IQWiG Reports – Commission No. A19-05

Doravirine/lamivudine/ tenofovir disoproxil fumarate (HIV infection) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Doravirin/Lamivudin/Tenofovirdisoproxilfumarat (HIV-Infektion) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 11 April 2019). 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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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

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List of abbreviations

Abbreviation	Meaning
3TC	lamivudine
ACT	appropriate comparator therapy
AE	adverse event
AIDS	acquired immunodeficiency syndrome
CDC	Centers for Disease Control and Prevention
CDC4	cluster of differentiation 4
DOR	doravirine
EFV	efavirenz
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HIV	human immunodeficiency virus
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NNRTI	non-nucleoside reverse transcriptase inhibitors
NRTI	nucleoside/nucleotide reverse transcriptase inhibitors
RCT	randomized controlled trial
RNA	ribonucleic acid
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
TDF	tenofovir disoproxil fumarate

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 fixed drug combination doravirine (DOR)/lamivudine (3TC)/tenofovir disoproxil fumarate (TDF) (DOR/3TC/TDF). 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 14 January 2019.

Research question

The aim of this report is to assess the added benefit of DOR/3TC/TDF in comparison with the appropriate comparator therapy (ACT) in adults infected with human immunodeficiency virus type 1 (HIV-1). The HI viruses must not have mutations known to be associated with resistances to the substance class of the non-nucleoside reverse transcriptase inhibitors (NNRTI), 3TC or TDF.

The G-BA's specification of the ACT resulted in 2 research questions, which are presented in the following Table 2:

Table 2: Research questions of the benefit assessment of DOR/3TC/TDF

Research question	**Subindication**	**ACT**[a]
1	Treatment-naive adults infected with HIV-1[b]	Rilpivirine or **dolutegravir**, each in combination with 2 nucleoside/nucleotide analogues (**tenofovir disoproxil**/tenofovir alafenamide **plus emtricitabine** or **abacavir plus lamivudine**)
2	Pretreated adults infected with HIV-1[b]	Individual antiretroviral therapy based on prior treatment(s) and under consideration of the reason for the switch of treatment, particularly treatment failure due to virologic failure and possible accompanying development of resistance, or due to side effects.

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: The HI viruses must not have mutations known to be associated with resistances to the substance class of the NNRTI, 3TC or TDF.
ACT: appropriate comparator therapy; 3TC: lamivudine; DOR: doravirine; HIV-1: human immunodeficiency virus type 1; G-BA: Federal Joint Committee; NNRTI: non-nucleoside reverse transcriptase inhibitor; TDF: tenofovir disoproxil fumarate

The company followed the G-BA's specification of the ACT for both research questions and chose dolutegravir (DTG) in combination with two nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) (DTG + 2 NRTI) from the options for treatment-naive adults.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 48 weeks were used for the derivation of the added benefit.

Results for research question 1 (treatment-naive adults)

Study pool and study characteristics

No RCTs of direct comparison were identified for the assessment of the added benefit of DOR/3TC/TDF in comparison with the ACT. The company therefore presented an adjusted indirect comparison between DOR/3TC/TDF and the ACT using the common comparator efavirenz (EFV). The comparison was conducted versus DTG + 2 NRTI. For DOR/3TC/TDF, one RCT was included for the indirect comparison and 2 RCTs were included for DTG.

Results at the analysis date "96 weeks" were used for the present benefit assessment.

Study with DOR/3TC/TDF

Study 021 is a double-blind, randomized parallel-group study on treatment-naive HIV-1 infected adults. HIV-1 ribonucleic acid (RNA) viral load of the patients had to be ≥ 1000 copies/mL at screening. Randomized treatment duration was 96 weeks.

Study 021 compared DOR/3TC/TDF with EFV/emtricitabine (FTC)/TDF. A total of 734 patients were randomly allocated to treatment with DOR/3TC/TDF (N = 368) or EFV/FTC/TDF (N = 366) in an allocation ratio of 1:1.

Primary outcome of the three studies was "virologic response". Patient-relevant outcomes were "overall survival", "morbidity" and "adverse events" (AEs).

Studies with Dolutegravir

The studies SINGLE and SPRING-1 are randomized parallel-group studies on treatment-naive HIV-1 infected adults with an HIV-1 RNA viral load of ≥ 1000 copies/mL at screening. The SINGLE study was conducted as double-blind trial and the SPRING-1 study was conducted in a partially blinded fashion. The randomized treatment phase was 96 weeks in both studies. Both studies were already known from the dossier assessment on DTG.

The SINGLE study compared DTG + Abacavir (ABC)/3TC with EFV/FTC/TDF. A total of 844 patients were randomly allocated to treatment with DTG + ABC/3TC (N = 422) or EFV/FTC/TDF (N = 422) in a 1:1 ratio.

SPRING-1 was a dose-ranging study. Only patients from the study arm in which the daily dose of 50 mg DTG (N = 51) for adults was administered in compliance with the Summary of Product Characteristics (SPC) were included in the present benefit assessment. Patients in the comparator arm (N = 52) received EFV. The study was open-label regarding the allocation of patients to DTG or EFV, only the daily administered DTG dose was blinded. The patients received a backbone therapy of either TDF/FTC or ABC/3TC in addition to the study medication.

Primary outcome of the three studies was "virologic response". Patient-relevant outcomes were "overall survival", "morbidity" and "AEs".

Similarity of the studies for the indirect comparison

The studies were sufficiently similar regarding the design. The impact of the partially differing applied backbone therapies of 2 NRTI on the results of the indirect comparison is considered to be negligible.

The demographic and clinical characteristics of the patients were largely balanced both between the individual study arms and between the 3 studies. Based on the data on baseline viral load, cluster of differentiation 4 (CD4) cell count and disease stage according to CDC classification, it must be assumed that the patient population did not differ notably with regards to the severity of the disease.

Overall, the suitability of the studies 021, SINGLE and SPRING-1 for an adjusted indirect comparison was thus not called into question.

Risk of bias

The risk of bias across outcomes was rated as low for the 3 studies.

Except for the CD4 cell count, the risk of bias for the results of the considered outcomes was rated as low in study 021.

In the SINGLE study, the risk of bias was rated as low for the results of all considered outcomes.

In the SPRING-1 study, the risk of bias was rated as low for the results of the outcomes "all-cause mortality", "AIDS-defining events" (CDC class C), "virologic response" and "serious adverse events" (SAEs). For the results on the outcome "CD4 cell count" and the side effect-related outcome "discontinuation due to AEs", the risk of bias was rated as high.

Mortality

All-cause mortality

The adjusted indirect comparison shows no statistically significant difference between DOR/3TC/TDF and DTG + 2 NRTI at week 96 for the outcome "all-cause mortality". This resulted in no hint of an added benefit of DOR/3TC/TDF in comparison with DTG + 2 NRTI; an added benefit is therefore not proven.

Morbidity

AIDS-defining events (CDC class C), supplementary consideration of the surrogate outcomes "virologic response" and "CD4 cell count"

The adjusted indirect comparison shows no statistically significant difference between DOR/3TC/TDF and DTG + 2 NRTI at week 96 for the outcome "AIDS-defining events" (CDC

class C) and for the surrogate outcome "virologic response" presented as additional information.

In the studies 021 and SPRING-1, the surrogate outcome "CD4 cell count" had a high risk of bias. Hence, no hint of greater or lesser harm from DOR/3TC/TDF vs. DTG + 2 NRTI was derived for this outcome in the adjusted indirect comparison.

Overall, this resulted in no hint of an added benefit of DOR/3TC/TDF in comparison with DOR + 2 NRTI for the outcome "AIDS-defining events" (CDC class C); an added benefit is therefore not proven.

Health-related quality of life

None of the studies included recorded health-related quality of life.

Side effects

SAEs, discontinuation due to AEs

The adjusted indirect comparison showed no statistically significant difference between DOR/3TC/TDF and DTG + 2 NRTI at week 96 for the outcomes "SAEs" and "discontinuation due to AEs". This resulted in no hint of greater or lesser harm from DOR/3TC/TDF in comparison with DTG + 2 NRTI; greater or lesser harm is therefore not proven.

Specific AEs

The company's analysis on specific AEs are incomplete, the specific AEs are therefore not presented. Irrespective of this, the analyses presented by the company only showed minor effects, if any, in all cases regarding specific AEs.

Results for research question 2 (pretreated adults)

The company presented no data on research question 2 (pretreated adults).

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, probability and extent of the added benefit of the drug DOR/3TC/TDF compared with the ACT for each research question are assessed as follows:

[3] 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). 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, added benefit not proven, or less benefit). For further details see [1,2].

Research question 1 (treatment-naive adults)

Overall, there were neither positive nor negative effects of DOR/3TC/TDF in comparison with DTG + 2 NRTI. An added benefit of DOR/3TC/TDF in comparison with the ACT DTG + 2 NRTI for treatment-naive HIV-1 infected[4] adults is therefore not proven.

Research question 2 (pretreated adults)

No data for the assessment of the added benefit were available for pretreated HIV-1 infected[4] adults. This resulted in no hint of an added benefit for this population; an added benefit is therefore not proven.

Summary

Table 3 presents a summary of probability and extent of the added benefit of DOR/3TC/TDF.

Table 3: DOR/3TC/TDF – probability and extent of added benefit

Subindication	**ACT**[a]	**Probability and extent of added benefit**
Treatment-naive adults infected with HIV-1[b]	Rilpivirine or **dolutegravir**, each in combination with 2 nucleoside/nucleotide analogues (**tenofovir disoproxil**/tenofovir alafenamide **plus emtricitabine** or **abacavir plus lamivudine**)	Added benefit not proven
Pretreated adults infected with HIV-1[b]	Individual antiretroviral therapy based on prior treatment(s) and under consideration of the reason for the switch of treatment, particularly treatment failure due to virologic failure and possible accompanying development of resistance, or due to side effects.	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: The HI viruses must not have mutations known to be associated with resistances to the substance class of NNRTI, 3TC or TDF.
ACT: appropriate comparator therapy; 3TC: lamivudine; DOR: doravirine; HIV-1: human immunodeficiency virus type 1; G-BA: Federal Joint Committee; NNRTI: non-nucleoside reverse transcriptase inhibitor; TDF: tenofovir disoproxil fumarate

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

[4] The HI viruses must not have mutations known to be associated with resistances to the substance class of the NNRTIs, 3TC or TDF.

2.2 Research question

The aim of this report is to assess the added benefit of DOR/3TC/TDF in comparison with the ACT in adults infected with HIV-1. The HI viruses must not have mutations known to be associated with resistances to the substance class of the NNRTIs, 3TC or TDF.

The G-BA's specification of the ACT resulted in two research questions, which are presented in the following:

Table 4: Research questions of the benefit assessment of DOR/3TC/TDF

Research question	**Subindication**	**ACT[a]**
1	Treatment-naive adults infected with HIV-1[b]	Rilpivirine or **dolutegravir**, each in combination with 2 nucleoside/nucleotide analogues (**tenofovir disoproxil**/tenofovir alafenamide **plus emtricitabine** or **abacavir plus lamivudine**)
2	Pretreated adults infected with HIV-1[b]	Individual antiretroviral therapy based on prior treatment(s) and under consideration of the reason for the switch of treatment, particularly treatment failure due to virologic failure and possible accompanying development of resistance, or due to side effects.

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: The HI viruses must not have mutations known to be associated with resistances to the substance class of the NNRTIs, 3TC or TDF.
ACT: appropriate comparator therapy; 3TC: lamivudine; DOR: doravirine; HIV-1: human immunodeficiency virus type 1; G-BA: Federal Joint Committee; NNRTI: non-nucleoside reverse transcriptase inhibitor; TDF: tenofovir disoproxil fumarate

The company followed the G-BA's specification of the ACT for both research questions and chose dolutegravir (DTG) in combination with two nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) (DTG + 2 NRTI) from the options for treatment-naive adults.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 48 weeks were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

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 DOR/3TC/TDF (status: 17 October 2018)

- bibliographical literature search on DOR/3TC/TDF (last search on 17 October 2018)
- search in trial registries for studies on DOR/3TC/TDF (last search on 17 October 2018)
- bibliographical literature search on the ACT (last search on 17 October 2018)
- search in trial registries for studies on the ACT (last search on 17 October 2018)

To check the completeness of the study pool:

- search in trial registries for studies on DOR (last search on 5 February 2019)
- search in trial registries for studies on DTG (last search on 5 February 2019)

Concurring with the company, no relevant RCT on the direct comparison of DOR/3TC/TDF in comparison with DTG in combination with other antiretroviral drugs was identified from the check of the completeness of the study pool.

The company identified 3 studies for an adjusted indirect comparison based on RCTs. For the indirect comparison presented by the company (see Section 2.3.1.1), no additional relevant studies were identified from the check of the completeness of the study pool.

2.3.1.1 Studies included

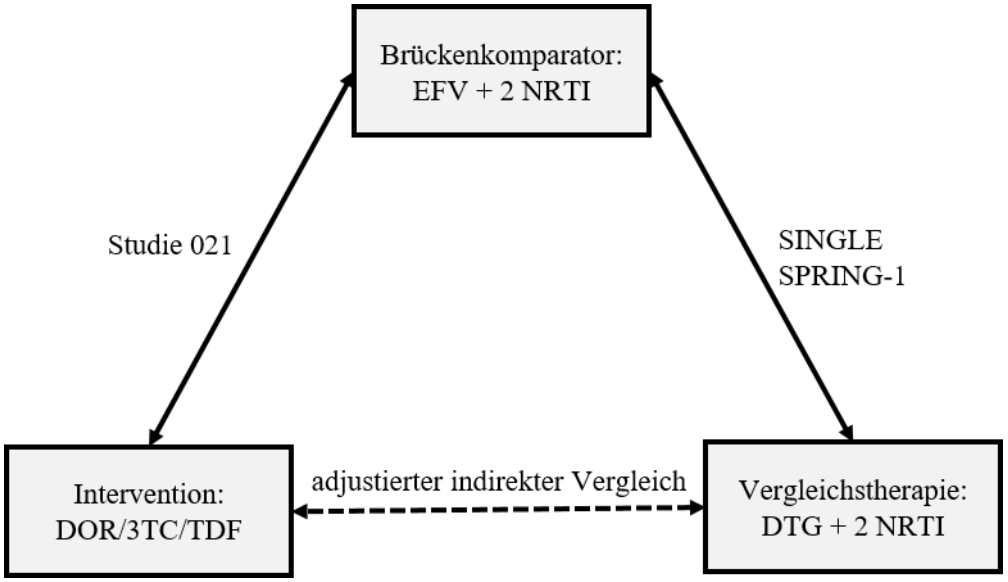
The company presented an adjusted indirect comparison using the common comparator EFV for the assessment of the added benefit of DOR/3TC/TDF. The comparison was conducted versus DTG + 2 NRTI. The company included 1 RCT for DOR/3TC/TDF and 2 RCTs for DTG. It justified the choice of the common comparator with the fact that EFV in combination with 2 NRTI (EFV + 2 NRTI) was used as comparator intervention in the only relevant study on DOR/3TC/TDF. Concurring with the company's assessment, EFV was considered the only suitable common comparator for the indirect comparison. The following Table 5 presents the studies on the indirect comparison.

Table 5: Study pool – RCT, indirect comparison: DOR/3TC/TDF vs. DTG + 2 NRTIa, treatment-naive adults

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[b] (yes/no)	Third-party study (yes/no)
Study with DOR/3TC/TDF			
021	Yes	Yes	No
Studies with DTG			
ING114467 (SINGLE[c])	No	No	Yes
ING112276 (SPRING-1[c])	No	No	Yes

a: See Table 7 for information on the combination partners in the individual studies.
b: Study sponsored by the company.
c: In the following tables, the study is referred to with this abbreviated form.
3TC: lamivudine; DOR: doravirine; DTG: dolutegravir; RCT: randomized controlled trial; TDF: tenofovir disoproxil fumarate; vs.: versus

The study pool concurred with the one of the company. Figure 1 shows a schematic representation of the indirect comparison.



3TC: lamivudine; DOR: doravirine; DTG: dolutegravir; EFV: efavirenz; NRTI: nucleoside/nucleotide reverse transcriptase inhibitor; TDF: tenofovir disoproxil fumarate

Figure 1: Study pool for the indirect comparison between DOR/3TC/TDF and DTG

Section 2.3.4 contains a reference list for the studies included.

2.3.1.2 Study characteristics

Table 6 and Table 7 describe the studies used for the benefit assessment.

Table 6: Characteristics of the studies included – RCT, indirect comparison: DOR/3TC/TDF vs. DTG + 2 NRTI, treatment-naive adults

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Study with DOR/3TC/TDF						
021	RCT, double-blind, parallel	HIV-1 infected adults not pretreated with an antiretroviral drug (≥ 18 years) with an HIV-1 RNA viral load of ≥ 1000 copies/mL at screening	DOR/3TC/TDF (N = 368) EFV/FTC/TDF (N = 366)	Screening: ≤ 45 days before randomization Treatment duration: 96 weeks[b] Observation period: 14 days	143 centres in Australia, Belgium, Canada, Chile, Columbia, Denmark, Germany, Guatemala, Honduras, Israel, Mexico, New Zealand, Peru, Portugal, Puerto Rico, Russia, Spain, South Africa, Switzerland, Taiwan, Thailand, United Kingdom, USA 06/2015–27 February 2018	Primary: virologic response at week 48 Secondary: morbidity, AEs

(continued)

Table 6: Characteristics of the studies included – RCT, indirect comparison: DOR/3TC/TDF vs. DTG + 2 NRTI, treatment-naive adults (continued)

Study		Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study
Studies with DTG						
SINGLE	RCT, double-blind, parallel	HIV-1 infected adults not pretreated with an antiretroviral drug (≥ 18 years) with an HIV-1 RNA viral load of ≥ 1000 copies/mL	DTG + ABC/3TC (N = 422) EFV/FTC/TDF (N = 422)	Screening: ≤ 28 days before randomization Treatment duration: 96 weeks[c] Observation period: ND	136 centres in Australia, Belgium, Canada, Denmark, France, Germany, Great Britain, Italy, the Netherlands, Romania, Spain and the United States 02/2011–12/2015	Primary: Virologic response at week 48 Secondary: Morbidity, all-cause mortality, AEs
SPRING-1	RCT, partially blinded (dose-ranging study: DTG dosages double-blind; EFV open-label), parallel	HIV-1 infected adults not pretreated with an antiretroviral drug (≥ 18 years) with an HIV-1 RNA viral load of ≥ 1000 copies/mL and CD4 ≥ 200 cells/mm^3	DTG 10 mg (N = 53)[d] DTG 25 mg (N = 52)[d] DTG 50 mg (N = 51) EFV 600 mg (N = 52) each in combination with either FTC/TDF or ABC/3TC	Screening: ≤ 35 days before randomization Treatment duration: 96 weeks[e] Observation period: 4 weeks	34 centres in France, Germany, Italy, Spain, Russia and USA 07/2009–12/2016	Primary: Virologic response at week 16 Secondary: Morbidity, all-cause mortality, AEs

(continued)

Table 6: Characteristics of the studies included – RCT, indirect comparison: DOR/3TC/TDF vs. DTG + 2 NRTI, treatment-naive adults (continued)

a: Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b: After the double-blind treatment phase, patients who were benefitting from the treatment according to the investigator's assessment had the opportunity to participate in an open extension phase DOR 100 mg + 2 NRTI (study 021: DOR/3TC/TDF) or up to 96 weeks (study 021).
c: After week 96, the patients could be further treated with DTG for up to 48 weeks.
d: The arm is not relevant for the assessment and is not shown in the next tables.
e: After the double-blind treatment phase, the patients in the DTG arms of the study could switch to open treatment with 50 mg DTG per day, until DTG became commercially available or until the development was completed. For patients in the EFV arm, the study ended after 96 weeks.
3TC: lamivudine; ABC: abacavir; AE: adverse event; CD4: cluster of differentiation 4; CDC: Centers for Disease Control and Prevention; DOR: doravirine; DTG: dolutegravir; EFV: efavirenz; FTC: emtricitabine; HIV: human immunodeficiency virus; N: number of randomized patients; NRTI: nucleoside/nucleotide reverse transcriptase inhibitor; RCT: randomized controlled trial; TDF: tenofovir disoproxil fumarate; vs.: versus

Table 7: Characteristics of the interventions – RCT, indirect comparison: DOR/3TC/TDF vs. DTG + 2 NRTI, treatment-naive adults

Study	Intervention/comparator therapy	Common comparator	Pretreatment and concomitant treatment
Study with DOR/3TC/TDF			
021	DOR 100 mg / 3TC 300 mg / TDF 300 mg + placebo for EFV/FTC/TDF once daily each, orally	EFV 600 mg / FTC 200 mg / TDF 300 mg + placebo for DOR/3TC/TDF once daily each, orally	**Prohibited prior and concomitant treatment:** ▪ after HIV diagnosis: antiretroviral therapies for a virus infection other than HIV-1 with drugs that also have an anti-HIV efficiency (e.g. adefovir, TDF, 3TC, FTC or entecavir) ▪ Immunomodulators or systemic immunosuppressants ≤ 1 month before the first administration of the study medication or an expectable start of these therapies during the study ▪ during the study: moderate or strong CYP3A4 inducers or substances that are metabolised by CYP3A4 ▪ further antiretroviral therapies during the study
Studies with DTG			
SINGLE	DTG 50 mg + ABC 600 mg / 3TC 300 mg + placebo for EFV/FTC/TDF once daily each, orally	EFV 600 mg / FTC 200 mg / TDF 300 mg + placebo for DTG + placebo for ABC/3TC once daily each, orally	**Non-permitted pretreatment:** ▪ HIV-1 immunotherapy vaccines ≤ 90 days before screening ▪ Immunomodulators, radiation therapy, chemotherapy ≤ 28 days before screening **Non-permitted concomitant treatment:** ▪ further antiretroviral therapies ▪ CYP3A4 inducers, inhibitors of CYP2C9, CYP2C19, CYP3A4 as well as their isoenzymes and drugs lowering the DTG serum level
SPRING-1	DTG 50 mg + FTC 200 mg / TDF 300 mg or ABC 600 mg/ 3TC 300 mg once daily each, orally	EFV 600 mg + FTC 200 mg/ TDF 300 mg or ABC 600 mg/ 3TC 300 mg once daily each, orally	**Non-permitted pretreatment:** ▪ HIV-1 immunotherapy vaccines ≤ 90 days before screening ▪ Immunomodulators, radiation therapy, chemotherapy ≤ 28 days before screening **Non-permitted concomitant treatment:** ▪ further antiretroviral therapy ▪ drugs with high interaction potential (e.g. carbamazepine, rifampicin, St. John's Wort, midazolam, cisapride)

3TC: lamivudine; ABC: abacavir; CYP: cytochrome P450; DOR: doravirine; DTG: dolutegravir; EFV: efavirenz; FTC: emtricitabine; HIV: human immunodeficiency virus; NRTI: nucleoside/nucleotide reverse transcriptase inhibitor; RCT: randomized controlled trial; TDF: tenofovir disoproxil fumarate; vs.: versus

Study design

Study with DOR/3TC/TDF

Study 021 is a double-blind, randomized parallel-group study on treatment-naive HIV-1 infected adults. HIV-1 RNA viral load of the patients had to be ≥ 1000 copies/mL at screening. Randomized treatment duration was 96 weeks.

Study 021 compared DOR/3TC/TDF with EFV/FTC/TDF. A total of 734 patients were randomly allocated to treatment with DOR/3TC/TDF (N = 368) or EFV/FTC/TDF (N = 366) in an allocation ratio of 1:1. Randomization was stratified by the HIV-1 RNA viral load (≤ 100 000 copies/mL, > 100 000 copies/mL) at the time point of screening as well as by hepatitis B and/or hepatitis C coinfection (yes, no) at the time point of screening.

Dosage of the study medication was in compliance with the respective SPC [3.4]. To maintain blinding, the patients received placebo once daily in addition to the study medication.

According to the SPC, DOR/3TC/TDF shall only be used when there are no resistances to the substance class of the NNRTIs, 3TC or TDF [3]. Only patients with confirmed sensitivity to all used substances were included in the study 021.

Primary outcome of the study was the virologic response at week 48 with a cut-off value of 50 HIV-1 RNA copies/mL. Patient-relevant outcomes were “overall survival”, “morbidity” and “AEs”.

Results of analysis time points “48 weeks” and “96 weeks” were available for the benefit assessment. The results at the analysis date of 96 weeks were used for the present benefit assessment.

Studies with Dolutegravir

The studies SINGLE and SPRING-1 are randomized parallel-group studies on treatment-naive HIV-1 infected adults with an HIV-1 RNA viral load of ≥ 1000 copies/mL at screening. At screening, the included patients were not allowed to have primary resistances. The SINGLE study was conducted as double-blind trial and the SPRING-1 study was conducted in a partially blinded fashion. The randomized treatment phase was 96 weeks in both studies. Both studies were already known from the dossier assessment on DTG [5].

The SINGLE study compared DTG + ABC/3TC with EFV/FTC/TDF. A total of 844 patients were randomly allocated to treatment with DTG + ABC/3TC (N = 422) or EFV/FTC/TDF (N = 422) in a 1:1 ratio.

In the SPRING-1 study, respective DTG doses of 10 mg, 25 mg or 50 mg were administered once daily in 3 study arms. Only patients from the study arm in which a daily dose of 50 mg DTG (N = 51) for adults was administered in compliance with the SPC [6] were included in the present benefit assessment. Patients in the comparator arm (N = 52) received EFV. The study was open-label regarding the allocation of patients to DTG or EFV, only the daily administered

DTG dose was blinded. The patients received a backbone therapy of either TDF/FTC or ABC/3TC in addition to the study medication.

Randomization was stratified by the HIV-1 RNA viral load (≤ 100 000 copies/mL, > 100 000 copies/mL) at the time point of screening in both studies. In the SINGLE study, randomization was also stratified by CD4 cell count (≤ 200 cells/µl, > 200 cells/µl); in the SPRING-1 study, randomization was stratified by backbone therapy (FTC/TDF, ABC/3TC).

Dosage in the SINGLE study as well as in the relevant treatment arms of the SPRING-1 study was in compliance with the respective SPC [6-10]. The patients in the SINGLE study received placebo in addition to the study medication to maintain blinding.

Primary outcome of both studies was the virologic response with the cut-off value 50 HIV-1 RNA copies/mL at week 16 (SPRING-1) or at week 48 (SINGLE).

Results of analysis time points "48 weeks" and "96 weeks" were available for both studies. The results at the analysis date of 96 weeks were used for the present benefit assessment.

Study population

Table 8 and Table 9 show the characteristics of the patients included in the studies.

Table 8: Characteristics of the study populations; (demography) - RCT, indirect comparison: DOR/3TC/TDF vs. DTG + 2 NRTI[a], treatment-naive adults

Study Group	N[b]	Age [years] mean (SD)	Sex [F/M] %	Ethnicity n (%)		Treatment discontinuation at week 96 n (%)
				White	Non-white	
Study with DOR/3TC/TDF						
021						
DOR/3TC/TDF	368	34 (11)	16/84	177 (48.6)	187 (51.4)	68 (18.5)[c]
EFV + 2 NRTI	366	33 (10)	15/85	170 (46.7)	194 (53.3)	88 (24.0)[c]
Studies with DTG						
SINGLE						
DTG + 2 NRTI	422	37 (11)	16/84	284 (68.6)	130 (31.4)[d]	72 (17.4)
EFV + 2 NRTI	422	36 (10)	15/85	285 (68.0)	133 (31.7)[d]	109 (26.0)
SPRING-1						
DTG + 2 NRTI	51	37 (9)	12/88	38 (74.5)	13 (25.5)	5 (9.8)
EFV + 2 NRTI	52	41 (11)	12/88	43 (86.0)	7 (14.0)	10 (19.2)

a: See Table 7 for information on the combination partners in the individual studies.
b: Number of randomized patients. Patients who received no treatment were not considered.
c: Unclear whether treatment or study were discontinued.
d: Institute's calculation.
3TC: lamivudine; DOR: doravirin; DTG: dolutegravir; EFV: efavirenz; F: female; M: male; n: number of patients with event; N: number of randomized patients; ND: no data; NRTI: nucleoside/nucleotide reverse transcriptase inhibitor; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Table 9: Characteristics of the study populations (disease severity at the start of the study) - RCT, indirect comparison: DOR/3TC/TDF vs. DTG + 2 NRTI[a], treatment-naive adults

Study Group	N[b]	HIV disease stage [CDC category] n (%)			Baseline viral load [HIV-1 RNA copies/mL] n (%)		CD4 cell count/µl at baseline [cells/µl] n (%)	
		asymptomatic	symptomatic	AIDS	≤ 100 000	> 100 000	≤ 200	> 200
Study with DOR/3TC/TDF								
021								
DOR/3TC/TDF	368	ND	ND	7 (1.9)	275 (75.5)[c]	89 (24.5)[c]	44 (12.1)	320 (87.9)
EFV + 2 NRTI	366	ND	ND	9 (2.5)	274 (75.3)[c]	90 (24.7)[c]	46 (12.6)	318 (87.4)
Studies with DTG								
SINGLE								
DTG + 2 NRTI	422	342 (83)	54 (13)	18 (4)	280 (68)	134 (32)	57 (13.8)[d]	357 (86.2)[d]
EFV + 2 NRTI	422	350 (84)	52 (12)	17 (4)	288 (69)	131 (31)	62 (14.8)[d]	357 (85.2)[d]
SPRING-1							< 300	≥ 300
DTG + 2 NRTI	51	41 (80)	10 (20)	0 (0)	39 (76.5)	12 (23.5)	22 (43.1)	29 (56.9)
EFV + 2 NRTI	52	45 (90)	4 (8)	1 (2)	39 (78.0)	11 (22.0)	26 (52.0)	24 (48.0)

a: See Table 7 for information on the combination partners in the individual studies.
b: Number of randomized patients. Patients who received no treatment were not considered.
c: HIV-1 RNA value at screening (stratification factor)
d: Institute's calculation based on data for 414 vs. 419 patients in the dolutegravir or the efavirenz arm.

3TC: lamivudine; AIDS: acquired immunodeficiency syndrome; CD4: cluster of differentiation 4; CDC: Centers for Disease Control and Prevention; DOR: doravirin; DTG: dolutegravir; EFV: efavirenz; HIV: human immunodeficiency virus; n: number of patients with event; N: number of randomized patients; ND: no data; NRTI: nucleoside/nucleotide reverse transcriptase inhibitor; RCT: randomized controlled trial; RNA: ribonucleic acid; SD: standard deviation; TDF: tenofovir disoproxil fumarate; vs.: versus

The demographic and clinical characteristics of the patients were largely balanced both between the individual study arms and between the 3 studies.

The clear majority of the patients in all 3 studies were male, and the mean age of the patients ranged between 33 and 41 years throughout all treatment arms. The proportion of white and non-white patients was balanced in the 021 study, in the studies SINGLE and SPRING-1, the proportion of white patients was clearly higher than that of non-white patients. The characteristic "ethnicity" is a relevant effect modifier in the present indication. However, potential effect modifications by the characteristic "ethnicity" in the studies SINGLE and SPRING-1 had already been investigated in the dossier assessment of dolutegravir (A14-08) [5]. There was no effect modification relevant for the result. In the majority of the patients, the viral load at the start of the study was ≤ 100 000 HIV-1 RNA copies/mL and the CD4 cell count was > 200 cells/µL. However, for the SPRING-1 study there are only data on the cut-off value 300 cells/µL. Information on the proportion of patients in the categories "asymptomatic" or "symptomatic" regarding the HIV disease stage according to CDC classification is not available for the 021 study. However, the proportion of patients in the category "AIDS" was ≤ 4% in all 3 studies.

The proportion of patients who discontinued treatment ranged between 10% (DTG arm of the SPRING-1 study) and 26% (EFV arm of the SINGLE study) in the individual studies.

2.3.1.3 Similarity of the studies for the indirect comparison

The available data on the study and intervention characteristics of the 3 studies showed that the studies were sufficiently similar regarding design. The impact of the partially differing applied backbone therapies of 2 NRTI (study 021 [EFV arm], SINGLE: FTC/TDF; SPRING-1: FTC/TDF or ABC/3TC; study 021 [DOR arm]: 3TC/TDF) on the results of the indirect comparison is considered to be negligible.

There were differences in geographical regions where the studies were conducted. Based on the data on baseline viral load, CD4 cell count and disease stage according to CDC classification, it must be assumed that the patient populations of the 3 studies did not differ notably with regards to the severity of the disease. The suitability of the studies for an adjusted indirect comparison was thus not called into question.

2.3.1.4 Risk of bias across outcomes (study level)

Table 10 shows the risk of bias across outcomes (risk of bias at study level).

Table 10: Risk of bias across outcomes (study level) – RCT, indirect comparisons: DOR/3TC/TDF vs. DTG + 2 NRTIa, treatment-naive adults

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
Studies with DOR							
021	Yes	Yes	Yes	Yes	Yes	Yes	Low
Studies with DTG							
SINGLE	Yes	Yes	Yes	Yes	Yes	Yes	Low
SPRING-1	Yes	Yes	No	No	Yes	Yes	Low

a: See Table 7 for information on the combination partners in the individual studies.
DOR: doravirine; DTG: dolutegravir; NRTI: nucleoside/nucleotide reverse transcriptase inhibitor; RCT: randomized controlled trial; vs.: versus

The risk of bias across outcomes was rated as low for the 3 studies. This concurs with the company's assessment. Limitations that might result from the open-label study design of the SPRING-1 study are described in Section 2.3.2.2 with the outcome-specific risk of bias.

2.3.2 Results on added benefit

2.3.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.6.5.3.2 of the full dossier assessment):

- Mortality
  - All-cause mortality
- Morbidity
  - AIDS-defining events (CDC class C)
  - presented as additional information: virologic response and CD4 cell count as surrogate outcomes for the patient-relevant outcome "AIDS-defining illnesses/death"
- health-related quality of life
- Side effects
  - SAEs
  - discontinuation due to AEs

- specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.6.5.3.2 of the full dossier assessment).

The company's analyses on specific AEs are incomplete (for a detailed justification, see Section 2.6.5.3.2 of the full dossier assessment). In the present benefit assessment, presentation of the specific AEs is therefore completely omitted. Irrespective of this, the analyses presented by the company only showed minor effects, if any, in all cases regarding specific AEs.

Table 11 shows for which outcomes data were available in the studies included.

Table 11: Matrix of outcomes – RCT, indirect comparison: DOR/3TC/TDF vs. DTG + 2 NRTI[a], treatment-naive adults

Study	Outcomes							
	All-cause mortality	AIDS-defining events (CDC class C)	Virologic response[b]	CD4 cell count[b]	Health-related quality of life	Serious adverse events	Discontinuation due to AEs	Specific AEs
Studies with DOR								
021	Yes	Yes	Yes	Yes	No[c]	Yes	Yes	Yes
Studies with DTG								
SINGLE	Yes	Yes	Yes	Yes	No[c]	Yes	Yes	Yes
SPRING-1	Yes	Yes	Yes	Yes	No[c]	Yes	Yes	Yes

a: See Table 7 for information on the combination partners in the individual studies.
b: The virologic response (analysis according to FDA snapshot algorithm or according to Time to Loss of Virologic Response (TLOVR) in the SPRING-1 study) as well as the CD4 cell count are presented as surrogate outcomes for the combined outcome "AIDS-defining illnesses/death" as supplementary information.
c: Outcome not recorded.

AE: adverse event; AIDS: acquired immunodeficiency syndrome; CD4: cluster of differentiation 4; CDC: Centers for Disease Control and Prevention; DOR: doravirine; DTG: dolutegravir; FDA: Food and Drug Administration; MedDRA: Medical Dictionary for Regulatory Activities; NRTI: nucleoside/nucleotide reverse transcriptase inhibitor; RCT: randomized controlled trial; TLOVR: Time to Loss of Virologic Response; vs.: versus

2.3.2.2 Risk of bias

Table 12 describes the risk of bias for the results of the relevant outcomes.

Table 12: Risk of bias across outcomes and outcome-specific risk of bias – RCT, indirect comparisons: DOR/3TC/TDF vs. DTG + 2 NRTI[a], treatment-naive adults

Study	Outcomes							
	All-cause mortality	AIDS-defining events (CDC class C)	Virologic response[b]	CD4 cell count[b]	Health-related quality of life	Serious adverse events	Discontinuation due to AEs	Specific AEs
Studies with DOR								
021	L	L	L	H[c]	–[d]	L	L	–[e]
Studies with DTG								
SINGLE	L	L	L	L	–[d]	L	L	–[e]
SPRING-1	L	L	L	H[f]	–[d]	L	H[g]	–[e]

a: See Table 7 for information on the combination partners in the individual studies.
b: The virologic response (analysis according to FDA snapshot algorithm or according to Time to Loss of Virologic Response (TLOVR) in the SPRING-1 study) as well as the CD4 cell count are presented as surrogate outcomes for the combined outcome "AIDS-defining illnesses/death" as supplementary information.
c: ITT principle violated: proportion of patients not considered > 10% (difference between the treatment arms > 7%).
d: Outcome not recorded.
e: Analyses on specific AEs incomplete, see Section 2.6.5.3.2 of the full dossier assessment.
f: ITT principle violated: proportion of missing values in the treatment arms 10% and 22%.
g: Subjectively reported outcome in open-label study.

AE: adverse event; AIDS: acquired immunodeficiency syndrome; CD4: cluster of differentiation 4; CDC: Centers for Disease Control and Prevention; DOR: doravirine; DTG: dolutegravir; FDA: Food and Drug Administration; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; NRTI: nucleoside/nucleotide reverse transcriptase inhibitor; RCT: randomized controlled trial; TLOVR: Time to Loss of Virologic Response; vs.: versus

Except for the CD4 cell count, the risk of bias for the results of the considered outcomes was rated as low in study 021. The high risk of bias for the results on the CD4 cell count results from the violation of the the intention to treat (ITT) principle by a relevant proportion of patients who had not been considered in the analysis (> 10%, difference between the treatment arms > 7%). This deviates from the assessment of the company, which assumed a low risk of bias for all outcomes rated as relevant by the company.

Concurring with the company, the risk of bias was rated as low for the results of all considered outcomes in the SINGLE study.

In the SPRING-1 study, the risk of bias was rated as low for the results of the outcomes "all-cause mortality", "AIDS-defining events" (CDC class C), "virologic failure" and "SAEs". The risk of bias for the results on the outcome "CD4 cell count" was rated as high due to the violation of the ITT principle by a high proportion of missing values of 10% or 22% that differs between the treatment arms [5]. The risk of bias for the side effect-related outcome "discontinuation due to AEs" was also rated as high. The high risk of bias is due to the lack of blinding in subjective recording of outcomes. The assessment deviates from that of the company, which assumed a lower risk of bias for the outcome "CD4 cell count".

2.3.2.3 Results

Table 13 and Table 14 summarize the results of the comparison of DOR/3TC/TDF with DTG + 2 NRTI in HIV-1 infected adults. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. Tables on common AEs are presented in Appendix A.

Table 13: Results (mortality, morbidity, side effects, dichotomous) – RCT, indirect comparison using common comparators: DOR/3TC/TDF vs. DTG + 2 NRTI[a], treatment-naive adults

Outcome category Outcome Comparison Study	DOR or DTG N	DOR or DTG Patients with event n (%)	EFV N	EFV Patients with event n (%)	Group difference RR [95% CI]; p-value[b]
Mortality					
All-cause mortality					
DOR/3TC/TDF vs. EFV + 2 NRTI					
021	364	0 (0)	364	2 (0.5)	0.20 [0.01; 4.15]; 0.298
DTG + 2 NRTI vs. EFV + 2 NRTI					
SINGLE	414	0 (0)	419	2 (0.5)	0.20 [0.01; 4.20] ND
SPRING-1	51	1 (2.0)	50	0 (0)	2.94 [0.12; 70.53] ND
Total[c]					0.67 [0.11; 3.99]; 0.655
Indirect comparison using common comparators[d]:					
DOR/3TC/TDF vs. DTG + 2 NRTI					0.30 [0.01 10.18]; 0.504
Morbidity					
AIDS-defining events (CDC class C)					
DOR/3TC/TDF vs. EFV + 2 NRTI					
021	364	0 (0)	364	2 (0.6)	0.20 [0.01; 4.15][e]; < 0.170[f]
DTG + 2 NRTI vs. EFV + 2 NRTI					
SINGLE	414	5 (1.2)	419	5 (1.2)	1.01 [0.30; 3.47][e] ND
SPRING-1	51	1 (2.0)	50	0 (0)	2.94 [0.12; 70.56][e] ND
Total[g]					1.19 [0.38; 3.68]; 0.763
Indirect comparison using common comparators[h]:					
DOR/3TC/TDF vs. DTG + 2 NRTI					0.17 [0.01; 4.28]; 0.280
Additional information: surrogate outcome "virologic response" (HIV RNA < 50 copies/mL)i					
DOR/3TC/TDF vs. EFV + 2 NRTI					
021	364	282 (77.5)	364	268 (73.6)	1.05 [0.97; 1.14]; 0.228
DTG + 2 NRTI vs. EFV + 2 NRTI					
SINGLE	414	319 (77.1)	419	293 (69.9)	1.10 [1.02; 1.20] ND
SPRING-1	51	45 (88.2)	50	36 (72.0)	1.23 [1.003; 1.50] ND
Total[c]					1.12 [1.03; 1.20]; 0.005
Indirect comparison using common comparators[d]:					
DOR/3TC/TDF vs. DTG + 2 NRTI					0.94 [0.84; 1.06]; 0.308

(continued)

Table 13: Results (mortality, morbidity, side effects, dichotomous) – RCT, indirect comparison using common comparators: DOR/3TC/TDF vs. DTG + 2 NRTI[a], treatment-naive adults (continued)

Outcome category Outcome Comparison Study	DOR or DTG N	 Patients with event n (%)	EFV N	 Patients with event n (%)	Group difference RR [95% CI]; p-value[b]
Health-related quality of life	Outcome not recorded				
Side effects					
AEs (additional information)					
DOR/3TC/TDF vs. EFV + 2 NRTI					
021	364	321 (88.2)	364	339 (93.1)	–
DTG + 2 NRTI vs. EFV + 2 NRTI					
SINGLE	414	376 (90.8)	419	394 (94.0)	–
SPRING-1	51	46 (90.2)	50	46 (92.0)	–
Serious adverse events					
DOR/3TC/TDF vs. EFV + 2 NRTI					
021	364	21 (5.8)	364	30 (8.2)	0.70 [0.41; 1.20]; 0.194
DTG + 2 NRTI vs. EFV + 2 NRTI					
SINGLE	414	44 (10.6)	419	50[j] (11.9)	0.89 [0.61; 1.30] ND
SPRING-1	51	7 (13.7)	50	7 (14.0)	0.98 [0.37; 2.59] ND
Total[c]					0.90 [0.63 1.29]; 0.569
Indirect comparison using common comparators[d]:					
DOR/3TC/TDF vs. DTG + 2 NRTI					0.78 [0.41; 1.48]; 0.441
Discontinuation due to AEs					
DOR/3TC/TDF vs. EFV + 2 NRTI					
021	364	11 (3.0)	364	27 (7.4)	0.41 [0.21 0.81]; 0.010
DTG + 2 NRTI vs. EFV + 2 NRTI					
SINGLE	414	14 (3.4)	419	52 (12.4)	0.27 [0.15; 0.48] ND
SPRING-1	51	2 (3.9)	50	5 (10.0)	0.39 [0.08; 1.93] ND
Total[c]					0.28 [0.17; 0.49]; < 0.001
Indirect comparison using common comparators[d]:					
DOR/3TC/TDF vs. DTG + 2 NRTI					1.44 [0.60; 3.44]; 0.414

(continued)

Table 13: Results (mortality, morbidity, side effects, dichotomous) – RCT, indirect comparison using common comparators: DOR/3TC/TDF vs. DTG + 2 NRTI[a], treatment-naive adults (continued)

a: See Table 7 for information on the combination partners in the individual studies.
b: Unless stated otherwise: two-sided p-value (Wald test)
c: Fixed-effect model (Mantel-Haenszel)
d: Indirect comparison according to Bucher [11].
e: Institute's calculation, asymptotic.
f: Institute's calculation, unconditional exact test (CSZ method according to [12]).
g: Institute's calculation, model with fixed effect (Mantel-Haenszel).
h: Institute's calculation, indirect comparison according to Bucher [11].
i: Analysis in accordance with snapshot algorithm (studies 021, SINGLE) or TLOVR (SPRING-1 study).
j: Information from Module 4 A; there is a discrepancy with the data in dossier assessment A14-08 Dolutegravir [5], see Appendix A, tables on common AEs. However, this discrepancy has no influence on the total result.

3TC: lamivudine; AE: adverse event; AIDS: acquired immunodeficiency syndrome; CDC: Centers for Disease Control and Prevention; CI: confidence interval; DOR: doravirine; DTG: dolutegravir; EFV: efavirenz; HIV: human immunodeficiency virus; n: number of patients with (at least 1) event; N: number of analysed patients; ND: no data; NRTI: nucleoside/nucleotide reverse transcriptase inhibitor; PT: Preferred Term; RCT: randomized controlled trial; RNA: ribonucleic acid; RR: relative risk; SOC: System Organ Class; SUE: serious adverse event; TDF: tenofovir disoproxil fumarate; TLOVR: Time to Loss of Virologic Response; vs.: versus

Table 14: Results (morbidity, continuous) – RCT, indirect comparison using common comparators: DOR/3TC/TDF vs. DTG + 2 NRTI[a], treatment-naive adults

Outcome category Outcome Comparison Study	DOR/3TC/TDF or DTG + 2 NRTI			EFV+ 2 NRTI			Group difference
	N[b]	Values at baseline mean (SD)	Change at end of study mean (SD)	N[b]	Values at baseline mean (SD)	Change at end of study mean (SD)	MD [95% CI]; p-value
Morbidity							
Additional information: surrogate outcome "CD4 cell count" (number/µL)							
DOR/3TC/TDF vs. EFV + 2 NRTI							
021	337	435.9 (ND)	237.7 [214.9; 260.6][c]	311	413.5 (ND)	223.0 [198.4; 247.6][c]	14.7 [−18.7; 48.2] ND
DTG + 2 NRTI vs. EFV + 2 NRTI							
SINGLE	414	349 (158.2)	324 (205.7)[d]	419	351 (157.5)	286 (196.0)[d]	43.95 [14.34; 73.55][e] ND
SPRING-1	51	327 (122.3)	338 (162.6)[d]	50	328 (106.5)	321 (218.9)[d]	17.0 [−65.5; 99.5] ND
Total[f]							40.79 [12.98; 68.61]; 0.004
Indirect comparison using common comparators[g]:							
DOR/3TC/TDF vs. DTG + 2 NRTI							–[h]

a: See Table 7 for information on the combination partners in the individual studies.
b: Number of analysed patients analysed at time point "96 weeks". The values at the start of the study can be based on other patient numbers.
c: 95% CI.
d: Values at the end of the study.
e: Difference of adjusted mean values [95% CI] from MMRM.
f: Model with random effects according to DerSimonian-Laird (essentially corresponds to a fixed-effect model if the data situation is homogeneous [$I^2 = 0$] [inverse variance]).
g: Indirect comparison according to Bucher [11]; for study 021, the standard errors of the changes at the end of the study were calculated from the respective confidence intervals.
h: No presentation of the effect estimate, because the adjusted indirect comparison only includes one study with a high outcome-specific risk of bias for DOR/3TC/TDF (see Section 2.6.5.3.1 of the full benefit assessment on indirect comparisons).
3TC: lamivudine; CD4: cluster of differentiation 4; CI: confidence interval; DOR: doravirine; DTG: dolutegravir; EFV: efavirenz; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; ND: no data; NRTI: nucleoside/nucleotide reverse transcriptase inhibitor; RCT: randomized controlled trial; SD: standard deviation; TDF: tenofovir disoproxil fumarate; vs.: versus

Based on the data available from the adjusted indirect comparison, at most hints, e.g. of an added benefit, could be derived (see Section 2.6.5.3.1 of the full dossier assessment).

The benefit assessment is based on the results at week 96. This concurs with the company's approach, which presented the results at week 48 in addition to those at week 96, but also used the data at week 96 for the assessment of the added benefit.

Mortality

All-cause mortality

The adjusted indirect comparison shows no statistically significant difference between DOR/3TC/TDF and DTG + 2 NRTI at week 96 for the outcome "all-cause mortality". This resulted in no hint of an added benefit of DOR/3TC/TDF in comparison with DTG + 2 NRTI; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

AIDS-defining events (CDC class C), supplementary consideration of the surrogate outcomes "virologic response" and "CD4 cell count"

The adjusted indirect comparison shows no statistically significant difference between DOR/3TC/TDF and DTG + 2 NRTI at week 96 for the outcome "AIDS-defining events" (CDC class C) and for the surrogate outcome "virologic response" presented as additional information.

The surrogate outcome "CD4 cell count" had a high risk of bias in the studies 021 and SPRING-1 (see Section 2.3.2.2). Hence, no hint of greater or lesser harm from DOR/3TC/TDF vs. DTG + 2 NRTI was derived for this outcome in the adjusted indirect comparison (see Section 2.6.5.3.1 of the full dossier assessment on indirect comparisons).

Overall, this resulted in no hint of an added benefit of DOR/3TC/TDF in comparison with DOR + 2 NRTI for the outcome "AIDS-defining events" (CDC class C); an added benefit is therefore not proven.

This concurs with the company's assessment.

Health-related quality of life

None of the studies included recorded health-related quality of life.

Side effects

SAEs

The adjusted indirect comparison shows no statistically significant difference between DOR/3TC/TDF and DTG + 2 NRTI at week 96 for the outcome "SAEs". This resulted in no hint of greater or lesser harm from DOR/3TC/TDF in comparison with DTG + 2 NRTI; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Discontinuation due to AEs

The adjusted indirect comparison shows no statistically significant difference between DOR/3TC/TDF and DTG + 2 NRTI at week 96 for the outcome "discontinuation due to AEs".

Hence, there was no greater or lesser harm from DOR/3TC/TDF versus DTG + 2 NRTI; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

2.3.2.4 Subgroups and other effect modifiers

The subgroup characteristics "age", "sex", "HIV-1 RNA baseline viral load" and "ethnicity" are basically relevant for the present benefit assessment. However, the subgroup analyses based on the indirect comparison presented by the company are incomplete. Therefore, no subgroup analyses are presented in the present situation of an indirect comparison. For detailed description, see Section 2.6.5.3.4 of the full dossier assessment.

2.3.3 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below. The various outcome categories and the effect sizes were taken into account. The methods used for this purpose are explained in the *General Methods* of IQWiG [2].

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 the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.3.2 (see Table 15).

Table 15: Extent of added benefit at outcome level: DOR/3TC/TDF vs. DTG + 2 NRTI

Outcome category **Outcome**	**DOR/3TC/TDF vs. DTG + 2 NRTI** **proportion of events (%)** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0–2.0% RR: 0.30 [0.01; 10.18]; p = 0.504	Lesser benefit/added benefit not proven
Morbidity		
AIDS-defining events (CDC class C)	0% vs. 1.2–2.0% RR: 0.17 [0.01; 4.28]; p = 0.280	Lesser benefit/added benefit not proven
Supplementary information:		
Virologic response	77.5% vs. 77.1–88.2% RR: 0.94 [0.84; 1.06]; p = 0.308	Lesser benefit/added benefit not proven
CD4 cell count/µL	-[c]	Lesser benefit/added benefit not proven
Health-related quality of life	Outcome not recorded	Lesser benefit/added benefit not proven
Side effects		
SAEs	5.8% vs. 10.6–13.7% RR: 0.78 [0.41; 1.48]; p = 0.441	Greater/lesser harm not proven
Discontinuation due to AEs	3.0% vs. 3.4–3.9% RR: 1.44 [0.60; 3.44]; p = 0.414	Greater/lesser harm not proven

a: Probability provided if a statistically significant and relevant effect is present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Since only one study with a high outcome-specific risk of bias is available for the comparison of DOR/3TC/TDF with the common comparator TDF, an added benefit cannot be derived from the indirect comparison due to the high uncertainty.

3TC: lamivudine; AE: adverse event; AIDS: acquired immunodeficiency syndrome; CD4: cluster of differentiation 4; CDC: Centers for Disease Control and Prevention; CI: confidence interval; CI_u: upper limit of confidence interval; DOR: doravirine; DTG: dolutegravir; MD: mean difference;
NRTI: nucleoside/nucleotide reverse transcriptase inhibitor; RR: relative risk; SAE: serious adverse event; TDF: tenofovir disoproxil fumarate; vs.: versus

2.3.3.2 Overall conclusion on added benefit

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

Table 16: Positive and negative effects from the assessment of DOR/3TC/TDF in comparison with DTG + 2 NRTI

Positive effects	**Negative effects**
-	-
Health-related quality of life: outcomes from this category were not recorded	
3TC: lamivudine; DOR: doravirine; DTG: dolutegravir; NRTI: nucleoside/nucleotide reverse transcriptase inhibitor; TDF: tenofovir disoproxil fumarate	

Overall, there were neither positive nor negative effects of DOR/3TC/TDF in comparison with DTG + 2 NRTI.

Overall, there was no hint of an added benefit of DOR/3TC/TDF in comparison with DTG + 2 NRTI for treatment-naive adults with HIV-1 infection; an added benefit is therefore not proven.

The assessment described above deviates from that of the company, which claimed an indication of a minor added benefit for treatment-naive adults with HIV-1 infection.

2.3.4 List of included studies

021

Merck Sharp & Dohme. Active comparator-controlled clinical trial to evaluate the safety and efficacy of MK-1439A once-daily versus ATRIPLA once-daily in treatment-naïve HIV-1 infected subjects: study MK-1439A-021; clinical study report [unpublished]. 2018.

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ViiV Healthcare. A trial comparing GSK1349572 50mg plus abacavir/lamivudine once daily to Atripla (also called The SINGLE Trial): study details [online]. In: ClinicalTrials.gov. 04.04.2018 [Accessed: 15.02.2019]. URL: https://clinicaltrials.gov/ct2/show/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: clinical trial results [online]. In: EU Clinical Trials Register. 13.08.2016 [Accessed: 15.02.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2010-020983-39/results.

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. 04.04.2018 [Accessed: 15.02.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT01263015.

ViiV Healthcare, GlaxoSmithKline. Protocol for: "Walmsley SL, Antela A, Clumeck N, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. N Engl J Med 2013;369:1807-18" [online]. 23.07.2013 [Accessed: 07.03.2019]. URL: https://www.nejm.org/doi/suppl/10.1056/NEJMoa1215541/suppl_file/nejmoa1215541_protocol.pdf.

ViiV Healthcare UK. 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. [Accessed: 15.02.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2010-020983-39.

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Stellbrink HJ, Reynes J, Lazzarin A, Voronin E, Pulido F, Felizarta F et al. Dolutegravir in antiretroviral-naive adults with HIV-1: 96-week results from a randomized dose-ranging study. AIDS 2013; 27(11): 1771-1778.

Van Lunzen J, Maggiolo F, Arribas JR, Rakhmanova A, Yeni P, Young B et al. Once daily dolutegravir (S/GSK1349572) in combination therapy in antiretroviral-naive adults with HIV: planned interim 48 week results from SPRING-1, a dose-ranging, randomised, phase 2b trial. Lancet Infect Dis 2012; 12(2): 111-118.

ViiV Healthcare. A dose ranging trial of GSK1349572 and 2 NRTI in HIV-1 infected, therapy naive subjects (ING112276): study details [online]. In: ClinicalTrials.gov. 16.01.2018 [Accessed: 15.02.2019]. URL: https://clinicaltrials.gov/ct2/show/NCT00951015.

ViiV Healthcare. A phase IIb study to select a once daily oral dose of GSK1349572 administered with either abacavir/lamivudine or tenofovir/emtricitabine in HIV-1 infected antiretroviral therapy naïve adult subjects: clinical trial results [online]. In: EU Clinical Trials Register. 30.12.2017 [Accessed: 15.02.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2009-010269-21/results.

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ViiV Healthcare UK. A Phase IIb study to select a once daily oral dose of GSK1349572 administered with either abacavir/lamivudine or tenofovir/emtricitabine in HIV-1 infected antiretroviral therapy naïve adult subjects [online]. In: EU Clinical Trials Register. [Accessed: 15.02.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2009-010269-21.

2.4 Research question 2: pretreated adults

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 DOR/3TC/TDF (status: 17 October 2018)
- bibliographical literature search on DOR/3TC/TDF (last search on 17 October 2018)
- search in trial registries for studies on DOR/3TC/TDF (last search on 17 October 2018)

To check the completeness of the study pool:

- search in trial registries for studies on DOR (last search on 5 February 2019)

In its dossier, the company presented no relevant study on research question 2. Nor was a relevant study identified from the check of the completeness.

2.4.2 Results on added benefit

The company presented no data for the assessment of the added benefit of DOR/3TC/TDF in comparison with the ACT in pretreated HIV-1 infected adults. Hence, there was no hint of an added benefit of DOR/3TC/TDF in comparison with the ACT; an added benefit is therefore not proven.

2.4.3 Probability and extent of added benefit

Since the company presented no data for the assessment of the added benefit of DOR/3TC/TDF in comparison with the ACT in pretreated HIV-1 infected adults, an added benefit of DOR/3TC/TDF is not proven for these patients.

This concurs with the assessment of the company, which claimed no added benefit for this patient group.

2.4.4 List of included studies

Not applicable as the company presented no data for research question 2 of the benefit assessment.

2.5 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of DOR/3TC/TDF in comparison with the ACT is summarized in Table 17.

Table 17: DOR/3TC/TDF – probability and extent of added benefit

Subindication	**ACT**[a]	**Probability and extent of added benefit**
Treatment-naive adults infected with HIV-1[b]	Rilpivirine or **dolutegravir**, each in combination with 2 nucleoside/nucleotide analogues (**tenofovir disoproxil**/tenofovir alafenamide **plus emtricitabine** or **abacavir plus lamivudine**)	Added benefit not proven
Pretreated adults infected with HIV-1[b]	Individual antiretroviral therapy based on prior treatment(s) and under consideration of the reason for the switch of treatment, particularly treatment failure due to virologic failure and possible accompanying development of resistance, or due to side effects.	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: The HI viruses must not have mutations known to be associated with resistances to the substance class of NNRTI, 3TC or TDF.
3TC: lamivudine; DOR: doravirine; HIV-1: human immunodeficiency virus type 1; G-BA: Federal Joint Committee; NNRTI: non-nucleoside reverse transcriptase inhibitor; TDF: tenofovir disoproxil fumarate

The approach for deriving an overall conclusion on the 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.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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