

IQWiG Reports – Commission No. A14-34

**Dolutegravir/abacavir/
lamivudine –
Benefit assessment according
to §35a Social Code Book V¹**

Extract

¹ Translation of Sections 2.1 to 2.7 of the dossier assessment *Dolutegravir/Abacavir/Lamivudin – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 18 December 2014). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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³ Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
3TC	lamivudine
ABC	abacavir
ACT	appropriate comparator therapy
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
CD4	cluster of differentiation 4
CDC	Centers for Disease Control and Prevention
DAIDS	DAIDS
DTG	dolutegravir
EFV	efavirenz
EQ-5D	European Quality of Life-5 Dimensions
FTC	emtricitabine
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HIV	human immunodeficiency virus
INI	integrase inhibitor
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MSDF	missing, switch or discontinuation = failure
NNRTI	non-NRTI
NRTI	nucleoside reverse transcriptase inhibitor
PT	Preferred Term
RCT	randomized controlled trial
RNA	ribonucleic acid
SAE	serious adverse event
SDM	symptom distress module
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
TDF	tenofovir
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug combination dolutegravir/abacavir/lamivudine (DTG/ABC/3TC). The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as “the company”). The dossier was sent to IQWiG on 12 September 2014.

Research question

The aim of this report was to assess the added benefit of the drug combination DTG/ABC/3TC compared with the appropriate comparator therapy (ACT) in adults and adolescents above 12 years of age infected with human immunodeficiency virus (HIV).

The G-BA’s specification of the ACT for different patient groups resulted in 4 research questions, which are presented in the following Table 2.

Table 2: Subindications and ACTs for the benefit assessment of DTG/ABC/3TC

Research question	Subindication	ACT specified by the G-BA
1	Treatment-naïve adults adults without previous ART	Efavirenz in combination with 2 nucleoside/nucleotide analogues (tenofovir plus emtricitabine or abacavir plus lamivudine)
2	Treatment-naïve adolescents adolescents above 12 years of age without previous ART	Efavirenz in combination with abacavir plus lamivudine
3	Adults with previous ART	
3a	Adults with previous ART for whom treatment with an integrase inhibitor is the first treatment option	Raltegravir in combination with individual backbone therapy based on prior treatment(s) and under consideration of the reason for the switch of treatment, particularly treatment failure due to virologic failure and possible accompanying development of resistance, or due to AEs. The respective approval of the drugs is to be considered.
3b	Adults with previous ART for whom treatment with an integrase inhibitor is a secondary treatment option	Individual ART based on prior treatment(s) and under consideration of the reason for the switch of treatment, particularly treatment failure due to virologic failure and possible accompanying development of resistance, or due to AEs. The respective approval of the drugs is to be considered.
4	Pretreated adolescents adolescents above 12 years of age with previous ART	
3TC: lamivudine; ABC: abacavir; ACT: appropriate comparator therapy; AE: adverse event; ART: antiretroviral therapy; DTG: dolutegravir; G-BA: Federal Joint Committee		

Regarding treatment-naive patients, the company followed both the differentiation between adults and adolescents, and the specification of the ACTs.

In pretreated patients in contrast, the company deviated from the G-BA and summarized the population of adults and adolescents up to 12 years of age, and specified individual antiretroviral therapy as ACT. Moreover, it further specified raltegravir as ACT, together with effective antiretroviral background therapy chosen for the individual patient, for the subpopulation of pretreated adults.

The assessment was based on patient-relevant outcomes. One direct comparative randomized controlled trial (RCT) was included in the assessment.

Results for research question 1: treatment-naive adults

The study pool included the studies SPRING-1 and SINGLE. However, only a subpopulation of the SPRING-1 study was relevant for this benefit assessment. The dossier contained no analyses on the relevant subpopulation. Hence the assessment was only conducted on the basis of the SINGLE study. Since the relevant subpopulation of the SPRING-1 study (33 patients in total) was notably smaller than the other relevant study, SINGLE (844 patients in total), this did not raise general doubts about the feasibility of the benefit assessment. However, the potential influence of the missing data from the SPRING-1 study was examined for the specific outcomes, using the results of the assessment of the single agent DTG. Heterogeneity with different direction of effects for the studies SPRING-1 and SINGLE was shown there for the outcome “severe adverse events (AEs) Division of AIDS (DAIDS) grade 3-4”. Hence sensitivity analyses were calculated to be able to estimate the possible influence of the missing relevant subpopulation of the SPRING-1 study on the overall result of the present dossier assessment.

The SINGLE study is a double-blind, randomized, active-controlled phase 3 study. In the study, 844 patients were randomly assigned to either DTG/ABC/3TC or to efavirenz/tenofovir/emtricitabine (EFV/TDF/FTC).

The risk of bias at study level was rated as low, but as potentially high for individual outcomes because of the respective large proportion of missing values.

Mortality

All-cause mortality

There was no statistically significant difference between the treatment groups in the SINGLE study. An added benefit of DTG/ABC/3TC compared with EFV/TDF/FTC for overall survival is therefore not proven.

Morbidity

AIDS-defining events (CDC class C events); surrogate outcomes “virologic response” and “CD4 cell count”

There was no statistically significant difference between the treatment groups for the outcome “acquired immunodeficiency syndrome [AIDS]-defining events (Centers for Disease Control and Prevention [CDC] class C events)”. For virologic response, there was a statistically significant effect in favour of DTG/ABC/3TC. However, patients were also categorized as non-responders for other reasons than virologic failure in the analysis of virologic response. A sensitivity analysis was therefore calculated for virologic failure, in which only patients were considered who were included in the analysis as non-responders for virologic reasons. The sensitivity analysis showed no statistically significant difference between the treatment groups. Hence the result on virologic response is not robust. For cluster of differentiation 4 (CD4) cell count, there was a statistically significant effect in favour of DTG/ABC/3TC. In the overall results on the outcome “AIDS-defining events (CDC class C events), an added benefit of DTG/ABC/3TC compared with EFV/TDF/FTC is not proven.

HIV symptoms (symptom distress module [SDM])

There was no statistically significant difference between the treatment groups in the SINGLE study. An added benefit of DTG/ABC/3TC compared with EFV/TDF/FTC for HIV symptoms is therefore not proven.

Health status (European Quality of Life-5 Dimensions visual analogue scale [EQ-5D VAS])

There was no statistically significant difference between the treatment groups in the SINGLE study. An added benefit of DTG/ABC/3TC compared with EFV/TDF/FTC for health status is therefore not proven.

Health-related quality of life

There were no evaluable data for health-related quality of life. An added benefit of DTG/ABC/3TC compared with EFV/TDF/FTC for health-related quality of life is therefore not proven.

Adverse events

Serious adverse events

There was no statistically significant difference between the treatment groups for the outcome “serious adverse events (SAEs)”. Greater/lesser harm from DTG/ABC/3TC compared with EFV/TDF/FTC for this outcome is therefore not proven.

Discontinuation due to adverse events

In the SINGLE study, there was a statistically significant difference in favour of DTG/ABC/3TC. There is an indication of lesser harm from DTG/ABC/3TC in comparison with EFV/TDF/FTC.

Severe adverse events (DAIDS grade 3-4)

For the SINGLE study, there was a statistically significant difference in favour of DTG/ABC/3TC. However, important heterogeneity with different direction of effects between the studies SPRING-1 and SINGLE had been shown in the assessment of the single agent DTG so that no common estimate was calculated. For the present dossier assessment, the company presented data on 17 patients who received DTG in combination with ABC/3TC and on the complete EFV arm (50 patients) for the SPRING-1 study. It was not clear from the information provided in the dossier how many of the 3 events observed in the EFV arm occurred in the relevant subpopulation (16 patients who received EFV/ABC/3TC). Sensitivity analyses showed that the influence of the missing relevant subpopulation of the SPRING-1 study for this outcome raised potential doubts about the result. Hence greater/lesser harm from DTG/ABC/3TC compared with EFV/TDF/FTC is not proven.

Nervous system disorders (based on the System Organ Class [SOC])

In the SINGLE study, there was a statistically significant difference in favour of DTG/ABC/3TC. There was an effect modification by the characteristic “sex”. The statistically significant result in favour of DTG/ABC/3TC persisted in male patients, whereas it was not statistically significant for female patients. As a result, an indication of lesser harm from DTG/ABC/3TC regarding nervous system disorders can be derived for men. For women in contrast, greater/lesser harm from DTG/ABC/3TC compared with EFV/TDF/FTC for this outcome is not proven.

Skin rash

For the SINGLE study, there was a statistically significant difference in favour of DTG/ABC/3TC. There is an indication of lesser harm from DTG/ABC/3TC in comparison with EFV/TDF/FTC.

Psychiatric disorders

For the SINGLE study, there was a statistically significant difference in favour of DTG/ABC/3TC. The effect size was only marginal, however, so that greater/lesser harm from DTG/ABC/3TC compared with EFV/TDF/FTC for this outcome is not proven.

Musculoskeletal and connective tissue disorders (SOC)

There was no statistically significant difference between the treatment groups for the SINGLE study. Greater/lesser harm from DTG/ABC/3TC compared with EFV/TDF/FTC for this outcome is therefore not proven.

Results for research question 2: treatment-naive adolescents

No data for a comparison of DTG/ABC/3TC versus the ACT were available for treatment-naive adolescents. Hence an added benefit of DTG/ABC/3TC is not proven for treatment-naive adolescents.

Results for research question 3: pretreated adults (3a and 3b)

The dossier contained no evaluable evidence for pretreated adults. The company included the SAILING study for pretreated adults. However, no relevant randomized comparison for the benefit assessment of the drug combination DTG/ABC/3TC can be derived from the SAILING study because of the study design. An added benefit of DTG/ABC/3TC is not proven for pretreated adults.

Results for research question 4: pretreated adolescents

No data for a comparison of DTG/ABC/3TC versus the ACT were available for pretreated adolescents. Hence an added benefit of DTG/ABC/3TC is not proven for pretreated adolescents.

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

On the basis of the results presented, the extent and probability of the added benefit of the drug combination DTG/ABC/3TC compared with the ACT is assessed as follows:

Relevant results were only available for research question 1 (treatment-naive adults). Overall, only positive effects of the fixed-dose combination DTG/ABC/3TC remain for this patient group, namely in the outcome category “non-serious/non-severe AEs” (extent: “considerable” in each case). The effect modification by the subgroup characteristic “sex” did not influence the overall conclusion on added benefit. It is to be noted that the positive effects only occurred in the area of AEs. However, from the results on all-cause mortality and AIDS-defining events of CDC class C in combination with the results on the surrogate outcomes “virologic response” and “CD4 cell count” additionally presented, there is no indication that DTG/ABC/3TC achieves worse results in comparison with EFV in combination with ABC/3TC or TDF/FTC with regard to these outcomes. In summary, there is therefore an indication of considerable added benefit of DTG/ABC/3TC versus the ACT EFV in combination with ABC/3TC or TDF/FTC for treatment-naive adults infected with HIV-1.

Table 3 presents a summary of the extent and probability of the added benefit of DTG/ABC/3TC.

⁴ On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data), see [1]. The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit), see [2].

Table 3: Drug combination DTG/ABC/3TC – extent and probability of added benefit

Research question	Subindication	ACT ^a	Extent and probability of added benefit
1	Treatment-naive adults	Efavirenz in combination with 2 nucleoside/nucleotide analogues (tenofovir plus emtricitabine or abacavir plus lamivudine)	Indication of an added benefit, extent: “considerable”
2	Treatment-naive adolescents above 12 years of age	Efavirenz in combination with abacavir plus lamivudine	Added benefit not proven
3	Adults with previous ART		
3a	Adults with previous ART for whom treatment with an integrase inhibitor is the first treatment option	Raltegravir in combination with individual backbone therapy based on prior treatment(s) and under consideration of the reason for the switch of treatment, particularly treatment failure due to virologic failure and possible accompanying development of resistance, or due to AEs. The respective approval of the drugs is to be considered.	Added benefit not proven
3b	Adults with previous ART for whom treatment with an integrase inhibitor is a secondary treatment option	Individual ART based on prior treatment(s) and under consideration of the reason for the switch of treatment, particularly treatment failure due to virologic failure and possible accompanying development of resistance, or due to AEs. The respective approval of the drugs is to be considered.	Added benefit not proven
4	Pretreated adolescents above 12 years of age		Added benefit not proven
<p>a: Presentation of the respective ACT specified by the G-BA. 3TC: lamivudine; ABC: abacavir; ACT: appropriate comparator therapy; AE: adverse event; ART: antiretroviral therapy; DTG: dolutegravir; G-BA: Federal Joint Committee</p>			

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research questions

The aim of this report was to assess the added benefit of the drug combination DTG/ABC/3TC compared with the ACT in adults and adolescents above 12 years of age infected with HIV.

The G-BA's specification of the ACT for different patient groups resulted in 4 research questions, which are presented in the following Table 4.

Table 4: ACT for the benefit assessment of DTG/ABC/3TC

Research question	Subindication	ACT specified by the G-BA
1	Treatment-naive adults adults without previous ART	Efavirenz in combination with 2 nucleoside/nucleotide analogues (tenofovir plus emtricitabine or abacavir plus lamivudine)
2	Treatment-naive adolescents adolescents above 12 years of age without previous ART	Efavirenz in combination with abacavir plus lamivudine
3	Adults with previous ART	
3a	Adults with previous ART for whom treatment with an integrase inhibitor is the first treatment option	Raltegravir in combination with individual backbone therapy based on prior treatment(s) and under consideration of the reason for the switch of treatment, particularly treatment failure due to virologic failure and possible accompanying development of resistance, or due to AEs. The respective approval of the drugs is to be considered.
3b	Adults with previous ART for whom treatment with an integrase inhibitor is a secondary treatment option	Individual ART based on prior treatment(s) and under consideration of the reason for the switch of treatment, particularly treatment failure due to virologic failure and possible accompanying development of resistance, or due to AEs. The respective approval of the drugs is to be considered.
4	Pretreated adolescents adolescents above 12 years of age with previous ART	
3TC: lamivudine; ABC: abacavir; ACT: appropriate comparator therapy; AE: adverse event; ART: antiretroviral therapy; DTG: dolutegravir; G-BA: Federal Joint Committee		

Regarding treatment-naive patients, the company followed both the differentiation between adults and adolescents, and the specification of the ACTs.

In pretreated patients in contrast, the company deviated from the G-BA and summarized the population of adults and adolescents up to 12 years of age, and specified individual antiretroviral therapy as ACT. Moreover, it further specified raltegravir as ACT, together with effective antiretroviral background therapy chosen for the individual patient, for the subpopulation of pretreated adults (see Section 2.8.1 of the full dossier assessment).

The assessment was based on patient-relevant outcomes. One direct comparative RCT was included in the assessment.

2.3 Research question 1: treatment-naive adults

2.3.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on DTG/ABC/3TC (studies completed up to 30 June 2014)
- bibliographical literature search on DTG/ABC/3TC (last search on 30 June 2014)
- search in trial registries for studies on DTG/ABC/3TC (last search on 2 July 2014)

To check the completeness of the study pool:

- search in trial registries for studies on DTG/ABC/3TC (last search on 29 September 2014)

No additional relevant study was identified from the check.

2.3.1.1 Studies included

The studies listed in the following Table 5 were included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: DTG/ABC/3TC vs. EFV in combination with ABC/3TC or TDF/FTC

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study ^a (yes/no)	Third-party study (yes/no)
ING112276 (SPRING-1)	Yes	Yes	No
ING114467 (SINGLE)	Yes	Yes	No

a: Study for which the company was sponsor, or in which the company was otherwise financially involved.
3TC: lamivudine; ABC: abacavir; DTG: dolutegravir; EFV: efavirenz; FTC: emtricitabine; RCT: randomized controlled trial; TDF: tenofovir; vs.: versus

The study pool for the benefit assessment of DTG/ABC/3TC concurred with that of the company. It included the studies ING112276 (SPRING-1) and ING114467 (SINGLE), hereinafter referred to as “SPRING-1” and “SINGLE”. In both studies, DTG/ABC/3TC was directly compared with the G-BA’s ACT (EFV in combination with TDF plus FTC or ABC plus 3TC). However, only a subpopulation of the SPRING-1 study was relevant for this benefit assessment. The dossier contained no analyses on the relevant subpopulation. Section 2.3.1.2 contains details about the characteristics of the 2 studies and an explanation of the availability of the data.

Section 2.3.4 contains a reference list for the studies included.

2.3.1.2 Study characteristics

Table 6 describes the studies used for the benefit assessment.

Table 6: Characteristics of the studies included – RCT, direct comparison: DTG/ABC/3TC vs. EFV in combination with ABC/3TC or TDF/FTC

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes ^a
SPRING-1	RCT, partially blinded (dose-ranging study: dolutegravir dosage double-blind; efavirenz open-label), parallel, multicentre	HIV-1 infected adult patients without previous antiretroviral treatment; baseline viral load at least 1,000 copies/mL	DTG 10 mg (N = 53) ^b DTG 25 mg (N = 52) ^b DTG 50 mg (N = 51) EFV 600 mg (N = 52) each in combination with either TDF + FTC or ABC + 3TC Relevant subpopulation thereof ^d : DTG 50 mg in combination with ABC + 3TC: n = 17 EFV 600 mg in combination with ABC + 3TC: n = 16	Screening phase: up to 35 days Treatment phase: 96 weeks ^c Follow-up: 4 weeks	34 centres in France, Germany, Italy, Spain, Russia and United States since 7/2009 Data cut-off at week 48: 11/2010 Data cut-off at week 96: 9/2011	<i>Primary outcome:</i> virologic response at week 16 <i>Secondary outcomes:</i> AIDS-defining events (CDC class C), virologic response at week 96; change in CD4 cell count; mortality, AEs
SINGLE	RCT, double-blind, parallel, double-dummy, multicentre	HIV-1 infected adult patients without previous antiretroviral treatment; baseline viral load at least 1000 copies/mL	DTG 50 mg (N = 422) EFV 600 mg (N = 422) DTG in combination with ABC + 3TC, EFV in combination with TDF + FTC	Screening phase: up to 28 days Treatment phase: 96 weeks followed by an open-label phase until 144 weeks	136 centres in Australia, Belgium, Canada, Denmark, France, Germany, Great Britain, Italy, the Netherlands, Romania, Spain and the United States since 2/2011 Data cut-off at week 48: 5/2012 Data cut-off at week 96: 5/2013	<i>Primary outcome:</i> virologic response at week 48 <i>Secondary outcomes:</i> AIDS-defining events (CDC class C), virologic response at week 96; change in CD4 cell count; HIV symptoms, mortality, AEs

(continued)

Table 6: Characteristics of the studies included – RCT, direct comparison: DTG/ABC/3TC vs. EFV in combination with ABC/3TC or TDF/FTC (continued)

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

b: Dosage in this arm does not concur with the German approval. This arm is no longer presented in the following tables.

c: After week 96, patients from the dolutegravir arms of the study could switch to an open-label treatment with dolutegravir 50 mg daily until dolutegravir is commercially available or the development is ended. For patients in the efavirenz arm, the study ended after 96 weeks.

d: On the side of the intervention, the subpopulation resulted from the drug combination DTG/ABC/3TC relevant for the research question, and for the comparator group, from the subpopulation who received EFV/ABC/3TC to maintain structural equality.

3TC: lamivudine; ABC: abacavir; AE: adverse event; AIDS: acquired immunodeficiency syndrome; CD4: cluster of differentiation 4; CDC: Centers for Disease Control and Prevention; DTG: dolutegravir; EFV: efavirenz; FTC: emtricitabine; HIV: human immunodeficiency virus; N: number of randomized patients; n: relevant subpopulation; RCT: randomized controlled trial; TDF: tenofovir; vs.: versus

Study SPRING-1

The SPRING-1 study is a randomized multicentre study. Treatment-naive HIV-1 infected adults were included in the study. DTG was investigated in 3 study arms with 10 mg/25 mg or 50 mg daily, and compared with EFV. In all arms, the study medication was combined with backbone therapy consisting of 2 nucleoside reverse transcriptase inhibitors (NRTIs) (TDF/FTC or ABC/3TC). The randomization of the patients was stratified according to HIV-1 ribonucleic acid (RNA) ($\leq 100\,000$ copies/mL or $> 100\,000$ copies/mL) and backbone therapy (TDF/FTC or ABC/3TC) in the study. The study duration was 96 weeks, followed by a still ongoing open-label phase.

Only a subpopulation was relevant for the present benefit assessment of the drug combination DTG/ABC/3TC. Firstly, these were the patients of the intervention arm, in which approval-compliant treatment with 50 mg DTG was administered, and of those only the subgroup of patients who additionally received ABC/3TC (N = 17). Correspondingly, only the patients were relevant from the control arm who received EFV in combination with ABC/3TC (N = 16). The combination of EFV with TDF/FTC was also considered to be the ACT. However, if a subpopulation of the DTG arm is compared with the total population of the EFV arm (N = 52), structural equality of the 2 treatment arms can no longer be assumed. The company only presented this kind of analyses, but no analysis of the populations described above. Hence the results of the SPRING-1 study could not be included in the present benefit assessment (see Section 2.8.2.3.2 of the full dossier assessment). Since the relevant subpopulation of the SPRING-1 study (33 patients in total) was notably smaller than the other relevant study, SINGLE (844 patients in total), this did not raise general doubts about the feasibility of the benefit assessment. However, it was examined at outcome level whether the SPRING-1 study raised potential doubts about the result of the SINGLE study.

Study SINGLE

The SINGLE study is a double-blind, randomized, active-controlled phase 3 study. It is a multicentre study conducted in Australia, Europe and America. Treatment-naive HIV-1 infected adults with a baseline viral load of at least 1000 copies/mL with a negative HLA-B*5701 allele assessment were included in the study. The randomization of the patients was stratified according to HIV-1 RNA ($\leq 100\,000$ copies/mL or $> 100\,000$ copies/mL) and CD4 cell count (≤ 200 cells/ μ L or > 200 cells/ μ L) in the study. The randomized study phase was 96 weeks, followed by a still ongoing open-label phase. Analyses after 48 and after 96 weeks were available. The benefit assessment was conducted based on the results after 96 weeks.

Table 7 characterizes the interventions in the SINGLE study.

Table 7: Characteristics of the interventions – RCT, direct comparison: DTG/ABC/3TC vs. EFV/TDF/FTC

Study	Intervention	Comparison	Concomitant medication
SINGLE	Dolutegravir 50 mg once daily + ABC/3TC 600 mg/300 mg as fixed-dose combination once daily + placebo for EFV/TDF/FTC fixed-dose combination once daily	Efavirenz 600 mg tenofovir 300 mg ^a emtricitabine 200 mg/ (EFV/TDF/FTC) as fixed-dose combination once daily + placebo for dolutegravir + placebo for ABC/3TC fixed-dose combination once daily	No other antiretroviral treatment allowed. Other drugs that are not allowed: inducers of the CYP3A4 enzyme, inhibitors of the enzymes CYP2C9, CYP2C19, CYP3A4 and their isoenzymes and drugs lowering the serum level of dolutegravir

a: 300 mg tenofovir disoproxil fumarate is equivalent to 136 mg tenofovir or 245 mg tenofovir disoproxil.
3TC: lamivudine; ABC: abacavir; DTG: dolutegravir; EFV: efavirenz; FTC: emtricitabine; RCT: randomized controlled trial; TDF: tenofovir; vs.: versus

The patients were randomly allocated to receive treatment with DTG in combination with the backbone therapy ABC/3TC (N = 422) or with EFV as fixed-dose combination with the backbone therapy TDF/FTC (N = 422). Hence the patients in the 2 study arms received different backbone therapies (ABC/3TC versus TDF/FTC). Since EFV as ACT can be combined both with ABC/3TC and with TDF/FTC, the SINGLE study was used for the benefit assessment despite the different backbone therapies. EFV was administered as fixed-dose drug combination with TDF/FTC. This fixed-dose combination is only approved for pretreated patients [3]. However, this was not a problem for the assessment because the respective individual substances are each approved for treatment-naïve patients [4-6].

Table 8 shows the characteristics of the patients in the SINGLE study.

Table 8: Characteristics of the study populations – RCT, direct comparison: DTG/ABC/3TC vs. EFV/TDF/FTC

Study characteristics category	DTG/ABC/3TC N = 422	EFV/TDF/FTC N = 422
Study SINGLE		
Age [years]: mean (SD)	37 (11)	36 (10)
Sex: [F/M], %	16/84	15/85
Ethnicity (%)		
white	69	68
non-white ^a	31	32
Study discontinuations, n (%)	72 (17)	109 (26)
Baseline viral load (copies/mL), n (%)		
≤ 100 000 HIV-1 RNA	280 (68)	288 (69)
> 100 000 HIV-1 RNA	134 (32)	131 (31)
CD4 cell count at the start of the study, n (%)		
< 350/μL	220 ^b (53)	221 ^b (53)
≥ 350/μL	194 ^b (47)	198 ^b (47)
HIV disease stage, n (%)		
asymptomatic	342 (83)	350 (84)
symptomatic	54 (13)	52 (12)
AIDS	18 (4)	17 (4)
a: This group includes Asians, blacks/patients of African heritage, native Americans/native Alaskans, Hawaiians/Pacific Islanders, and others.		
b: Institute's calculation.		
3TC: lamivudine; ABC: abacavir; AIDS: acquired immunodeficiency syndrome; CD4: cluster of differentiation 4; DTG: dolutegravir; EFV: efavirenz; F: female; HIV: human immunodeficiency virus; M: male; N: number of randomized patients; n: number of patients with event; RCT: randomized controlled trial; RNA: ribonucleic acid; SD: standard deviation; TDF: tenofovir; vs.: versus		

There were no important differences between the treatment groups with regard to age, sex and ethnicity. The patients were between 36 and 37 years old on average. Notably more men than women were enrolled in the study. The proportion of whites was considerably larger than the proportion of non-whites. With regard to disease severity, the vast majority of the patients was asymptomatic and only very few patients already had AIDS.

Table 9 shows the risk of bias at study level.

Table 9: Risk of bias at study level – RCT, direct comparison: DTG/ABC/3TC vs. EFV/TDF/FTC

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
SINGLE	Yes	Yes	Yes	Yes	Yes	Yes	Low

3TC: lamivudine; ABC: abacavir; DTG: dolutegravir; EFV: efavirenz; FTC: emtricitabine; RCT: randomized controlled trial; TDF: tenofovir; vs.: versus

The risk of bias at study level was rated as low for the SINGLE study. This concurs with the company's assessment.

2.3.2 Results on added benefit

2.3.2.1 Outcomes included

The following patient-relevant outcomes were considered in this assessment (for reasons, see Section 2.8.2.4.3 of the full dossier assessment):

- Mortality
 - all-cause mortality
- Morbidity
 - AIDS-defining events (CDC class C events)
 - presented as additional information: virologic response and CD4 cell count as surrogate outcomes for the patient-relevant outcome "AIDS-defining illnesses/death"
 - HIV symptoms (HIV-SDM)
 - health status (EQ-5D VAS)
- Health-related quality of life
- Adverse events
 - overall rate of SAEs
 - discontinuation due to AEs
 - severe AEs (DAIDS grade 3-4)
 - nervous system disorders (SOC)
 - skin rash (Preferred Term [PT])
 - psychiatric disorders (SOC)
 - musculoskeletal and connective tissue disorders (SOC)

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in its dossier (Module 4). In addition to the company’s dossier, the outcome “AIDS-defining events (CDC class C events)” was included in the benefit assessment because this outcome directly represents the AIDS-defining illnesses important in the therapeutic indication.

Table 10 shows for which outcomes data were available in the studies included.

Table 10: Matrix of outcomes – RCT, direct comparison: DTG/ABC/3TC vs. EFV/TDF/FTC

Study	Outcomes													
	All-cause mortality	AIDS-defining events (CDC class C events)	Virologic response ^a	CD4 cell count ^a	HIV symptoms (HIV-SDM)	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Discontinuation due to AEs	Severe AEs (DAIDS grade 3-4)	Nervous system disorders	Skin rash	Psychiatric disorders	Musculoskeletal and connective tissue disorders
SINGLE	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y

a: Virologic response and CD4 cell count as surrogate outcomes for the combined outcome “AIDS-defining illnesses/death” are presented as additional information.

3TC: lamivudine; ABC: abacavir; AE: adverse event; AIDS: acquired immunodeficiency syndrome; CD4: cluster of differentiation 4; CDC: Centers for Disease Control and Prevention; DAIDS: Division of AIDS; DTG: dolutegravir; EFV: efavirenz; EQ-5D: European Quality of Life-5 Dimensions; FTC: emtricitabine; HIV: human immunodeficiency virus; HIV-SDM: HIV symptom distress module; N: no; RCT: randomized controlled trial; SAE: serious adverse event; TDF: tenofovir; VAS: visual analogue scale; vs.: versus; Y: yes

2.3.2.2 Risk of bias

Table 11 shows the risk of bias for these outcomes.

Table 11: Risk of bias at study and outcome level – RCT, direct comparison: DTG/ABC/3TC vs. EFV/TDF/FTC

Study	Study level	Outcomes													
		All-cause mortality	AIDS-defining events (CDC class C events)	Virologic response	CD4 cell count	HIV symptoms (HIV-SDM)	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Discontinuation due to AEs	Severe AEs (DAIDS grade 3-4)	Nervous system disorders	Skin rash	Psychiatric disorders	Musculoskeletal and connective tissue disorders
SINGLE	L	L	L	L	L	H ^a	H ^a	-	L	L	L	L	L	L	L

a: LOCF analysis potentially highly biased (proportion of imputed values > 10%).
3TC: lamivudine; ABC: abacavir; AE: adverse event; AIDS: acquired immunodeficiency syndrome; CD4: cluster of differentiation 4; CDC: Centers for Disease Control and Prevention; DAIDS: Division of AIDS; DTG: dolutegravir; EFV: efavirenz; EQ-5D: European Quality of Life-5 Dimensions; FTC: emtricitabine; H: high; HIV: human immunodeficiency virus; HIV-SDM: HIV symptom distress module; L: low; LOCF: last observation carried forward; RCT: randomized controlled trial; SAE: serious adverse event; TDF: tenofovir; VAS: visual analogue scale; vs.: versus

The assessment of the risk of bias concurs with that of the company.

2.3.2.3 Results

Table 12 summarizes the results on the comparison of DTG/ABC/3TC with EFV/TDF/FTC in treatment-naïve adults infected with HIV-1. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations. The results at the analysis date of 96 weeks were used in the benefit assessment. In principle, it is possible to derive indications, e.g. of an added benefit of DTG/ABC/3TC, from one study with a low risk of bias, if there are no outcome-specific reasons against it. This evaluation contradicts that of the company, which derived proof of added benefit.

The potential influence of the missing data from the SPRING-1 study was examined for the specific outcomes, using the results of the assessment of the single agent DTG [7]. Heterogeneity with different direction of effects for the studies SPRING-1 and SINGLE was shown there for the outcome "severe AEs DAIDS grade 3-4". Hence sensitivity analyses were calculated to be able to estimate the possible influence of the missing relevant subpopulation of the SPRING-1 study on the overall result of the present dossier assessment (see Section 2.8.2.3.2 of the full dossier assessment).

Table 12: Results – RCT, direct comparison: DTG/ABC/3TC vs. EFV/TDF/FTC (week 96), treatment-naïve adults

Study outcome category outcome	DTG/ABC/3TC		EFV/TDF/FTC		DTG/ABC/3TC vs. EFV/TDF/FTC		
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI]; p-value		
SINGLE							
Mortality							
All-cause mortality	414	0 (0)	419	2 (0.5)	0.20 [0.01; 4.20]; 0.302		
Morbidity							
AIDS-defining events (CDC class C events)	414	5 (1.2) ^a	419	5 (1.2) ^a	1.01 [0.30; 3.47]; > 0.999 ^b		
Additional information: surrogate outcome “virologic response” (< 50 RNA copies/mL) ^c	414	319 (77.1)	419	293 (69.9)	1.10 [1.02; 1.20]; 0.020		
	N	Values at start of study mean (SE)	Change at end of study mean (SE)	N	Values at start of study mean (SE)	Change at end of study mean (SE)	Adjusted mean difference [95% CI]; p-value
<i>Additional information: surrogate outcome “CD4 cell count” (number/μL)</i>	414 ^d	349 (158.2)	324 (205.7)	419 ^d	351 (157.5)	286 (196.0)	43.95 ^e [14.34; 73.55]; 0.004
Symptoms							
symptom bother score	391 ^d	12.9 (12.03)	-1.07 ^f (0.48)	391 ^d	12.8 (12.30)	-2.00 ^f (0.48)	0.94 [-0.40; 2.27]; 0.168
Health status							
EQ-5D (VAS)	411	78.21 (20.79)	6.19 ^f (0.74)	413	78.73 (22.00)	5.65 ^f (0.74)	0.54 [-1.52; 2.59]; 0.606
Health-related quality of life							
No evaluable data							

(continued)

Table 12: Results – RCT, direct comparison: DTG/ABC/3TC vs. EFV/TDF/FTC (week 96), treatment-naïve adults (continued)

Study outcome category outcome	DTG/ABC/3TC		EFV/TDF/FTC		DTG/ABC/3TC vs. EFV/TDF/FTC RR [95% CI]; p-value
	N	Patients with events n (%)	N	Patients with events n (%)	
Adverse events					
AEs	414	376 (90.8)	419	394 (94.0)	
SAEs	414	44 (10.6)	419	51 (12.2) ^a	0.87 [0.60; 1.28]; 0.497 ^b
Discontinuation due to AEs	414	14 (3.4) ^a	419	52 (12.4)	0.27 [0.15; 0.48]; < 0.001
Severe AEs (DAIDS grade 3-4)	414	57 (13.8)	419	83 (19.8)	0.70 [0.51; 0.95]; 0.020 ^b
Nervous system disorders	414	121 (29.2)	419	225 (53.7)	0.54 [0.46; 0.65]; < 0.001
Skin rash	414	19 (5)	419	60 (14)	0.32 [0.19; 0.53]; < 0.001 ^b
Psychiatric disorders	414	144 (34.8)	419	178 (42.5)	0.82 [0.69; 0.97]; 0.023
Musculoskeletal and connective tissue disorders	414	109 (26.3)	419	93 (22.2)	1.12 [0.88; 1.43]; 0.362
<p>a: Institute's calculation. b: Institute's calculation (unconditional exact test (CSZ method according to [8])). c: Analysed with the MSDF algorithm. d: Number of patients analysed at 96 weeks. The values at the start of the study can be based on other patient numbers. e: Difference adjusted mean values (95% CI, p-value) from repeated measures mixed model analysis of the ITT population. The adjusted mean value is the mean change in CD4 cell count from baseline to week 96 in each study arm with the following covariables: treatment, visit, baseline plasma HIV-1 RNA level, baseline CD4 cell count, treatment*visit interaction, baseline plasma HIV-1 RNA level*visit interaction and baseline CD4 cell count*visit interaction; unstructured covariance matrix. f: Adjusted change in mean at the end of the study. Adjusted for baseline, baseline viral load, and CD4 cell count, as well as for sex, ethnicity and age; unless stated otherwise, LOCF analysis of the ITT population. 3TC: lamivudine; ABC: abacavir; AE: adverse event; AIDS: acquired immunodeficiency syndrome; CD4: cluster of differentiation 4; CDC: Centers for Disease Control and Prevention; CI: confidence interval; CSZ: convexity, symmetry, z score; DAIDS: Division of AIDS; DTG: dolutegravir; EFV: efavirenz; EQ-5D: European Quality of Life-5 Dimensions; FTC: emtricitabine; HIV: human immunodeficiency virus; ITT: intention to treat; LOCF: last observation carried forward; MSDF: missing, switch or discontinuation = failure; N: number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; RNA: ribonucleic acid; RR: relative risk; SAE: serious adverse event; SE: standard error; TDF: tenofovir; VAS: visual analogue scale; vs.: versus</p>					

Mortality

All-cause mortality

Only few events occurred in all-cause mortality and there was no statistically significant difference of the results between the treatment groups in the SINGLE study. An added benefit of DTG/ABC/3TC compared with EFV/TDF/FTC for overall survival is therefore not proven.

This concurs with the company's assessment.

Morbidity

AIDS-defining events (CDC class C events); surrogate outcomes “virologic response” and “CD4 cell count”

Only few events occurred for the outcome “**AIDS-defining events (CDC class C events)**”, and there was no statistically significant difference between the treatment groups. For **virologic response**, there was a statistically significant effect in favour of DTG/ABC/3TC. It is possible, however, that this result was influenced by the algorithm used by the company for the analysis of virologic response (see Section 2.8.2.4.3 of the full dossier assessment). As a result of the algorithm, patients were also categorized as non-responders for other reasons than virologic failure, e.g. in case of discontinuation due to AEs. For this reason, a sensitivity analysis was calculated for virologic failure, in which only patients were considered who were included in the analysis as non-responders for virologic reasons. Table 13 shows the result of this sensitivity analysis.

Table 13: Results on morbidity (virologic non-response, analysis without non-virologic non-responders) – RCT, direct comparison: DTG/ABC/3TC vs. EFV/TDF/FTC (week 96), treatment-naïve adults

Outcome category outcome study	DTG/ABC/3TC		EFV/TDF/FTC		DTG/ABC/3TC vs. EFV/TDF/FTC
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI]; p-value
Morbidity					
Sensitivity value for the surrogate outcome “virologic non-responders”					
SINGLE ^a	414	42 (10)	419	42 (10)	1.01 [0.67; 1.52]; 0.971 ^b
a: Analysed with the MSDF algorithm; only patients were counted in the present analysis who were included in the analysis as non-responders for virologic reasons. b: Institute's calculation, unconditional exact test (CSZ method according to [8]). 3TC: lamivudine; ABC: abacavir; CI: confidence interval; CSZ: convexity, symmetry, z score; DTG: dolutegravir; EFV: efavirenz; FTC: emtricitabine; MSDF: missing, switch or discontinuation = failure; N: number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; RR: relative risk; TDF: tenofovir; vs.: versus					

The result of the sensitivity analysis showed no statistically significant difference between the treatment groups. Hence the result on virologic response was not robust after MSDF (missing,

switch or discontinuation = failure) algorithm and was biased in favour of DTG/ABC/3TC by events such as discontinuations due to AEs. Although there was a statistically significant effect in favour of DTG/ABC/3TC for **CD4 cell count**, summarizing the results on the outcome “AIDS-defining events (CDC class C events), an added benefit of DTG/ABC/3TC in comparison with EFV/TDF/FTC is therefore not proven.

This contradicts the company’s assessment, which derived proof of added benefit of DTG/ABC/3TC from the virologic response. The company did not present the outcomes “AIDS-defining events (CDC class C events)” and “CD4 cell count” in Module 4 of its dossier.

HIV symptoms (SDM)

There was no statistically significant difference between the treatment groups in the SINGLE study. An added benefit of DTG/ABC/3TC compared with EFV/TDF/FTC for HIV symptoms is therefore not proven.

This concurs with the company’s assessment.

Health status (EQ-5D VAS)

There was no statistically significant difference between the treatment groups in the SINGLE study. An added benefit of DTG/ABC/3TC compared with EFV/TDF/FTC for this outcome is therefore not proven.

This concurs with the company’s assessment. However, the company presented the outcome as quality of life outcome.

Health-related quality of life

There were no evaluable data on health-related quality of life for the SINGLE study (for reasons see Section 2.8.2.4.3 of the full dossier assessment). An added benefit of DTG/ABC/3TC compared with EFV/TDF/FTC for health-related quality of life is therefore not proven.

In its consequence, this concurs with the company’s assessment, which, deviating from the present benefit assessment, categorized results on EQ-5D as quality of life.

Adverse events

The AEs, SAEs, discontinuations due to AEs and severe AEs (DAIDS grade 3-4) that most commonly occurred in the SINGLE study are presented in Appendix A of the full dossier assessment.

Serious adverse events

There was no statistically significant difference between the treatment groups for the outcome “SAEs”. Greater/lesser harm from DTG/ABC/3TC compared with EFV/TDF/FTC for this outcome is therefore not proven.

This concurs with the company’s assessment.

Discontinuation due to adverse events

In the SINGLE study, there was a statistically significant difference in favour of DTG/ABC/3TC. There is an indication of lesser harm from DTG/ABC/3TC in comparison with EFV/TDF/FTC.

The company also derived lesser harm from DTG/ABC/3TC, but with the certainty of results “proof”.

Severe adverse events (DAIDS grade 3-4)

For the SINGLE study, there was a statistically significant difference in favour of DTG/ABC/3TC.

As described in Section 2.3.1.2, it was examined whether the missing amount of data for the relevant subpopulation of the SPRING-1 study had consequences for the results at outcome level. In the dossier assessment of the single agent DTG [7], the meta-analysis of the studies SPRING-1 and SINGLE showed important heterogeneity ($p < 0.2$) with different direction of effects for the outcome “severe AEs (DAIDS grade 3-4)” so that no common estimate was calculated. For the present dossier assessment, the company presented data on 17 patients who received DTG in combination with ABC/3TC and on the complete EFV arm (50 patients) for the SPRING-1 study. It was not clear from the information provided in the dossier how many of the 3 events observed in the EFV arm occurred in the relevant subpopulation (16 patients who received EFV/ABC/3TC). A sensitivity analysis with 3 events under EFV/ABC/3TC showed no change of the result (meta-analysis statistically significant in favour of DTG/ABC/3TC). In a sensitivity analysis with 0 events under EFV/ABC/3TC, the meta-analysis was heterogeneous with qualitative interaction.

Hence greater/lesser harm from DTG/ABC/3TC compared with EFV/TDF/FTC for this outcome is not proven.

This concurs with the company’s assessment.

Nervous system disorders (SOC)

In the SINGLE study, there was a statistically significant difference in favour of DTG/ABC/3TC. There is an indication of lesser harm from DTG/ABC/3TC in comparison with EFV/TDF/FTC.

The company also derived lesser harm from DTG/ABC/3TC, but with the certainty of results “proof”.

Skin rash (PT)

For the SINGLE study, there was a statistically significant difference in favour of DTG/ABC/3TC. There is an indication of lesser harm from DTG/ABC/3TC in comparison with EFV/TDF/FTC.

The company also derived lesser harm from DTG/ABC/3TC, but with the certainty of results “proof”. Moreover, the company used a deviating operationalization for this outcome (see Section 2.8.2.4.3 of the full dossier assessment).

Psychiatric disorders (SOC)

For the SINGLE study, there was a statistically significant difference in favour of DTG/ABC/3TC. However, there was only a marginal effect size (the upper confidence interval is above the threshold of 0.9; outcome category “non-severe/non-serious AEs” [1]) so that greater/lesser harm from DTG/ABC/3TC is not proven.

This contradicts the company’s assessment, which claimed proof of added benefit.

Musculoskeletal and connective tissue disorders (SOC)

There was no statistically significant difference between the treatment groups for the SINGLE study. Greater/lesser harm from DTG/ABC/3TC compared with EFV/TDF/FTC for this outcome is therefore not proven.

This concurs with the company’s assessment.

2.3.2.4 Subgroups and other effect modifiers

Selected subgroups were investigated for the presence of heterogeneous treatment effects in order to identify possible effect modifications. The company presented the corresponding analyses for the outcomes it rated as relevant. Hence there were no subgroup analyses for the outcomes “AIDS-defining events (CDC class C events)”, which were additionally rated as relevant, and on the surrogate outcome “CD4 cells” presented as additional information, and they could also not be subsequently calculated from the available documents. The subgroup results on virologic response are also not presented because this additional surrogate outcome cannot be interpreted in isolation.

Subgroup analyses for the following characteristics were considered:

- age ($</\geq$ 36 years)
- sex
- ethnicity (whites/non-whites)
- baseline viral load (\leq 100 000/ $>$ 100 000 HIV-1 RNA copies/mL)

The subgroup characteristics presented by the company and the cut-off values were specified a priori in the SINGLE study.

Only the results on subgroups and outcomes with at least indications of an interaction between treatment effect and subgroup characteristic and with statistically significant results in at least one subgroup are presented below. The prerequisite for proof of different subgroup effects is a statistically significant interaction ($p < 0.05$). A p-value ≥ 0.05 and < 0.2 provides an indication of an effect modification.

Table 14 shows the results regarding the subgroup analyses.

Table 14: Subgroups with at least indications of interaction – RCT, direct comparison: DTG/ABC/3TC vs. EFV/TDF/FTC (week 96), treatment-naïve adults

Study outcome characteristic subgroup	DTG/ABC/3TC		EFV/TDF/FTC		DTG/ABC/3TC vs. EFV/TDF/FTC	
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI]	p-value
SINGLE						
Severe AEs (DAIDS grade 3-4)						
Age						
< 36 years	202	23 (11)	215	45 (21)	0.54 [0.34; 0.87]	0.010
≥ 36 years	212	34 (16)	204	38 (19)	0.86 [0.57; 1.31]	0.486
					Interaction:	0.151 ^a
Discontinuation due to adverse events						
Ethnicity						
white	284	13 (5)	285	35 (12)	0.37 [0.20; 0.69]	0.002
non-white	130	1 (<1)	133	17 (13)	0.06 [0.01; 0.45]	0.006
					Interaction:	0.088 ^a
Nervous system disorders						
Sex						
men	347	94 (27)	356	202 (57)	0.48 [0.39; 0.58]	< 0.001
women	67	27 (40)	63	23 (37)	1.10 [0.71; 1.71]	0.658
					Interaction:	< 0.001 ^a
Psychiatric disorders						
Age						
< 36 years	202	76 (38)	215	87 (40)	0.93 [0.73; 1.18]	0.553
≥ 36 years	212	68 (32)	204	91 (45)	0.72 [0.56; 0.92]	0.009
					Interaction:	0.145 ^a
Musculoskeletal and connective tissue disorders						
Sex						
male	347	86 (25)	356	82 (23)	1.08 [0.83; 1.40]	0.587
female	67	23 (34)	63	11 (17)	1.97 [1.05; 3.69]	0.036
					0.51 [0.27; 0.95] ^b	
					Interaction:	0.084 ^a
a: Institute's calculation.						
b: Institute's calculation; RR: proportion of events EFV/TDF/FTC vs. DTG/ABC/3TC (reversed direction of effect to derive the extent of added benefit).						
3TC: lamivudine; ABC: abacavir; AIDS: acquired immunodeficiency syndrome; CI: confidence interval; DAIDS: Division of AIDS; DTG: dolutegravir; EFV: efavirenz; FTC: emtricitabine; N: number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; RR: relative risk; TDF: tenofovir; vs.: versus						

Severe adverse events (DAIDS grade 3-4)

For the SINGLE study, there was an indication of an effect modification by the characteristic “age” for the outcome “severe AEs (DAIDS grade 3-4)”.

There was a statistically significant result in favour of DTG/ABC/3TC for people under 36 years of age, which was not statistically significant for people over 36 years of age.

Since the influence of the missing results of the SPRING-1 study was considered important for the relevant subpopulation regarding this outcome and because there was no information on the results in the subgroups for the relevant subpopulation of the SPRING-1 study, the influence of the missing results of the SPRING-1 study for the relevant subpopulation for the subgroup analysis cannot be estimated. The results of the subgroup analysis for the outcome are not considered further (see Section 2.3.2.3).

Discontinuation due to adverse events

For the SINGLE study, there was an indication of an effect modification by the characteristic “ethnicity” for the outcome “discontinuation due to AEs”.

The result showed a statistically significant result in favour of DTG/ABC/3TC both for the group of non-whites and for the group of whites. An indication of lesser harm from DTG/ABC/3TC can still be assumed for both groups. As there are no differing conclusions on added benefit for the 2 groups, and this is only an indication of an interaction, the result of this subgroup analysis has no consequences for the assessment and is not considered further.

Nervous system disorders

There was proof of an effect modification by the characteristic “sex” for the outcome “nervous system disorders (SOC)”.

The statistically significant result in favour of DTG/ABC/3TC persisted in male patients, whereas it was not statistically significant for female patients. As a result, an indication of lesser harm from DTG/ABC/3TC can be derived for men. For women in contrast, greater/lesser harm from DTG/ABC/3TC compared with EFV/TDF/FTC for this outcome is not proven.

Psychiatric disorders

There was an indication of an effect modification by the characteristic “age” for the outcome “psychiatric disorders”.

There was a statistically significant result in favour of DTG/ABC/3TC for people over 36 years of age, which was not statistically significant for people under 36 years of age. However, the result for people over 36 years of age only showed a marginal effect size (the upper confidence interval is above the threshold of 0.9; outcome category “non-severe/non-serious AEs” [1]) so that greater/lesser harm from DTG/ABC/3TC is not proven. Since it was

only an indication of an effect modification and no different conclusions on the added benefit resulted from it for the 2 groups, the result of this subgroup analysis is not considered further.

Musculoskeletal and connective tissue disorders

There was an indication of an effect modification by the characteristic “sex” for the outcome “musculoskeletal and connective tissue disorders”.

There was a statistically significant result in favour of EFV/TDF/FTC for female patients, which was not statistically significant for male patients. However, the result for female patients only showed a marginal effect size (the upper confidence interval is above the threshold of 0.9; outcome category “non-severe/non-serious AEs” [7]) so that greater/lesser harm from DTG/ABC/3TC is not proven. Since it was only an indication of an effect modification and no different conclusions on the added benefit resulted from it for the 2 groups, the result of this subgroup analysis is not considered further.

2.3.3 Extent and probability of added benefit

The derivation of extent and probability of added benefit in treatment-naive adults is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

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

2.3.3.1 Assessment of added benefit at outcome level

The available data presented in Section 2.3.2 result in indications of lesser harm from DTG/ABC/3TC than from EFV/TDF/FTC for the outcomes “discontinuation due to AEs”, “nervous system disorders” and “skin rash”.

There are effect modifications for the characteristic “sex”.

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: DTG/ABC/3TC vs. EFV/TDF/FTC (week 96), treatment-naïve adults

Outcome category outcome	DTG/ABC/3TC vs. EFV/TDF/FTC proportion of events/MD effect estimate [95% CI] p-value probability^a	Derivation of extent^b
Mortality		
All-cause mortality	0% vs. 0.5% RR: 0.20 [0.01; 4.20] p = 0.302	Added benefit not proven
Morbidity		
AIDS-defining events (CDC class C events) <i>Additional information: surrogate outcome “virologic response”</i> <i>Additional information: surrogate outcome “CD4 cell count”</i>	1% vs. 1% RR 1.01 [0.30; 3.47] p > 0.999 ^c result not robust ^d 324 vs. 286 MD: 43.95 [14.34; 73.55] p = 0.004	Added benefit not proven
HIV symptoms (SDM) symptom bother score	-1.07 vs. -2.00 MD: 0.94 [-0.40; 2.27] p = 0.168	Added benefit not proven
Health status EQ-5D VAS	6.19 vs. 5.65 MD: 0.54 [-1.52; 2.59] p = 0.606	Added benefit not proven
Health-related quality of life		
No evaluable data		
Adverse events		
SAEs	11% vs. 12% RR: 0.87 [0.60; 1.28]; p = 0.497 ^c	Greater/lesser harm not proven
Discontinuation due to AEs	3% vs. 12% RR: 0.27 [0.15; 0.48] p < 0.001 probability: “indication”	Outcome category: non-serious/non-severe AEs CI _u < 0.80 lesser harm extent: “considerable”
Severe AEs (DAIDS grade 3-4)	Not interpretable due to the lack of relevant amount of data ^e	Greater/lesser harm not proven

(continued)

Table 15: Extent of added benefit at outcome level: DTG/ABC/3TC vs. EFV/TDF/FTC (week 96), treatment-naïve adults (continued)

Outcome category outcome	DTG/ABC/3TC vs. EFV/TDF/FTC proportion of events/MD effect estimate [95% CI] p-value probability^a	Derivation of extent^b
Nervous system disorders		
men	27% vs. 57% RR: 0.48 [0.39; 0.58] p < 0.001 probability: “indication”	Outcome category: non-serious/non-severe AEs CI _u < 0.80 lesser harm extent: “considerable”
women	40% vs. 37% RR: 1.10 [0.71; 1.71] p = 0.658	Greater/lesser harm not proven
Skin rash	5% vs. 14% RR: 0.32 [0.19; 0.53] p < 0.001 ^c probability: “indication”	Outcome category: non-serious/non-severe AEs CI _u < 0.80 lesser harm extent: “considerable”
Psychiatric disorders	35% vs. 42% RR: 0.82 [0.69; 0.97] p = 0.023	Outcome category: non-serious/non-severe AEs CI _u > 0.90 Greater/lesser harm not proven
Musculoskeletal and connective tissue disorders	26% vs. 22% RR: 1.12 [0.88; 1.43] p = 0.362	Greater/lesser harm not proven
<p>a: Probability provided if statistically significant differences were present.</p> <p>b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.</p> <p>c: Institute’s calculation [8].</p> <p>d: See results of the sensitivity analysis in Section 2.3.2.3.</p> <p>e: Important heterogeneity between the studies SPRING-1 and SINGLE was shown for the outcome in the assessment of the single agent DTG [7]. The results of the relevant subpopulation of the SPRING-1 study are missing for the present dossier assessment, which is why the result of the SINGLE study cannot be interpreted.</p> <p>3TC: lamivudine; ABC: abacavir; AE: adverse event; AIDS: acquired immunodeficiency syndrome; CDC: Centers for Disease Control and Prevention; CI: confidence interval; CI_u: upper limit of CI; DAIDS: Division of AIDS; DTG: dolutegravir; EFV: efavirenz; EQ-5D: European Quality of Life-5 Dimensions; FTC: emtricitabine; HIV: human immunodeficiency virus; MD: mean difference; RCT: randomized controlled trial; SAE: serious adverse event; SDM: symptom distress module; TDF: tenofovir; VAS: visual analogue scale; vs.: versus</p>		

2.3.3.2 Overall conclusion on added benefit

Table 16 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 16: Positive and negative effects from the assessment of the drug combination DTG/ABC/3TC in comparison with EFV in combination with ABC/3TC or TDF/FTC in treatment-naïve adults

Positive effects	Negative effects
Non-serious/non-severe adverse events <ul style="list-style-type: none"> ▪ discontinuation due to AEs: indication of lesser harm – extent: “considerable” ▪ skin rash (PT): indication of lesser harm – extent: “considerable” ▪ nervous system disorders (SOC) <ul style="list-style-type: none"> ▫ men: indication of lesser harm – extent: “considerable” 	–
3TC: lamivudine; ABC: abacavir; AE: adverse event; DTG: dolutegravir; EFV: efavirenz; FTC: emtricitabine; PT: Preferred Term; SOC: System Organ Class; TDF: tenofovir	

Overall, only positive effects remain in the outcome category “non-serious/non-severe AEs” (extent: “considerable” in each case). The effect modification by the subgroup characteristic “sex” did not influence the overall conclusion on added benefit.

It is to be noted that positive effects only occurred in the area of AEs. However, from the results on all-cause mortality and AIDS-defining events of CDC class C in combination with the results on the surrogate outcomes “virologic response” and “CD4 cell count” additionally presented, there is no indication that DTG/ABC/3TC achieves worse results in comparison with EFV in combination with ABC/3TC or TDF/FTC with regard to these outcomes.

In summary, there is an indication of considerable added benefit of DTG/ABC/3TC versus the ACT EFV in combination with ABC/3TC or TDF/FTC for treatment-naïve adults infected with HIV-1.

2.3.4 List of included studies

SPRING-1

There were no relevant data on the SPRING-1 study. The dossier assessment of the single agent DTG [7] and the dossier on the drug combination DTG/ABC/3TC were used to estimate the missing amount of data.

SINGLE

Eron J Jr, Rockstroh J, Pozniak A, Elliott J, Small C, Johnson M et al. Dolutegravir treatment response by baseline viral load and NRTI backbone in treatment-naïve HIV-infected individuals. J Int AIDS Soc 2012; 15(Suppl 4): 121.

ViiV Healthcare. A trial comparing GSK1349572 50mg plus abacavir/lamivudine once daily to atripla (also called the SINGLE trial): study results [online]. In: Clinicaltrials.gov. 29 May 2014 [accessed: 24 October 2014]. URL:

<http://clinicaltrials.gov/ct2/show/results/NCT01263015>.

ViiV Healthcare. A phase 3, randomized, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to atripla over 96 weeks in HIV-1 infected antiretroviral therapy naive adult subjects [online]. In: EU Clinical Trials Register. 11 November 2010 [accessed: 30 October 2014]. URL: <https://www.clinicaltrialsregister.eu/ctr-search/trial/2010-020983-39/DE>.

ViiV Healthcare. A phase 3, randomized, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to atripla over 96 weeks in HIV-1 infected antiretroviral therapy naive adult subjects [online]. In: Pharmnet.Bund Klinische Prüfungen. [Accessed: 27 November 2013]. URL: <http://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.htm>.

ViiV Healthcare. A phase III, randomized, double-blind study of the safety and efficacy of dolutegravir plus abacavir-lamivudine fixed-dose combination therapy administered once daily compared to atripla over 96 weeks in HIV-1 infected antiretroviral therapy naive adult subjects: study no ING114467; clinical study report [unpublished]. 2012.

ViiV Healthcare. A phase III, randomized, double-blind study of the safety and efficacy of GSK1349572 plus abacavir-lamivudine fixed-dose combination therapy administered once daily compared to atripla over 96 weeks in HIV-1 infected antiretroviral therapy naive adult subjects: study no ING114467; clinical study report [unpublished]. 2013.

ViiV Healthcare. A randomized, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to atripla over 96 weeks in HIV-1 infected antiretroviral therapy naive adult subjects: result summary [online]. In: GlaxoSmithKline Clinical Study Register. [Accessed: 30 October 2014]. URL: <http://www.gsk-clinicalstudyregister.com/study/114467#rs>.

ViiV Healthcare. A trial comparing GSK1349572 50mg plus abacavir/lamivudine once daily to atripla (also called the SINGLE trial) [online]. In: ClinicalTrials.gov. 29 May 2014 [accessed: 30 October 2014]. URL: <http://ClinicalTrials.gov/show/NCT01263015>.

ViiV Healthcare. Post-Hoc Analyses ING114467 (SINGLE Study) [unpublished]. 2014.

Walmsley SL, Antela A, Clumeck N, Duiculescu D, Eberhard A, Gutierrez F et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. *N Engl J Med* 2013; 369(19): 1807-1818.

2.4 Research question 2: treatment-naive adolescents above 12 years of age

2.4.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on DTG/ABC/3TC (studies completed up to 30 June 2014)
- bibliographical literature search on DTG/ABC/3TC (last search on 30 June 2014)
- search in trial registries for studies on DTG/ABC/3TC (last search on 2 July 2014)

To check the completeness of the study pool:

- search in trial registries for studies on DTG/ABC/3TC (last search on 29 September 2014)

No additional relevant study was identified from the check.

2.4.2 Results on added benefit

No data were available for treatment-naive adolescents. An added benefit of DTG/ABC/3TC versus the ACT is therefore not proven for this subpopulation.

2.4.3 Extent and probability of added benefit

As the company presented no data for treatment-naive adolescents, an added benefit of DTG/ABC/3TC is not proven for this subpopulation.

2.5 Research question 3: pretreated adults

The ACT resulted in a differentiation of the research question on pretreated adults in pretreated adults for whom treatment with an integrase inhibitor (INI) is the first treatment option (research question 3a), and pretreated adults for whom treatment with an INI is a secondary treatment option (research question 3b).

Since no studies providing relevant randomized results were identified for the 2 subquestions, the description of the results is not divided in the subsequent sections.

2.5.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on DTG/ABC/3TC (studies completed up to 30 June 2014)
- bibliographical literature search on DTG/ABC/3TC (last search on 30 June 2014)
- search in trial registries for studies on DTG/ABC/3TC (last search on 2 July 2014)

To check the completeness of the study pool:

- search in trial registries for studies on DTG/ABC/3TC (last search on 29 September 2014)

No additional relevant study was identified from the check.

No relevant study was available for the research question on pretreated adults (research question 3a or 3b). In contrast, the company included the SAILING study for pretreated adults. The reasons for the non-consideration of the SAILING study are explained below.

Table 17 shows the characteristics of the SAILING study.

Table 17: Characteristics of the SAILING study – RCT, direct comparison: dolutegravir vs. raltegravir in combination with individual background therapy

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes ^a
SAILING	RCT, double-blind, parallel, double-dummy, multicentre	HIV-1 infected adult patients with previous ART, without previous INI treatment and baseline viral load of > 400 copies/mL. Moreover, they had to have resistance to at least 2 ART drug classes.	Dolutegravir 50 mg ^b (N = 360) raltegravir 800 mg ^b (N = 364) in each case in addition to optimized individual antiretroviral background therapy Relevant subpopulation thereof: dolutegravir in combination with ABC + 3TC: n < 2% of the total population ^c raltegravir in combination with ABC + 3TC: n < 3% of the total population ^c	Screening phase: up to 42 days Treatment phase: 48 weeks ^b Follow-up: 4 weeks	156 centres in Australia, Europe, North and South America, Russia, South Africa and Taiwan since 10/2010 data cut-off at week 48: 2/2013	<i>Primary outcome:</i> virologic response at week 48 <i>Secondary outcomes:</i> AIDS-defining events (CDC class C), virologic response at week 96; change in CD4 cell count; mortality, AEs

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

b: After week 48, the patients from the dolutegravir arm could switch to an open-label phase.

c: Information from the CSR on the background therapy with ABC/3TC: 7 patients in the dolutegravir arm and 9 patients in the raltegravir arm (mITT population).

3TC: lamivudine; ABC: abacavir; AE: adverse event; AIDS: acquired immunodeficiency syndrome; ART: antiretroviral therapy; CSR: clinical study report; CDC: Centers for Disease Control and Prevention; CD4: cluster of differentiation 4; HIV: human immunodeficiency virus; INI: integrase inhibitor; mITT: modified intention to treat; N: number of randomized patients; n: relevant subpopulation; RCT: randomized controlled trial; vs.: versus

The SAILING study is a double-blind, parallel, double-dummy, active-controlled phase 3 study. It is a multicentre study conducted in countries in America, Australia and Europe, as well as in Russia, South Africa and Taiwan. The randomized study phase was 48 weeks, followed by a still ongoing open-label phase. HIV-1 positive pretreated adult patients were enrolled in the study. The patients in the SAILING study were not allowed to be pretreated with INIs and had to have resistance to at least 2 drugs from 2 different antiretroviral therapy (ART) drug classes (NRTI, non-NRTI [NNRTI], protease inhibitors, fusion inhibitors or chemokine receptor antagonists). DTG (N = 360) was compared with raltegravir (N = 364) in the study. Like DTG, raltegravir is a drug from the INI class. Each patient received an individual background therapy in addition to the study medication. The individual background therapy was defined by the doctors before randomization. It was selected based on the patient's resistances and had to consist of at least 1 and no more than 2 fully active antiretroviral agents. During the study it was allowed to switch one drug of the background therapy due to intolerance, but only within the drug class.

Due to the multiple resistances to antiretroviral drugs from different drug classes in the patients included in the SAILING study, it was assumed that treatment with an INI was the first treatment option in the patients investigated. Hence the study could be used in the benefit assessment of the single agent DTG for patients for whom INI is the first treatment option [7].

However, no relevant randomized comparison for the benefit assessment of the drug combination DTG/ABC/3TC can be derived in principle from the SAILING study because of the study design. The reasons for this are as follows:

- In the study, not primarily the drug combination DTG/ABC/3TC is primarily investigated, but DTG plus individual background therapy. This means that the intervention did not concur with the research question to be investigated.
- At most patients of the intervention arm who received DTG in combination with ABC/3TC were relevant for the present benefit assessment. However, these were only very few patients (N = 7 according to the clinical study report of the 360 patients in total in the DTG arm).
- In contrast, all patients of the comparator arm (N = 364) were treated with the ACT specified by the G-BA (raltegravir plus individual background therapy). If the few patients of the intervention arm were compared with the total population of the comparator arm, structural equality of the 2 treatment arms could no longer be assumed and the results would be potentially biased.
- In case of an exclusive consideration of the patients in both study arms who received ABC/3TC as backbone therapy, treatment of the patients considered would not concur with the ACT specified by the G-BA (raltegravir plus individual background therapy) on the side of the comparator arm. The reason for this is that it can be assumed that those patients for whom the combination of raltegravir plus ABC/3TC is the optimum individual background therapy, only constitute a small subpopulation, which cannot be

clearly defined, within the total research question 3a (raltegravir plus individual background therapy).

In summary, the SAILING study provided no relevant results for the research question on the drug combination DTG/ABC/3TC in pretreated adults for whom treatment with an INI constitutes the first treatment option. It is therefore not considered further (see Section 2.8.2.3.2 of the full dossier assessment). No study was presented that investigated pretreated adults for whom treatment with an INI is a secondary treatment option.

This concurs with the company's assessment, which considered the analysis it presented on the SAILING study (5 versus 361 patients) as not interpretable.

2.5.2 Results on added benefit

There were no relevant data for pretreated adults for whom treatment with an INI is the first treatment option. An added benefit of DTG/ABC/3TC versus the ACT is therefore not proven for this subpopulation (research question 3a).

There were no data for pretreated adults for whom treatment with an INI is a secondary treatment option. An added benefit of DTG/ABC/3TC versus the ACT is therefore not proven for this subpopulation (research question 3a).

2.5.3 Extent and probability of added benefit

Since the company presented no relevant data for pretreated adults, an added benefit of DTG/ABC/3TC is not proven for adults for whom an INI is the first treatment option or for adults for whom an INI is a secondary treatment option.

2.6 Research question 4: pretreated adolescents above 12 years of age

2.6.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on DTG/ABC/3TC (studies completed up to 30 June 2014)
- bibliographical literature search on DTG/ABC/3TC (last search on 30 June 2014)
- search in trial registries for studies on DTG/ABC/3TC (last search on 2 July 2014)

To check the completeness of the study pool:

- search in trial registries for studies on DTG/ABC/3TC (last search on 29 September 2014)

No additional relevant study was identified from the check.

2.6.2 Results on added benefit

No data were available for pretreated adolescents. An added benefit of DTG/ABC/3TC versus the ACT is therefore not proven for this subpopulation.

2.6.3 Extent and probability of added benefit

As the company presented no data for pretreated adolescents above 12 years of age, an added benefit of DTG/ABC/3TC is not proven for this subpopulation.

2.7 Extent and probability of added benefit – summary

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

Table 18 presents a summary of the extent of the added benefit of DTG/ABC/3TC.

Table 18: Drug combination DTG/ABC/3TC – extent and probability of added benefit

Research question	Subindication	ACT ^a	Extent and probability of added benefit
1	Treatment-naive adults	Efavirenz in combination with 2 nucleoside/nucleotide analogues (tenofovir plus emtricitabine or abacavir plus lamivudine)	Indication of an added benefit, extent: “considerable”
2	Treatment-naive adolescents above 12 years of age	Efavirenz in combination with abacavir plus lamivudine	Added benefit not proven
3	Adults with previous ART		
3a	Adults with previous ART for whom treatment with an integrase inhibitor is the first treatment option	Raltegravir in combination with individual backbone therapy based on prior treatment(s) and under consideration of the reason for the switch of treatment, particularly treatment failure due to virologic failure and possible accompanying development of resistance, or due to AEs. The respective approval of the drugs is to be considered.	Added benefit not proven
3b	Adults with previous ART for whom treatment with an integrase inhibitor is a secondary treatment option	Individual ART based on prior treatment(s) and under consideration of the reason for the switch of treatment, particularly treatment failure due to virologic failure and possible accompanying development of resistance, or due to AEs. The respective approval of the drugs is to be considered.	Added benefit not proven
4	Pretreated adolescents above 12 years of age		Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. 3TC: lamivudine; ABC: abacavir; ACT: appropriate comparator therapy; AE: adverse event; ART: antiretroviral therapy; DTG: dolutegravir; G-BA: Federal Joint Committee			

In summary, there is an indication of an added benefit with the extent “considerable” for treatment-naive adults. For treatment-naive adolescents, an added benefit is not proven. An added benefit is not proven for pretreated adults for whom treatment with an INI is the first treatment option, for pretreated adults for whom treatment with an INI is a secondary treatment option, and for pretreated adolescents above 12 years of age.

The overall assessment for adults deviates from the company's approach. The company claimed proof of major added benefit for treatment-naive adults, and an indication of non-quantifiable added benefit for pretreated adults.

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

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The full report (German version) is published under <https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/a14-34-dolutegravir/abacavir/lamivudin-nutzenbewertung-gemaess-35a-sgb-v-dossierbewertung.6370.html>.