessment.

2.4.4 Subgroup analyses

In order to analyse possible effect modifiers, the respective subgroups were investigated using the Q statistic for random effects. This was carried out as far as possible for the subgroup characteristics presented in the dossier of age (< 55 years; ≥ 55 years), gender and backbone therapy (tenofovir/emtricitabine; abacavir/lamivudine; zidovudine/lamivudine). The analysis of the approval population already constitutes a subgroup analysis based on the study population with respect to the characteristic "baseline viral load", so that the primary analysis itself can be accepted as a representation of the disease severity. The named cut-off points 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 approval population. No results for the additionally included outcome "all-cause mortality" were available from subgroup analyses. However, such an analysis could not be undertaken anyway, because only one patient died.

Only results for subgroups in which an interaction could be demonstrated, are shown 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 analyses for the characteristic "gender" produced proof of differing effects in men and women in virological response. The subgroup analyses for the outcome "psychiatric events" produce proof of an interaction of treatment with backbone therapy. For the outcome "neurological events", there was an indication of an interaction by the characteristic "age". For the outcomes "health-related quality of life", "adverse events", "serious adverse events", "discontinuations due to adverse events" and "skin events", there were no differing treatment effects neither for the characteristic "age" nor for "gender" or "backbone therapy".

The results and conclusions regarding the characteristics and outcomes with an indication or proof of an effect modification are shown below.

Viral load (virological response)

Table 14 shows the results in the subgroups; Figure 10 shows the related analysis.

Table 14: Subgroups, viral load (virological response) according to gender, rilpivirine vs. efavirenz

Outcome	Rilpivirine		Efavirenz		Rilpivirine vs. efavirenz
Study Gender	**N[a]**	**Patients with events n (%)**	**N[a]**	**Patients with events n (%)**	**RR [95% CI][b] p-value[c]**
Viral load (virological response)					
C204					
Men	40	35 (87.5)	40	33 (82.5)	0.71 [0.25; 2.06]
Women	21	16 (76.2)	16	13 (81.3)	1.27 [0.35; 4.54]
C209					
Men	132	122 (92.4)	127	107 (84.3)	0.48 [0.23; 0.99]
Women	49	40 (81.6)	36	29 (80.6)	0.94 [0.39; 2.30]
C215					
Men	128	117 (91.4)	112	90 (80.4)	0.44 [0.22; 0.86]
Women	59	53 (89.8)	55	50 (90.9)	1.12 [0.36; 3.46]
Meta-analysis					
Men					0.50 [0.32; 0.77]
Women					1.06 [0.58; 1.96]
					p = 0.048

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: Institute's calculation (interaction test). Q statistic with random effects.
CI: confidence interval; N: number of analysed patients; n: number of patients with event; RR: relative risk

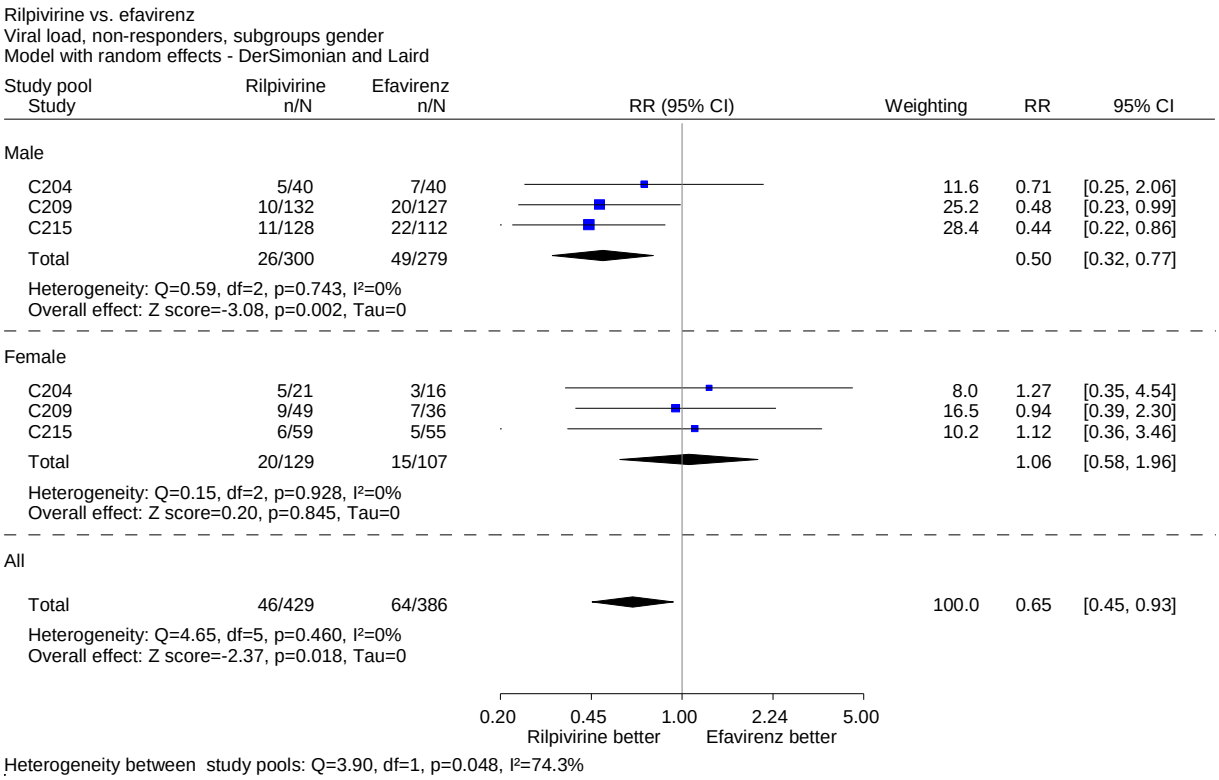


Figure 10: Meta-analysis, subgroups according to gender, viral load (virological response – non-responders), rilpivirine vs. efavirenz, interaction test p = 0.048

For the outcome "viral load" defined via the virological response, the interaction test using the Q statistic for random effects showed proof ($p < 0.05$) of an effect modification through the characteristic "gender" that necessitated a separate consideration of the results for men and women.

In men, a higher proportion of patients treated with rilpivirine achieved a virological response than those given efavirenz. The result of the meta-analysis was statistically significant for this subgroup of men and there was no heterogeneity.

In women, there was no substantial difference in proportions of patients with virological response between rilpivirine and efavirenz. 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. In summary, there is proof of added benefit of rilpivirine compared to efavirenz for the outcome "viral load" (virological response) for men. On the other hand, an added benefit is not proven for women. This assessment differs from that of the company, which, although it identified an indication of a relevant effect modification, nevertheless derived an overall added benefit for this outcome and did not differentiate according to this characteristic.

However, at outcome level, it should be considered that viral load (virological response) is not clearly validated as a surrogate and is merely rated as a surrogate "of sufficient validity" (see Section 2.7.2.9.4 of the full dossier assessment). Account is taken below of this increased uncertainty by the rating of extent of the added benefit ("non-quantifiable").

Neurological events

Figure 11 shows the meta-analysis of the 3 relevant studies on the comparison of rilpivirine vs. efavirenz for the outcome "neurological events", divided according to the characteristic "age" (< / ≥ 55 years).

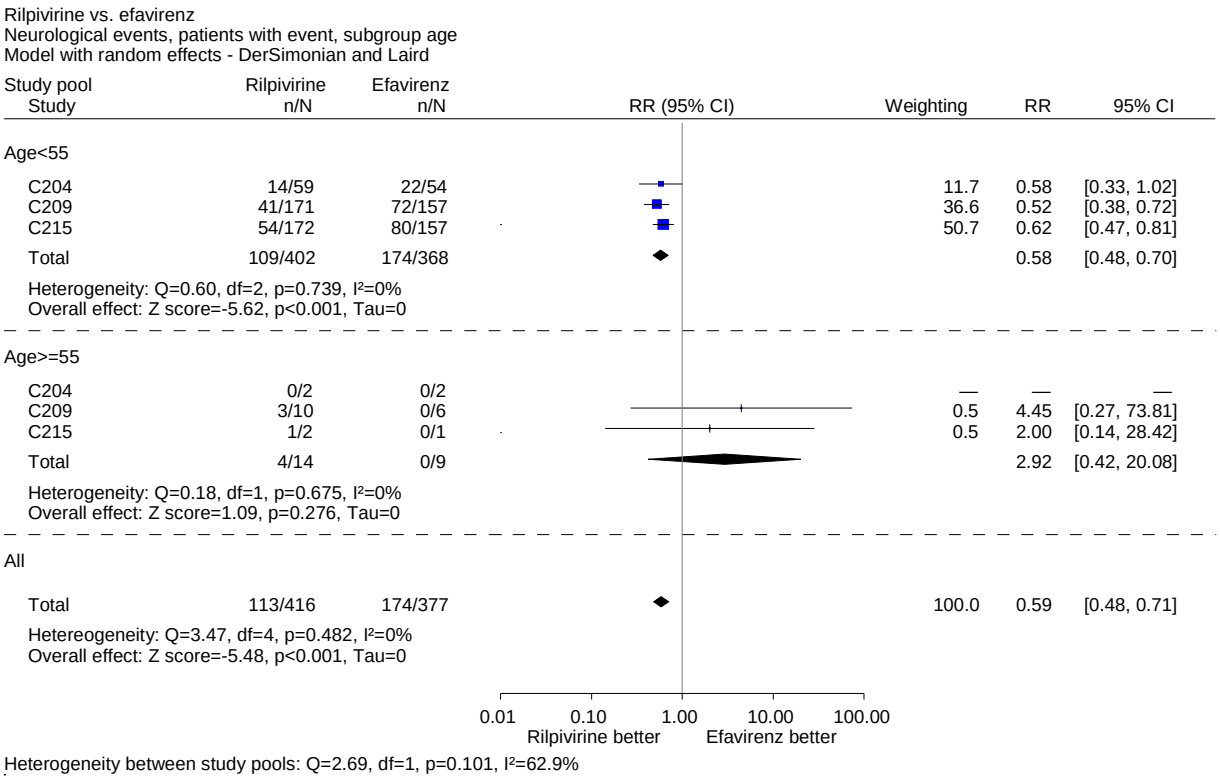


Figure 11: Meta-analysis, subgroups according to age (< / ≥ 55 years), neurological events, rilpivirine vs. efavirenz, interaction test p = 0.101

For the outcome "neurological events", the interaction test using the Q statistic for random effects showed an indication ($p < 0.2$) of an effect modification by the characteristic "age". In patients < 55 years there were statistically significantly fewer neurological events under treatment with rilpivirine than under efavirenz. This statistically significant effect is no longer seen in the group of patients ≥ 55 years. Since the interaction shown is, however, based solely on the markedly different sample sizes (770 patients < 55 years, 23 patients ≥ 55 years) so that the confidence interval for patients over 55 completely covers that for patients under 55, no reliable result can be deduced from these data. It was noticeable in the analysis of subgroups according to age that in Study C215, 13 and 9 patients in the respective treatment arms were not included in the analysis.

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

Psychiatric events

Figure 12 shows the meta-analysis of the 3 relevant studies on the comparison of rilpivirine vs. efavirenz for the outcome "psychiatric events" divided according to the 3 backbone therapies used in the studies.

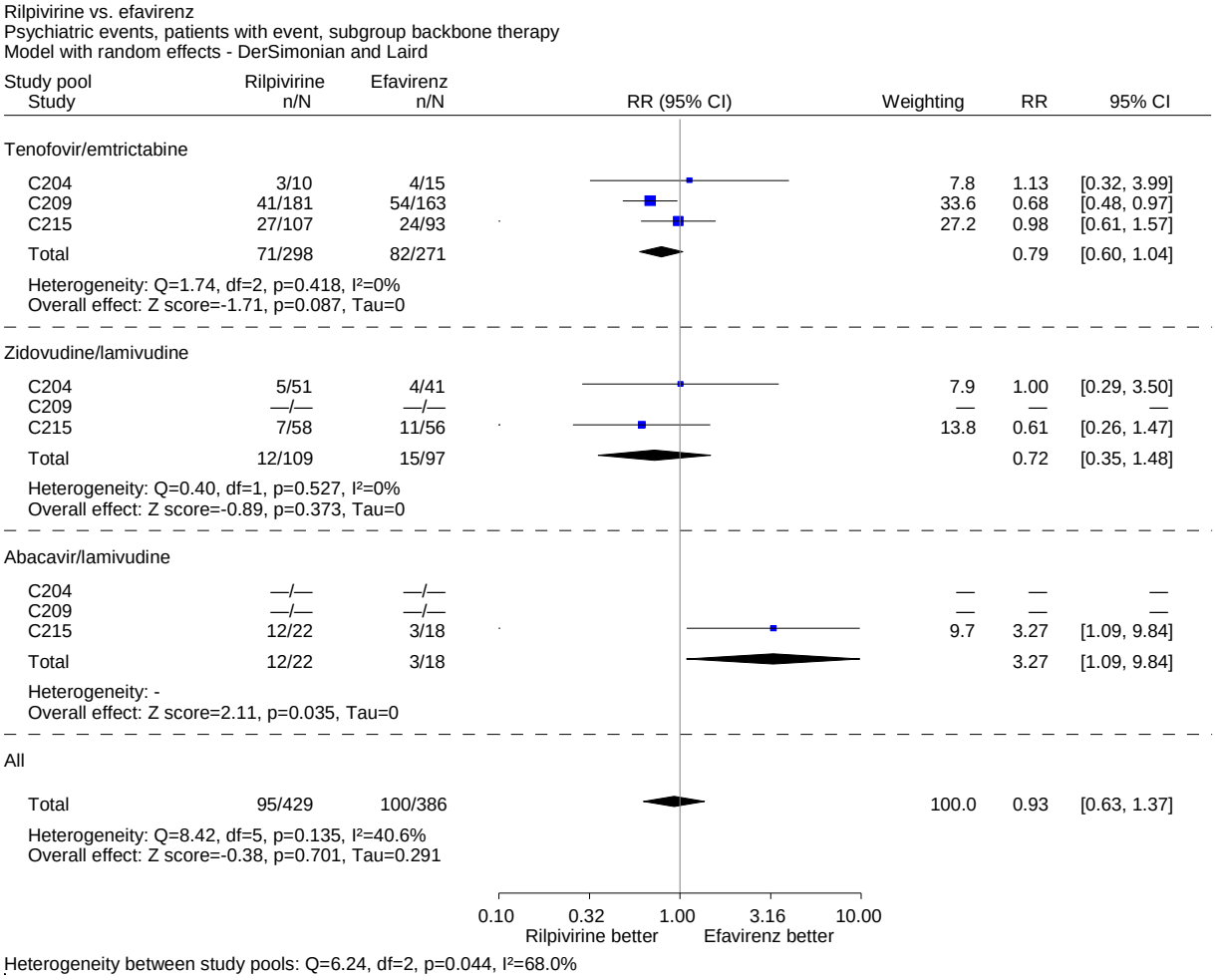


Figure 12: Meta-analysis, subgroups according to backbone therapy, psychiatric events, rilpivirine vs. efavirenz, interaction test p = 0.044

For the outcome "psychiatric events", the interaction test using the Q statistic for random effects showed proof ($p < 0.05$) of an effect modification by the characteristic "backbone therapy". The result was not statistically significant in the case of the combination with the two backbone therapies tenofovir/emtricitabine or zidovudine/lamivudine. However, under the backbone therapy abacavir/lamivudine there were statistically significantly fewer psychiatric events in combination with efavirenz than in combination with rilpivirine. Due to the low sample size, the result is, however, very imprecise. The lower limit of the confidence

interval at 1.09 is also only just above 1 (group equality). Hence it is not ruled out that this effect is only marginal and does not reach the relevant extent required for the determination of added benefit.

This proof of an interaction therefore does not lead to separate overall conclusions on added benefit for the different backbone therapies.

Further information about choice of outcome, risk of bias at outcome level and outcome results can be found in Module 4, Sections 4.3.1.2.2 and 4.3.1.3 of the dossier and in Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.

2.5 Extent and probability of the added benefit

The derivation of extent and probability of the added benefit for antiretroviral-naïve adult patients infected with human immunodeficiency virus type 1 (HIV-1) with a viral load of ≤ 100 000 HIV-1 RNA copies/ml at outcome level is shown below, taking into account the various outcome categories and effect sizes. The methods used are explained in Appendix A of Benefit Assessment A11-02 [3].

The approach for deriving an overall conclusion regarding added benefit based on the aggregation of the 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 the added benefit at outcome level

The data presented in Section 2.4 for antiretroviral-naïve adult **men** with an HIV-1 infection and a viral load of ≤ 100,000 HIV-1 RNA copies/ml produced proof of an added benefit for the outcome "viral load" (virological response) and an indication of lesser harm in relation to neurological events. Viral load represents a sufficiently valid surrogate for the combined outcome "AIDS-defining diseases/death", which was rated as severe/serious symptoms.

For antiretroviral-naïve adult **women** with an HIV-1 infection and a viral load of ≤ 100,000 HIV-1 RNA copies/ml there was an indication of lesser harm for the outcome "neurological events".

The extent of the respective added benefit at outcome level was estimated from these results (see Table 15).

Table 15: Extent of added benefit at outcome level: rilpivirine vs. efavirenz

		Effect estimator [95% CI]/ Proportion of events rilpivirine vs. efavirenz/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. Mean –0.97 [–2.54; 0.59] p = 0.22 Result not statistically significant. Mean –1.34 [–3.39; 0.71] p = 0.20	Added benefit / greater risk of harm not proven.
Adverse events			
AEs (overall rate)		RR 1.01 [0.97; 1.06] 89.5% vs. 88.3% p = 0.587	Greater/lesser harm not proven.
SAEs (overall rate)		RR 0.81 [0.49; 1.35] 6.3% vs. 7.8% p = 0.423	Greater/lesser harm not proven.
Discontinuation due to AEs (overall rate)		Summary analysis of patients with discontinuation 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.

(continued on next page)

Table 15: Extent of added benefit at outcome level: rilpivirine vs. efavirenz (continued)

	Effect estimator [95% CI]/ Proportion of events rilpivirine vs. efavirenz/p-value/ probability[a]	**Derivation of extent[b]**
Skin events	Summary analysis of skin events 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.
Neurological events	RR 0.59 [0.49; 0.71] 27.3% vs. 46.4% $p < 0.001$ Probability: "indication"	Outcome category: non-serious/non-severe adverse events $CI_o < 0.8$[f] Lesser harm, extent "considerable"
Psychiatric events	RR 0.86 [0.62; 1,20] 22.1% vs. 25.9% $p = 0.370$	Greater/lesser harm not proven.

a: Probability given if differences were statistically significant.
b: Estimations of effect size carried out according to outcome category with different limits based on the upper limit of the confidence interval (CI_o), see [3].
c: Too small a proportion of patients with event.
d: The virological response was assessed as a sufficiently valid surrogate for a patient-relevant outcome (combined outcome of "AIDS-defining diseases/death") for consideration in the benefit assessment (for detailed reasoning, see Section 2.7.2.9.4 of the full dossier assessment).
e: Population divided due to proof of an interaction and effect modification by the characteristic "gender".
f: Because upper limit of the confidence interval is below the specified threshold of 0.8.
AE: adverse event, CI: confidence interval, CI_o: upper limit of confidence interval, RR: relative risk, SAE: serious adverse event, vs.: versus

Additional comments of IQWiG

The benefit assessment relates solely to results at the time of the 48-week analysis, because not all the analyses after 96 weeks were available (see Section 2.7.2.4.3 of the full dossier assessment). Since the duration of treatment in the therapeutic indication is long-term in nature, consideration of results at the later analysis time after 96 weeks is basically meaningful. The results available for this time are additionally shown in Appendix A of the full dossier assessment.

Unlike the analysis after 48 weeks, results on the outcome "AIDS-defining diseases/death" (considered via the surrogate viral load [virological response]) after 96 weeks showed no statistically significant difference. However, there are no data from subgroup analyses for the characteristic "gender" for the time of 96 weeks. It is therefore unclear whether the deviating result for men and women applies to the same extent.

2.5.2 Overall conclusion on added benefit

The summary of results that determine the overall conclusion on added benefit is shown in Table 16 and Table 17, divided according to the relevant subgroups.

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

Table 16: Men: positive and negative effects of rilpivirine

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

In the global assessment, there remain 2 positive results of differing certainty (one proof and one indication) for the group of men in favour of rilpivirine. For the outcome "viral load" (virological response) the extent is "non-quantifiable", for the outcome "neurological events (AE)", it is "considerable".

In the global 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, it was, however, possible - because of the sufficient validity of the surrogate - 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 over efavirenz.

Table 17: Women: positive and negative effects of rilpivirine

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

In the global assessment, for the group of women there remains one positive result in favour of rilpivirine with the extent "considerable" and the probability "indication" (neurological events, AE). 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 (extent: "considerable") of an added benefit of rilpivirine over efavirenz.

2.5.3 Additional information about the added benefit on use of the ACT specified by the G-BA

In most cases in the 3 relevant studies, only the backbone therapies specified by the G-BA when designating the ACT were used (in approx. 75% of patients). From the analyses of potential effect modifiers, no different conclusions regarding added benefit arose for the different backbone therapies.

Overall, it is therefore not to be assumed that the results of this benefit assessment would differ substantially if the ACT were to be restricted to the backbone therapies specified by the G-BA.

2.6 List of included studies

C204

Pozniak AL, Morales-Ramirez J, Katabira E, Steyn D, Lupo SH, Santoscoy M et al. Efficacy and safety of TMC278 in antiretroviral-naive HIV-1 patients: week 96 results of a phase IIb randomized trial. AIDS 2010; 24(1): 55-65.

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; 48-week interim clinical research report [unpublished]. 2007.

Tibotec. A phase IIb randomized, partially blinded, dose-finding trial of TMC278 in antiretroviral naive HIV-1 infected subjects: 96-week analysis; study TMC278-C204; 96-week clinical research report [unpublished]. 2009.

Tibotec Pharmaceuticals. TMC278-C204: TMC278 in treatment naive HIV-1 infected subjects [online]. In: ClinicalTrials.gov. 07.07.2011 [accessed 29.02.2012]. URL: http://www.clinicaltrials.gov/ct2/show/NCT00110305.

Tibotec Pharmaceuticals. TMC278-C204: TMC278 in treatment naive HIV-1 infected subjects [online]. In: International Clinical Trials Registry Platform. 12.07.2011 [accessed 29.02.2012]. URL: http://apps.who.int/trialsearch/Trial.aspx?TrialID=NCT00110305.

C209

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.

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-naive HIV-1 infected subjects; study TMC278-TiDP6-C209; week 48 analysis report [unpublished]. 2010.

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-naive HIV-1 infected subjects; study TMC278-TiDP6-C209; week 96 analysis report [unpublished]. 2011.

Tibotec Pharmaceuticals. TMC278-TiDP6-C209: a clinical trial in treatment naive HIV-1 patients comparing TMC278 to efavirenz in combination with tenofovir + emtricitabine [online]. In: ClinicalTrials.gov. 07.12.2011 [accessed 29.02.2012]. URL: http://www.clinicaltrials.gov/ct2/show/NCT00540449.

Tibotec Pharmaceuticals. TMC278-TiDP6-C209: a clinical trial in treatment naive HIV-1 patients comparing TMC278 to efavirenz in combination with tenofovir + emtricitabine [online]. In: International Clinical Trials Registry Platform. 03.05.2011 [accessed 29.02.2012]. URL: http://apps.who.int/trialsearch/Trial.aspx?TrialID=NCT00540449.

C215

Cohen CJ, Andrade-Villanueva J, Clotet B, Fourie J, Johnson MA, Ruxrungtham K et al. Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naive adults infected with HIV-1 (THRIVE): a phase 3, randomised, non-inferiority trial. Lancet 2011; 378(9787): 229-237.

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-naive HIV-1 infected subjects; study TMC278-TiDP6-C215; week 48 analysis report [unpublished]. 2010.

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-naive HIV-1 infected subjects: study TMC278-TiDP6-C215; week 96 analysis report [unpublished]. 2011.

Tibotec Pharmaceuticals. TMC278-TiDP6-C215: a clinical trial in treatment naive HIV-subjects patients comparing TMC278 to efavirenz in combination with 2 nucleoside/nucleotide reverse transcriptase inhibitors [online]. In: ClinicalTrials.gov. 06.12.2011 [accessed 29.02.2012]. URL: http://www.clinicaltrials.gov/ct2/show/NCT00543725.

Tibotec Pharmaceuticals. TMC278-TiDP6-C215: a clinical trial in treatment naive HIV-subjects patients comparing TMC278 to efavirenz in combination with 2 nucleoside/nucleotide reverse transcriptase inhibitors [online]. In: International Clinical Trials Registry Platform. 19.07.2011 [accessed 29.02.2012]. URL: http://apps.who.int/trialsearch/Trial.aspx?TrialID=NCT00543725.

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Please see full dossier assessment for full reference list.

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2. Institute for Quality and Efficiency in Health Care. General methods: version 4.0 [online]. 23.09.2011 [accessed 05.05.2012]. URL: https://www.iqwig.de/download/General_Methods_4-0.pdf.

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