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Doravirine (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 (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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List of abbreviations

Abbreviation	Meaning
ABC	abacavir
ACT	appropriate comparator therapy
AE	adverse event
DOR	doravirine
DTG	dolutegravir
EFV	efavirenz
FTC	emtricitabine
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HIV-1	human immunodeficiency virus type 1
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
RCT	randomized controlled trial
RNA	ribonucleic acid
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
TDF	tenofovir disoproxil fumarate
/r	boosted with ritonavir

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 doravirine (DOR). 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 in combination with other antiretroviral drugs 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).

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

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.
DOR: doravirine; HIV-1: human immunodeficiency virus type 1; G-BA: Federal Joint Committee; NNRTI: non-nucleoside reverse transcriptase inhibitor

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 in combination with other antiretroviral drugs in comparison with the ACT. Therefore, the company presented a total of 6 RCTs for 2 adjusted indirect comparisons of DOR in combination with 2 NRTI (DOR + 2 NRTI) with DTG + 2 NRTI using the common comparators efavirenz (EFV) and ritonavir-boosted darunavir (DRV/r). An adjusted indirect comparison was conducted using the common comparator EFV with two studies for DOR or DTG each, as well as another adjusted indirect comparison using the common comparator DRV/r with one study for DOR and one for DTG. The results of the two indirect comparisons were summarized in a meta-analysis, if possible.

The results at the analysis date of 96 weeks were used for the present benefit assessment.

Studies with DOR

Studies 007, 018 and 021 were double-blind, randomized parallel-group studies on treatment-naive HIV-1 infected adults. The HIV-1 ribonucleic acid (RNA) viral load of the patients had to be ≥ 1000 copies/mL at screening. Randomized treatment duration was 96 weeks in all three studies.

Study 007 was a dose-ranging study, in which DOR was compared with EFV, each with a fixed combination of emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) (FTC/TDF). Within this study, 108 patients were treated with DOR (100 mg) + FTC/TDF, and 109 patients were treated with EFV + FTC/TDF for 96 weeks.

In study 018, DOR was compared with DRV/r, each with a fixed combination of FTC/TDF or ABC/3TC, study 021 compared the fixed combinations DOR/3TC/TDF and EFV/FTC/TDF. In study 018, a total of 769 patients were allocated to treatment with DOR (N = 385) or DRV/r (N = 384) in a 1:1 ratio. In study 021, a total of 734 patients were allocated to treatment with DOR/3TC/TDF (N = 368) or EFV/FTC/TDF (N = 366) also in a 1:1 ratio.

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

Studies with DTG

The studies FLAMINGO, SINGLE and SPRING-1 were 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 FLAMINGO study was an open-label study, 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 all three studies. The studies SINGLE and SPRING-1 are already known from the dossier assessment on DTG.

In the FLAMINGO study, DTG was compared with DRV/r, each with the fixed combination of FTC/TDF or ABC/3TC, the SINGLE study compared DTG + ABC/3TC with EFV/FTC/TDF. In the FLAMINGO study, a total of 488 patients were randomly allocated to treatment with DTG + 2 NRTI (N = 243) or DRV/r + 2 NRTI (N = 245) in a ratio of 1:1. In the SINGLE study, a total of 844 patients were randomly allocated to treatment with DTG + ABC/3TC (N = 422) or EFV/FTC/TDF (N = 422) also in a 1:1 ratio.

The SPRING-1 study was a dose-ranging study on DTG. Only patients from the study arm in which a daily dose of 50 mg DTG for adults (N = 51) 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 with regard to the allocation of patients to DTG or EFV, only the daily DTG dose was blinded. Patients received a backbone therapy of either TDF/FTC or ABC/3TC in addition to the study medication.

The 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 available data on the study and intervention characteristics of the 6 studies showed that the studies were sufficiently similar regarding the design and the used common comparators EFV and DRV/r. The impact of the partially differing backbone therapies of 2 NRTI on the results of the indirect comparison was considered to be negligible.

The demographic and clinical characteristics of the patients were largely balanced both between the individual treatment arms and between the 6 studies. Based on the data on baseline viral load, Cluster of Differentiation 4 (CD4) cell count and HIV disease stage according to Centers for Disease Control and Prevention (CDC) classification, it must be assumed that the patients did not differ notably with regards to the severity of the disease. The suitability of the studies 007, 018, 021, FLAMINGO, SINGLE and SPRING-1 for an adjusted indirect comparison was thus not called into question.

Risk of bias

Except for the CD4 cell count, the risk of bias for the results of the considered outcomes was rated as low in the studies 007, 018 and 021.

The outcome-specific risk of bias for the available results was rated as low in the FLAMINGO study, except for the side effect-related outcome “discontinuation due AEs”.

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

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

Mortality

All-cause mortality

Pooling of the two adjusted indirect comparisons in a meta-analysis showed no statistically significant difference between DOR + 2 NRTI and DTG + 2 NRTI at week 96 for the outcome "all-cause mortality". This resulted in no hint of an added benefit of DOR + 2 NRTI 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 outcome "AIDS-defining events" was not recorded in the 007 study. In the FLAMINGO study, there are no results for this outcome at week 96; indirect comparison using the common comparator DRV/r is therefore impossible. Based on the available data, indirect comparison using the common comparator DRV/r was also impossible for the outcome "CD4 cell count", because the FLAMINGO study only provides information on the median of the CD4 cell count in the treatment arms.

Indirect comparison using the common comparator EFV showed no statistically significant difference between DOR + 2 NRTI and DTG + 2 NRTI at week 96, neither for the outcome "AIDS-defining events (CDC class C)" nor for "CD4 cell count" presented as additional information. Pooling of the two adjusted indirect comparisons in a meta-analysis showed no statistically significant difference between DOR + 2 NRTI and DTG + 2 NRTI at week 96 for the outcome "virologic response", which was presented as additional information.

Overall, there was no hint of an added benefit of DOR + 2 NRTI in comparison with DTG + 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

Pooling of the two adjusted indirect comparisons in a meta-analysis yielded no statistically significant difference between DOR + 2 NRTI and DTG + 2 NRTI at week 96 for the outcomes "SAEs" and "discontinuation due to AEs". Hence, there was no hint of greater or lesser harm

from DOR + 2 NRTI versus DTG + 2 NRTI for these outcomes; greater or lesser harm is therefore not proven.

Specific AEs

The company's analyses on specific AEs are incomplete, presentation of the specific AEs is therefore completely omitted. Irrespective of this, the analyses on specific AEs presented by the company only showed minor effects, if any, in all cases.

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 in combination with other antiretroviral drugs versus the ACT are assessed as follows:

Research question 1 (treatment-naive adults)

Overall, there were neither positive nor negative effects of DOR + 2 NRTI in comparison with DTG + 2 NRTI. An added benefit of DOR + 2 NRTI 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)

Data for the assessment of the added benefit of DOR in combination with other antiretroviral drugs versus the ACT are not available for pretreated HIV-1[4] infected 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.

[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].

[4] The HI viruses must not have mutations known to be associated with resistances to the substance class of the NNRTI.

Table 3: DOR – 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 the NNRTI.
DOR: doravirine; HIV-1: human immunodeficiency virus type 1; G-BA: Federal Joint Committee; NNRTI: non-nucleoside reverse transcriptase inhibitor

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

2.2 Research question

The aim of this report is to assess the added benefit of DOR in combination with other antiretroviral drugs versus 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 NNRTI.

The G-BA's specification of the ACT resulted in two research questions, which are presented in the following Table 4:

Table 4: Research questions of the benefit assessment of DOR

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.
DOR: doravirine; HIV-1: human immunodeficiency virus type 1; G-BA: Federal Joint Committee; NNRTI: non-nucleoside reverse transcriptase inhibitor

The company followed the G-BA's specification of the ACT for both research questions and chose 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 (status: 17 October 2018)
- bibliographical literature search on DOR (last search on 17 October 2018)
- search in trial registries for studies on DOR (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 in combination with other antiretroviral drugs versus DTG + 2 NRTI was identified from the check of the completeness of the study pool.

The company identified 6 studies for two adjusted indirect comparison based on RCTs. For the indirect comparisons presented by the company (see 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 2 adjusted indirect comparisons with a total of six RCTs for the assessment of the added benefit of DOR in combination with other antiretroviral drugs. The comparison was conducted versus DTG + 2 NRTI.

On the one hand, the company presented an adjusted indirect comparison using the common comparator EFV with two studies each for DOR or DTG. On the other hand, it presented a further adjusted indirect comparison using the common comparator ritonavir-boosted darunavir (DRV/r) with 1 study each for DOR and DTG. The company justified the choice of the common comparators EFV and DRV/r with the fact that they had been used as comparator therapy in the studies conducted with DOR. Concurring with the company's assessment, EFV and DRV/r are suitable common comparators for an adjusted indirect comparison.

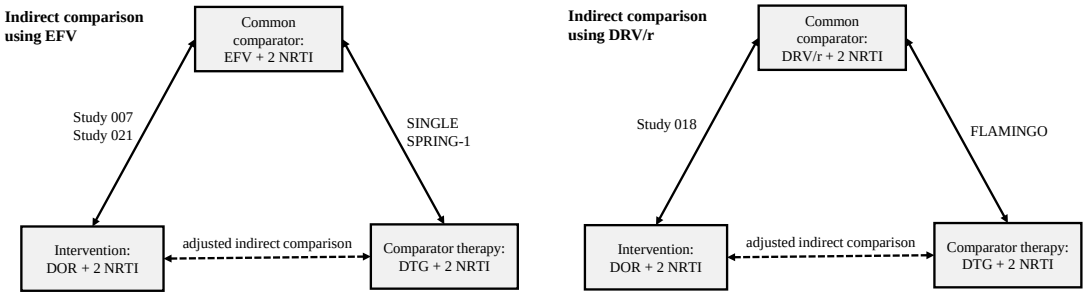
The following Table 5 presents the studies on the two adjusted indirect comparisons.

Table 5: Study pool – RCT, indirect comparisons: DOR + 2 NRTI[a] vs. DTG + 2 NRTI[a], 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)
Indirect comparison with the common comparator EFV			
Studies with DOR			
007	Yes	Yes	No
021	Yes	Yes	No
Studies with DTG			
ING114467 (SINGLE[c])	No	No	Yes
ING112276 (SPRING-1[c])	No	No	Yes
Indirect comparison using the common comparator DRV/r			
Studies with DOR			
018	Yes	Yes	No
Studies with DTG			
ING114915 (FLAMINGO[c])	No	No	Yes

a: See Table 7 for information on the combination partners in the individual studies.
b: Study for which the company was sponsor.
c: In the following tables, the study is referred to with this abbreviated form.
/r: boosted with ritonavir; DOR: doravirine; DTG: dolutegravir; DRV: darunavir; NRTI: nucleoside/nucleotide reverse transcriptase inhibitor; RCT: randomized controlled trial; vs.: versus

The study pool concurred with that of the company. Figure 1 shows a schematic representation of the two indirect comparisons.



DOR: doravirine; DRV: darunavir; DTG: dolutegravir; EFV: efavirenz; NRTI: nucleoside/nucleotide reverse transcriptase inhibitor; /r: boosted with ritonavir

Figure 1: Study pool for the indirect comparison between DOR and DTG

The company did not summarize the two indirect comparisons in quantitative terms. However, depending on the given data situation, not only a qualitative, but also a quantitative analysis of the two indirect comparisons makes sense. Deviating from the company's approach, the results of the two indirect comparisons were thus summarized in a meta-analysis, if possible (see

Section 2.6.5.3.1 of the full dossier assessment). Accordingly, the 6 studies underlying these two individual comparisons are also considered jointly in the following Section 2.3.1.2.

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 + 2 NRTI 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]
Studies with DOR						
007	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 and ≥ 100[b] CD4 cells/mm^3	Phase I: DOR 25 mg (N = 41)[c] DOR 50 mg (N = 43)[c] DOR 100 mg (N = 42) DOR 200 mg (N = 41)[c] EFV 600 mg (N = 43) Phase II: DOR 100 mg (N = 66) EFV 600 mg (N = 66) each in combination with FTC/TDF relevant population of phase I + II: DOR 100 mg (N = 108) EFV 600 mg (N = 109)	Screening: ≤ 45 days before randomization Treatment duration: 96 weeks Observation period: 14 days	73 centres in Australia, Belgium, Canada, France, Germany, Netherlands, Poland, Puerto Rico, Romania, Russia, Spain, USA 10/2012-03/2016	Primary: virologic response at week 24 Secondary: Morbidity, AEs

(continued)

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Studies with DOR						
018	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 (N = 385) DRV/r (N = 384) each in combination with TDF/FTC or ABC/3TC	Screening: ≤ 45 days before randomization Treatment duration: 96 weeks[d] Observation period: 14 days	133 centres in: Argentina, Australia, Austria, Canada, Chile, Denmark, France, Germany, Italy, Puerto Rico, Romania, Russia, South Africa, Spain, United Kingdom, USA 12/2014-07/2018	Primary: virologic response at week 48 Secondary: morbidity, AEs
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[d] Observation period: 14 days	143 centres in Australia, Belgium, Canada, Chile, Columbia, Denmark, Germany, Guatemala, Honduras, Israel, Italy, Mexico, New Zealand, Peru, Portugal, Puerto Rico, Russia, Spain, South Africa, Switzerland, Taiwan, Thailand, United Kingdom, USA 06/2015-02/2018	Primary: virologic response at week 48 Secondary: morbidity, AEs

(continued)

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Studies with DTG						
FLAMINGO	RCT, 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	DTG (N = 243) DRV/r (N = 245) each in combination with either FTC/TDF or ABC/3TC	Screening: ND Treatment duration: 96 weeks[e] Observation period: ND	64 centres in France, Germany, Italy, Puerto Rico, Romania, Russia, Spain, Switzerland, USA 10/2011-12/2016	Primary: virologic response at week 48 Secondary: morbidity, AEs
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[f] Observation period: ND	136 centres in Australia, Belgium, Canada, Denmark, France, Germany, Great Britain, Italy, Netherlands, Romania, Spain and USA 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 ≥ 200 CD4 cells/mm^3	DTG 10 mg (N = 53)[c] DTG 25 mg (N = 52)[c] 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[g] 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 + 2 NRTI 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: In France: 200 cells/mm^3 by way of Amendment 9
c: The arm is not relevant for the assessment and is no longer presented in the following tables.
d: After the double-blind treatment phase patients who benefitted 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 018: TDF or TAF or ABC each in combination with FTC or 3TC, either in fixed or in non-fixed combination; study 021: DOR/3TC/TDF) for up to 192 weeks (study 018) or up to 96 weeks (study 021).
e: After the double-blind treatment phase, 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, or until they no longer benefitted from the treatment.
f: After week 96, the patients could undergo further treatment with DTG for up to 48 weeks.
g: After the double-blind treatment phase, 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; /r: boosted with ritonavir; ABC: abacavir; AE: adverse event; CD4: cluster of differentiation 4; CDC: Centers for Disease Control and Prevention; DOR: doravirine; DRV: darunavir; DTG: dolutegravir; EFV: efavirenz; FTC: emtricitabine; HIV: human immunodeficiency virus; ND: no data; N: number of randomized patients; NRTI: nucleoside/nucleotide reverse transcriptase inhibitor; RCT: randomized controlled trial; RNA: ribonucleic acid; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate; vs.: versus

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

Study	Intervention/comparator therapy	Common comparator	Pretreatment and concomitant treatment
Studies with DOR			
007	DOR 100 mg + Placebo for EFV + FTC 200 mg / TDF 300 mg once daily each, orally	EFV 600 mg + Placebo for DOR + FTC 200 mg / TDF 300 mg 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 immunosuppressants (exception: short-term administration of glucocorticoids [e. g. for the treatment of asthma exacerbations]) within 1 month before the first administration of the study medication and during the study ▪ During the study: potent inducers of the drug metabolism or of CYP3A4, potent inhibitors of the drug glucuronidation or of CYP3A ▪ Further antiretroviral therapies during the study
018	DOR 100 mg + Placebo for DRV + Placebo for RTV + FTC 200 mg / TDF 300 mg[a] or ABC 600 mg / 3TC 300 mg once daily each, orally	DRV/r 800 mg/100 mg + Placebo for DOR + FTC 200 mg / TDF 300 mg[a] or ABC 600 mg / 3TC 300 mg 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 via CYP3A4 ▪ Further antiretroviral therapies during the study
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:** ▪ see information on study 018 **Allowed concomitant treatment:** ▪ see information on study 018

(continued)

Table 7: Characteristics of the interventions – RCT, indirect comparison: DOR + 2 NRTI vs. DTG + 2 NRTI, treatment-naive adults (continued)

Study	Intervention/comparator therapy	Common comparator	Prior and concomitant treatment
Studies with DTG			
FLAMINGO	DTG 50 mg + FTC 200 mg / TDF 300 mg or ABC 600 mg / 3TC 300 mg once daily each, orally	DRV/r 800 mg/100 mg + FTC 200 mg / TDF 300 mg or ABC 600 mg / 3TC 300 mg once daily each, orally	**Prohibited prior treatment:** ▪ HIV-1 immunotherapy vaccines ≤ 90 days before screening ▪ Immunomodulators, radiation therapy, chemotherapy ≤ 28 days before screening **Prohibited concomitant treatment:** ▪ Expectable start of a treatment against hepatitis C
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	**Prohibited prior treatment:** ▪ HIV-1 immunotherapy vaccines ≤ 90 days before screening ▪ Immunomodulators, radiation therapy, chemotherapy ≤ 28 days before screening **Prohibited concomitant treatment:** ▪ Further antiretroviral therapies ▪ CYP3A4 inducers, inhibitors of CYP2C9, CYP2C19, CYP3A4 and 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	**Prohibited prior treatment:** ▪ HIV-1 immunotherapy vaccines ≤ 90 days before screening ▪ Immunomodulators, radiation therapy, chemotherapy ≤ 28 days before screening **Prohibited concomitant treatment:** ▪ Further antiretroviral therapy ▪ Drugs with high interaction potential (e.g. carbamazepine, rifampicin, St. John's Wort, midazolam, cisapride)

a: Administration of FTC/TDF every 2 days was recommended for patients with a creatinine clearance between 30 mL/min and 49 mL/min. Treatment with FTC/TDF should be discontinued at a creatinine clearance ≤ 30 ml/min.

3TC: lamivudine; /r: boosted with ritonavir; ABC: abacavir; CYP: cytochrome P450; DOR: doravirine; DRV: darunavir; DTG: dolutegravir; EFV: efavirenz; FTC: emtricitabine; HIV: human immunodeficiency virus; RCT: randomized controlled trial; RTV: ritonavir; TDF: tenofovir disoproxil fumarate; vs.: versus

Study design

Studies with DOR

Studies 007, 018 and 021 were double-blind, randomized parallel-group studies on treatment-naive HIV-1 infected adults. The HIV-1 RNA viral load of the patients had to be ≥ 1000 copies/mL at screening. Randomized treatment duration was 96 weeks in all three studies.

Study 007 compared DOR with EFV in 2 study phases, each with a fixed combination of FTC and TDF (FTC/TDF). In phase I (dose-ranging period) of the study, DOR was administered in 4 treatment arms, at first once daily in doses of 25 mg, 50 mg, 100 mg or 200 mg respectively over 24 weeks, thereafter, all patients were further treated with 100 mg DOR until week 96. Only patients who, in accordance with the SPC [3], received 100 mg DOR (N=42) for 96 weeks were included in the present assessment. In phase I of study 007, 43 patients received treatment with EFV + FTC/TDF. After specification of the DOR dose, further patients who received either DOR 100 mg (N=66) or EFV (N=66) for 96 weeks, each in combination with FTC/TDF, were included in phase II of the study. In study 007, a total of 108 patients were thus treated with DOR (100 mg) + FTC/TDF, and 109 patients were treated with EFV + FTC/TDF for 96 weeks each.

In study 018, DOR was compared with DRV/r, each with a fixed combination of FTC/TDF or ABC/3TC, study 021 compared the fixed combinations DOR/3TC/TDF and EFV/FTC/TDF. In study 018, a total of 769 patients were randomly allocated to treatment with DOR (N = 385) or DRV/r (N = 384) in a 1:1 ratio. In study 021, a total of 734 patients were randomly allocated to treatment with DOR/3TC/TDF (N = 368) or EFV/FTC/TDF (N = 366) also in a 1:1 ratio.

In all 3 studies, randomization was stratified by HIV-1 RNA viral load (≤ 100 000 copies/ml, > 100 000 copies/ml) at the time point of screening. In all 3 studies, randomization was stratified by HIV-1 RNA viral load (≤ 100 000 copies/ml, > 100 000 copies/mL) at the time point of screening. In study 018, randomization was additionally stratified by backbone therapy (FTC/TDF, ABC/3TC), and in study 021 by hepatitis B and/or hepatitis C coinfection at the time point of screening (yes, no).

In all 3 studies, the dosage was in compliance with the respective SPCs [3-10]. To maintain blinding, the patients of all 3 studies received placebo once daily in addition to the study medication.

In accordance with the SPC, DOR in combination with other antiretroviral drugs shall only be used when there are no resistances to the class of NNRTI [3]. Only patients with confirmed sensitivity to all substances used in the respective study were included in studies 018 and 021. According to the inclusion criteria of study 007, sensitivity to DOR was not explicitly checked, however, patients were not allowed to have resistances to FTC, TDF and/or EFV. The most common NNRTI resistance-associated mutations are recorded through testing for resistances to EFV [11,12]. Moreover, virologic resistance to DOR only occurred in 1 patient during the course of the study.

Primary outcome of the 3 studies was the virologic response at week 24 (study 007) or at week 48 (studies 018 and 021). In study 007, the threshold value for the primary outcome was 40 HIV-1 RNA copies/mL; in studies 018 and 021, it was 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 DTG

The studies FLAMINGO, SINGLE and SPRING-1 were 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 FLAMINGO study was an open-label study, the SINGLE study was conducted as a double-blind trial and the SPRING-1 study was conducted in a partially blinded fashion. In all 3 studies, the randomized treatment phase was 96 weeks. The studies SINGLE and SPRING-1 are already known from the dossier assessment on DTG [13].

In the FLAMINGO study, DTG was compared with DRV/r, each with a fixed combination of FTC/TDF or ABC/3TC, the SINGLE study compared DTG + ABC/3TC with EFV/FTC/TDF. In the FLAMINGO study, a total of 488 patients were randomly allocated to treatment with DTG + 2 NRTI (N = 243) or DRV/r + 2 NRTI (N = 245) in a ratio of 1:1. In the SINGLE study, a total of 844 patients were randomly allocated to treatment with DTG + ABC/3TC (N = 422) or EFV/FTC/TDF (N = 422) also in a 1:1 ratio.

Only patients from the study arm in which a daily dose of 50 mg DTG for adults (N = 51) was administered in compliance with the SPC [14] were included in the present benefit assessment. Patients in the comparator arm (N = 52) received EFV. The study was open-label with regard to the allocation of patients to DTG or EFV, only the daily DTG dose was blinded. Patients received a backbone therapy of either TDF/FTC or ABC/3TC in addition to the study medication.

In all 3 studies, randomization was stratified by HIV-1 RNA viral load (≤ 100 000 copies/ml, > 100 000 copies/mL) at the time point of screening. 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).

In the studies FLAMINGO and SINGLE as well as in the relevant treatment arms of the SPRING-1 study, dosage was in compliance with the respective SPCs [4-9,14]. The patients in the SINGLE study received placebo in addition to the study medication to maintain blinding.

Primary outcome of the 3 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 (FLAMINGO, SINGLE).

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.

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 + 2 NRTI[a] 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	
Studies with DOR						
007						
DOR + 2 NRTI	108	37 (11)	8/92	86 (79.6)	22 (20.4)	ND[c]
EFV + 2 NRTI	109	35 (9)	6/94	87 (80.6)	21 (19.4)	ND[c]
018						
DOR + 2 NRTI	385	35 (11)	17/83	280 (73.1)	103 (26.9)	91 (23.6)[d]
DRV/r + 2 NRTI	384	36 (11)	15/85	280 (73.1)	103 (26.9)	110 (28.6)[d]
021						
DOR + 2 NRTI	368	34 (11)	16/84	177 (48.6)	187 (51.4)	68 (18.5)[d]
EFV + 2 NRTI	366	33 (10)	15/85	170 (46.7)	194 (53.3)	88 (24.0)[d]
Studies with DTG						
FLAMINGO						
DTG + 2 NRTI	243	34 [18-67][e]	13/87	173 (71.5)	68 (28.1)	34[f] (14.1)
DRV/r + 2 NRTI	245	34 [19-67][e]	17/83	176 (72.7)	66 (27.3)	52[f] (21.5)
SINGLE						
DTG + 2 NRTI	422	37 (11)	16/84	284 (68.6)	130 (31.4)[g]	72 (17.4)
EFV + 2 NRTI	422	36 (10)	15/85	285 (68.0)	133 (31.7)[g]	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: 21 (19.4%) patients in the DOR arm and 24 (22.0 %) in the EFV arm discontinued the study.
d: Unclear whether treatment or study were discontinued.
e: Median [min; max]
f: Information from [15]; deviating information in [16]: DTG arm: n = 33; DRV arm: n = 54).
g: Institute's calculation.
/r: boosted with ritonavir; DOR: doravirine; DRV: darunavir; DTG: dolutegravir; EFV: efavirenz; F: female; M: male; ND: no data; n: number of patients with event; N: number of randomized patients; 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 + 2 NRTI[a] 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
Studies with DOR								
007								
DOR + 2 NRTI	108	ND	ND	4 (3.7)	70 (64.8)[c]	38 (35.2)[c]	7 (6.5)	101 (93.5)
EFV + 2 NRTI	109	ND	ND	7 (6.5)	68 (63.0)[c]	40 (37.0)[c]	10 (9.3)	98 (90.7)
018								
DOR + 2 NRTI	385	ND	ND	12 (3.1)	290 (75.7)[c]	93 (24.3)[c]	42 (11.0)	341 (89.0)
DRV/r + 2 NRTI	384	ND	ND	12 (3.1)	289 (75.5)[c]	94 (24.5)[c]	67 (17.5)	316 (82.5)
021								
DOR + 2 NRTI	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								
FLAMINGO								
DTG + 2 NRTI	243	ND	ND	ND	181 (74.8)	61 (25.2)	23 (9.5)	219 (90.5)
DRV/r + 2 NRTI	245	ND	ND	ND	181 (75.8)	61 (25.2)	24 (9.9)	218 (90.1)
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)

(continued)

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

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 arm or in the efavirenz arm.
/r: boosted with ritonavir; AIDS: acquired immunodeficiency syndrome; CD4: cluster of differentiation 4; CDC: Centers for Disease Control and Prevention; DOR: doravirine; DRV: darunavir; 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; vs.: versus

The demographic and clinical characteristics of the patients were largely balanced both between the individual study arms and between the 6 studies.

The clear majority of the patients in all 6 studies were male, and the mean age of the patients ranged between 33 and 41 years throughout all treatment arms. On the FLAMINGO study there are only data on the median age (34 years). Except for study 021, in which the proportion of white and non-white patients was balanced, the proportion of white patients was clearly greater than the proportion of non-white patients in all studies. The majority of the patients had viral loads of ≤ 100 000 HIV-1 RNA copies/ml at the start of the study; 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. Data on the individual categories ("asymptomatic", "symptomatic", acquired immunodeficiency syndrome [AIDS]) regarding the HIV disease stage according to CDC classification are not available for all studies. According to the inclusion criteria, inclusion of patients with diseases according to CDC class C (AIDS-defining events) at screening were not allowed in the FLAMINGO study. The proportion of patients with AIDS at the start of the study was overall low in the remaining studies and ranged between 0% (DTG arm of the SPRING-1 study) and 6.5% (EFV arm of study 007).

The proportion of patients who discontinued treatment ranged between 10% (DTG arm of the SPRING-1 study) and about 29 % (DRV/r arm of SINGLE 018) 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 6 studies showed that they were sufficiently similar regarding their design. The impact of the partially differing backbone therapies of 2 NRTI (studies 007, 021 [EFV arm], SINGLE: FTC/TDF; studies 018, FLAMINGO, 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 partially differences in geographical regions where the studies were conducted. However, based on the data on baseline viral load, CD4 cell count and HIV disease stage according to CDC classification, it must be assumed that the patients 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 + 2 NRTI[a] vs. DTG + 2 NRTI[a], 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							
007	Yes	Yes	Yes	Yes	Yes	Yes	Low
018	Yes	Yes	Yes	Yes	Yes	Yes	Low
021	Yes	Yes	Yes	Yes	Yes	Yes	Low
Studies with DTG							
FLAMINGO	Yes	Yes	No	No	Yes	Yes	Low
SINGLE	Yes	Yes	Yes	Yes	Yes	Yes	Low
PRING-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 6 studies. This concurs with the company's assessment Limitations that might result from the open-label study design of the studies FLAMINGO and SPRING-1 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

- Serious adverse events (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 reasons, 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 regarding specific AEs, if any, in all cases.

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

Table 11: Matrix of outcomes – RCT, indirect comparison: DOR + 2 NRTI[a] 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								
007	Yes	No[c]	Yes	Yes	No[c]	Yes	Yes	Yes
018	Yes	Yes	Yes	Yes	No[c]	Yes	Yes	Yes
021	Yes	Yes	Yes	Yes	No[c]	Yes	Yes	Yes
Studies with DTG								
FLAMINGO	Yes	No[d]	Yes	Yes	No[c]	Yes	Yes	Yes
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, in the SPRING-1 study, according to TLOVR) 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.
d: Data on week 96 are missing.
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; 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 comparison: DOR + 2 NRTI[a] 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								
007	N	-[c]	N	H[d]	-[c]	N	N	-[e]
018	N	N	N	H[d]	-[c]	N	N	-[e]
021	N	N	N	H[d]	-[c]	N	N	-[e]
Studies with DTG								
FLAMINGO	N	–[f]	N	N	-[c]	N	H[g]	-[e]
SINGLE	N	N	N	N	-[c]	N	N	-[e]
SPRING-1	N	N	N	H[h]	-[c]	N	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, in the SPRING-1 study, according to TLOVR) 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.
d: ITT principle violated: proportion of patients not considered > 10%.
e: Analyses on specific AEs incomplete, see Section 2.6.5.3.2 of the full dossier assessment.
f: No data were available on this outcome.
g: Subjectively reported outcome in open-label study.
h: ITT principle violated: proportion of missing values in the treatment arms 10% or 22%.
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; 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 the studies 007, 018 and 021. The high risk of bias for the results on the CD4 cell count results from the violation of the intention to treat (ITT) principle by a relevant proportion of patients (> 10%) who had not been considered in the analysis. This deviates from the assessment of the company, which assumed a low risk of bias for all outcomes rated as relevant by it.

The outcome-specific risk of bias for the available results was rated as low in the FLAMINGO study, except for the side effect-related outcome “discontinuation due AEs”. The high risk of bias for the results on the outcome “discontinuation due to AEs” results from the open-label study design. This concurs with the company’s assessment.

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 [13]. 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 on the comparison of DOR with DTG, each in combination with 2 NRTI, in treatment-naive HIV-1 infected adults. As far as results from both indirect comparisons using the common comparators EFV and DRV/r were available, these were summarized in a meta-analysis. The forest plots of the meta-analyses calculated by the Institute can be found in Appendix A.1 of the full dossier assessment. Where necessary, data from the company’s dossier were supplemented with the Institute’s calculations. Tables on common AEs are presented in Appendix A.2 of the full dossier assessment. The available data did not permit a presentation of the common SAEs and discontinuations due to AEs in study 007.

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

Outcome category Outcome Comparison Study	DOR + 2 NRTI or DTG + 2 NRTI N	 Patients with event n (%)	EFV + 2 NRTI or DRV/r + 2 NRTI N	 Patients with event n (%)	Group difference RR [95% CI]; p-value[b]
Mortality					
All-cause mortality					
DOR + 2 NRTI vs. EFV + 2 NRTI					
007	108	0 (0)	108	0 (0)	–
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 the common comparator EFV[d]:					
DOR + 2 NRTI vs. DTG + 2 NRTI					0.30 [0.01; 10.18]; 0.504
DOR + 2 NRTI vs. DRV/r + 2 NRTI					
018	383	3 (0.8)	383	1 (0.3)	3.00 [0.31; 28.71][e]; < 0.378[f]
DTG + 2 NRTI vs. DRV/r + 2 NRTI					
FLAMINGO	242	1 (0.4)	242	0 (0)	3.00 [0.12; 73.28][e]; < 0.410[f]
Indirect comparison using the common comparator DRV/r[g]:					
DOR + 2 NRTI vs. DTG + 2 NRTI					1.00 [0.02; 50.07]; > 0.999
indirect comparison (total)[h]:					
DOR + 2 NRTI vs. DTG + 2 NRTI					0.51 [0.04 6.81]; 0.610

(continued)

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

Outcome category **Outcome** **Comparison** **Study**	**DOR + 2 NRTI or DTG + 2 NRTI** **N**	**Patients with event n (%)**	**EFV + 2 NRTI or DRV/r + 2 NRTI** **N**	**Patients with event n (%)**	**Group difference** **RR [95% CI]; p-value[b]**
Morbidity					
AIDS-defining events (CDC class C)					
DOR + 2 NRTI vs. EFV + 2 NRTI					
007	Outcome not recorded				
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[i]					1.19 [0.38; 3.68]; 0.763
Indirect comparison using the common comparator EFV[g]:					
DOR + 2 NRTI vs. DTG + 2 NRTI					0.17 [0.01; 4.28]; 0.280
DOR + 2 NRTI vs. DRV/r + 2 NRTI					
018	383	0 (0)	383	6 (1.6)	0.08 [0.00; 1.36][e]; < 0.015[f]
DTG + 2 NRTI vs. DRV/r + 2 NRTI					
FLAMINGO		ND[j]		ND[j]	ND

(continued)

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

Outcome category **Outcome** **Comparison** **Study**	**DOR + 2 NRTI or DTG + 2 NRTI** **N**	**Patients with event n (%)**	**EFV + 2 NRTI or DRV/r + 2 NRTI** **N**	**Patients with event n (%)**	**Group difference** **RR [95% CI]; p-value[b]**
Supplementary: surrogate outcome "virologic response" (HIV-1 RNA < 50 copies/mL)[k]					
DOR + 2 NRTI vs. EFV + 2 NRTI					
007	108	82 (75.9)	108	82 (75.9)	1.00 [0.86; 1.16]; ND
021	364	282 (77.5)	364	268 (73.6)	1.05 [0.97; 1.14]; 0.228
Total[c]					1.04 [0.97; 1.12]; 0.289
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 the common comparator EFV[d]:					
DOR + 2 NRTI vs. DTG + 2 NRTI					0.93 [0.84; 1.04]; 0.190
DOR + 2 NRTI vs. DRV/r + 2 NRTI					
018	379	277 (73.1)	376	248 (66.0)	1.11 [1.01; 1.22]; 0.034
DTG + 2 NRTI vs. DRV/r + 2 NRTI					
FLAMINGO	242	194 (80.2)	242	164 (67.8)	1.18 [1.06; 1.32]; 0.002
Indirect comparison using the common comparator DRV/r[d]:					
DOR + 2 NRTI vs. DTG + 2 NRTI					0.94 [0.81; 1.08]; 0.371
indirect comparison (total)[h]:					
DOR + 2 NRTI vs. DTG + 2 NRTI					0.93 [0.86; 1.02]; 0.116
Health-related quality of life	Outcome not recorded				

(continued)

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

Outcome category Outcome Comparison Study	DOR + 2 NRTI or DTG + 2 NRTI N	 Patients with event n (%)	EFV + 2 NRTI or DRV/r + 2 NRTI N	 Patients with event n (%)	Group difference RR [95% CI]; p-value[b]
Side effects					
AEs (additional information)					
DOR + 2 NRTI vs. EFV + 2 NRTI					
007	108	97 (89.8)	108	104 (96.3)	–
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)	–
DOR + 2 NRTI vs. DRV/r + 2 NRTI					
018	383	324 (84.6)	383	317 (82.8)	–
DTG + 2 NRTI vs. DRV/r + 2 NRTI					
FLAMINGO	242	222 (91.7)	242	217 (89.7)	–
SAEs					
DOR + 2 NRTI vs. EFV + 2 NRTI					
007	108	11 (10.2)	108	13 (12.0)	0.85 [0.40; 1.80]; ND
021	364	21 (5.8)	364	30 (8.2)	0.70 [0.41; 1.20]; 0.194
Total[c]					0.74 [0.48; 1.15]; 0.187
DTG + 2 NRTI vs. EFV + 2 NRTI					
SINGLE	414	44 (10.6)	419	50[l] (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 with the common comparator EFV[d]:					
DOR + 2 NRTI vs. DTG + 2 NRTI					0.83 [0.47; 1.45]; 0.505
DOR + 2 NRTI vs. DRV/r + 2 NRTI					
018	383	27 (7.0)	383	33 (8.6)	0.82 [0.50; 1.33]; 0.421
DTG + 2 NRTI vs. DRV/r + 2 NRTI					
FLAMINGO	242	36 (14.9)	242	21 (8.7)	1.71 [1.03; 2.85]; 0.038
Indirect comparison using the common comparator DRV/r[d]:					
DOR + 2 NRTI vs. DTG + 2 NRTI					0.48 [0.24; 0.97]; 0.040
indirect comparison (total)[h]:					
DOR + 2 NRTI vs. DTG + 2 NRTI					0.67 [0.43; 1.04]; 0.072

(continued)

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

Outcome category **Outcome** **Comparison** **Study**	**DOR + 2 NRTI or DTG + 2 NRTI**		**EFV + 2 NRTI or DRV/r + 2 NRTI**		**Group difference**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value[b]**
Discontinuation due to AEs					
DOR + 2 NRTI vs. EFV + 2 NRTI					
007	108	5 (4.6)	108	11 (10.2)	0.45 [0.16; 1.26]; ND
021	364	11 (3.0)	364	27 (7.4)	0.41 [0.21; 0.81]; 0.010
Total[c]					0.42 [0.24; 0.74]; 0.003
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 the common comparator EFV[d]:					
DOR + 2 NRTI vs. DTG + 2 NRTI					1.49 [0.68; 3.26]; 0.322
DOR + 2 NRTI vs. DRV/r + 2 NRTI					
018	383	6 (1.6)	383	13 (3.4)	0.46 [0.18; 1.20]; 0.113
DTG + 2 NRTI vs. DRV/r + 2 NRTI					
FLAMINGO	242	7 (2.9)	242	15 (6.2)	0.47 [0.19; 1.12]; 0.089
Indirect comparison using the common comparator DRV/r[d]:					
DOR + 2 NRTI vs. DTG + 2 NRTI					0.99 [0.27; 3.63]; 0.987
indirect comparison (total)[h]:					
DOR + 2 NRTI vs. DTG + 2 NRTI					1.34 [0.68; 2.61]; 0.397

(continued)

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

a: See Table 7 for information on the combination partners in the individual studies.
b: Unless otherwise stated: two-sided p-value (Wald test).
c: Meta-analysis from fixed-effect model (Mantel-Haenszel).
d: Indirect comparison according to Bucher [17].
e: Institute's calculation, asymptotic.
f: Institute's calculation, unconditional exact test (CSZ method according to [18]).
g: Institute's calculation, indirect comparison according to Bucher [17].
h: Institute's calculation, pooling of the indirect comparisons, fixed-effect model (inverse variance).
i: Institute's calculation, model with fixed effect (Mantel-Haenszel).
j: According to [16], HIV-1-associated progression (change of the symptoms compared with CDC class C event, newly occurred event according to CDC class C or death) occurred in none of the patients until week 48.
k: Analysis in accordance with snapshot algorithm (studies 007, 018, 021, SINGLE, FLAMINGO) or TLOVR (SPRING-1 study).
l: Information from Module 4 A; this differs from the information provided in dossier assessment A14-08 Dolutegravir [13], see Appendix A.2 of the full dossier assessment. However, this discrepancy has no impact on the overall result.

/r: boosted with ritonavir; AE: adverse event; AIDS: acquired immunodeficiency syndrome; CDC: Centers for Disease Control and Prevention; DOR: doravirine; DRV: darunavir; 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; RCT: randomized controlled trial; RNA: ribonucleic acid; RR: relative risk; SAE: serious adverse event; TLOVR: Time to Loss of Virologic Response; vs.: versus

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

Outcome category	DOR + 2 NRTI or DTG + 2 NRTI			EFV + 2 NRTI or DRV/r + 2 NRTI			Group difference
Outcome Comparison Study	N[b]	Values at baseline mean (SD)	Change at end of study mean [95% CI][c]	N[b]	Values at baseline mean (SD)	Change at end of study mean [95% CI][c]	MD [95% CI]; p-value
Morbidity							
Supplementary: surrogate outcome "CD4 cell count/µL"							
DOR + 2 NRTI vs. EFV + 2 NRTI							
007	95	435.6 (ND)	259.2 [220.0; 298.3]	93	455.9 (ND)	263.6 [218.1; 309.1]	-4.4 [-64.0; 55.1]; ND
021	337	435.9 (ND)	237.7 [214.9; 260.6]	311	413.5 (ND)	223.0 [198.4; 247.6]	14.7 [-18.7; 48.2]; ND
Total[d]							10.1 [-19.0; 39.3]; 0.497
DTG + 2 NRTI vs. EFV + 2 NRTI							
SINGLE	414	349 (158.2)	324 (205.7)[e]	419	351 (157.5)	286 (196.0)[e]	43.95 [14.34; 73.55][f]; ND
SPRING-1	51	327 (122.3)	338 (162.6)[e]	50	328 (106.5)	321 (218.9)[e]	17.0 [-65.5; 99.5]; ND
Total[g]							40.79 [12.98; 68.61]; 0.004
Indirect comparison using the common comparator EFV[h]:							
DOR + 2 NRTI vs. DTG + 2 NRTI							-30.67 [-70.97; 9.63]; 0.136
DOR + 2 NRTI vs. DRV/r							
018	342	429.6 (ND)	224.1 [200.8; 247.4]	327	405.0 (ND)	206.7 [184.9; 228.5]	17.4 [-14.5; 49.3]; ND
DTG + 2 NRTI vs. DRV/r							
FLAMINGO	242	390 [290; 500][i]	260 [185; 400][i]	242	400 [300; 530][i]	250 [130; 400][i]	ND

a: See Table 7 for information on the combination partners in the individual studies.
b: Number of patients analysed at time point 96 weeks. The values at the start of the study can be based on other patient numbers.
c: Missing values were imputed using an observed failure approach (baseline value transferred for patients who had discontinued treatment due to lack of effectiveness and exclusion of other patients with missing values).
d: Fixed-effect model.
f: Values at the end of the study, mean (SD).
e: Difference of adjusted mean values [95% CI] from MMRM model.
g: 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]).
h: Indirect comparison according to Bucher [17].
i: Median [25% quantile; 75% quantile].

CD4: cluster of differentiation 4; CI: confidence interval; DOR: doravirine; DTG: dolutegravir; EFV: efavirenz; MD: mean difference; N: number of analysed patients; NRTI: nucleoside/nucleotide reverse transcriptase inhibitor; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Based on the available data from the two adjusted indirect comparisons, at most indications, e.g. of an added benefit, could be derived from the meta-analysis of the indirect comparisons (see Section 2.6.5.3.1 of the full dossier assessment). This deviates from the company's approach, which did not summarize the two indirect comparisons in a meta-analysis.

Only the results at week 96 were used for the benefit assessment. 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

Pooling of the two adjusted indirect comparisons in a meta-analysis showed no statistically significant difference between DOR + 2 NRTI and DTG + 2 NRTI at week 96 for the outcome "all-cause mortality". This resulted in no hint of an added benefit of DOR + 2 NRTI 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 outcome "AIDS-defining events" was not recorded in the 007 study. In the FLAMINGO study, there are no results for this outcome at week 96; an indirect comparison using the common comparator DRV/r is therefore impossible. Based on the available data, indirect comparison using the common comparator DRV/r was also impossible for the outcome "CD4 cell count", because the FLAMINGO study only provides information on the median of the CD4 cell count in the treatment arms.

An indirect comparison using the common comparator EFV shows no statistically significant difference between DOR + 2 NRTI and DTG + 2 NRTI at week 96, neither for the outcome "AIDS-defining events (CDC class C)" nor for the outcome "CD4 cell count" presented as additional information. Pooling of the two adjusted indirect comparisons in a meta-analysis showed no statistically significant difference between DOR + 2 NRTI and DTG + 2 NRTI at week 96 for the outcome "virologic response", which was presented as additional information.

Overall, there was no hint of an added benefit of DOR + 2 NRTI in comparison with DTG + 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

Pooling of the two adjusted indirect comparisons in a meta-analysis showed no statistically significant difference between DOR + 2 NRTI and DTG + 2 NRTI at week 96 for the outcome "SAEs". Hence, there was no hint of greater or lesser harm from DOR + 2 NRTI versus DTG + 2 NRTI; greater or lesser harm is therefore not proven.

This deviates from the company's assessment, which derived an indication of an added benefit of DOR + 2 NRTI vs. DTG + 2 NRTI on the basis of the indirect comparison using the common comparator DRV/r.

Discontinuation due to AEs

Pooling of the two adjusted indirect comparisons in a meta-analysis showed no statistically significant difference between DOR + 2 NRTI and DTG + 2 NRTI at week 96 for the outcome "discontinuation due to AEs". Hence, there was no hint of greater or lesser harm from DOR + 2 NRTI 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, performance of subgroup analyses for the adjusted indirect comparison was not possible on the basis of the available data. This concurs with the company's approach. For reasons, 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 [19].

The procedure for deriving an overall conclusion on added benefit based on the aggregation of the conclusions deduced 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 2.3.2.3 (see Table 15).

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

Outcome category **Outcome**	**DOR + 2 NRTI vs. DTG + 2 NRTI proportion of events (%) or MD** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
All-cause mortality[c]	0-0.8% vs. 0-2.0% RR: 0.51 [0.04; 6.81]; p = 0.610	Lesser benefit/added benefit not proven
Morbidity		
AIDS-defining events (CDC class C)[d]	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[c]	73.1-77.5% vs. 77.1-88.2% RR: 0.93 [0.86; 1.02]; p = 0.116	Lesser benefit/added benefit not proven
CD4 cell count/µL[d]	Mean: 237.2-259.2 vs. 324-338 MD: -30.67 [-70.97; 9.63]; p = 0.136	Lesser benefit/added benefit not proven
Health-related quality of life	outcome not recorded	Lesser benefit/added benefit not proven
Side effects		
SAEs[c]	5.8-10.2% vs. 10.6-14.9% RR: 0.67 [0.43; 1.04]; p = 0.072	Greater/lesser harm not proven
Discontinuation due to AEs[c]	1.6-4.6% vs. 2.9-3.9% RR: 1.34 [0.68; 2.61]; p = 0.397	Greater/lesser harm not proven

a: Probability provided if there is a statistically significant and relevant effect.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Indirect comparison using common comparators EFV and DRV/r summarized in a meta-analysis.
d: Indirect comparison using the common comparator EFV.
/r: boosted with ritonavir; 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; DRV: darunavir; DTG: dolutegravir; EFV: efavirenz; MD: mean difference; NRTI: nucleoside/nucleotide reverse transcriptase inhibitor; RR: relative risk; SAE: serious adverse event; 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 added benefit.

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

Positive effects	**Negative effects**
–	–
Health-related quality of life: outcomes from this category were not recorded	
DOR: doravirine; DTG: dolutegravir; NRTI: nucleoside/nucleotide reverse transcriptase inhibitor	

In the overall assessment, there were neither positive nor negative effects of DOR + 2 NRTI in comparison with DTG + 2 NRTI.

Overall, there was no hint of an added benefit of DOR + 2 NRTI 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 non-quantifiable added benefit for treatment-naive adults with HIV-1 infection.

2.3.4 List of included studies

007

Merck Sharp & Dohme. Multicenter, double-blind, randomized, 2-part, dose ranging study to compare the safety, and antiretroviral activity of MK-1439 plus TRUVADA versus efavirenz plus TRUVADA in antiretroviral treatment-naïve, HIV-1 infected patients: study MK-1439-007; study protocol amendment 07 [unpublished]. 2012.

Merck Sharp & Dohme. Multicenter, double-blind, randomized, 2-part, dose ranging study to compare the safety, and antiretroviral activity of MK-1439 plus TRUVADA versus efavirenz plus TRUVADA in antiretroviral treatment-naïve, HIV-1 infected patients: study MK-1439-007; clinical study report [unpublished]. 2017.

Merck Sharp & Dohme. A dose-ranging study to compare doravirine (MK-1439) plus TRUVADA versus efavirenz plus TRUVADA in human immunodeficiency virus (HIV)-1 Infected participants (MK-1439-007): study details [online]. In: ClinicalTrials.gov. 29/08/2018 [Accessed: 15/02/2019]. URL: https://clinicaltrials.gov/ct2/show/NCT01632345.

Merck Sharp & Dohme. A dose-ranging study to compare doravirine (MK-1439) plus TRUVADA versus efavirenz plus TRUVADA in human immunodeficiency virus (HIV)-1 infected participants (MK-1439-007): study results [online]. In: ClinicalTrials.gov. 29/08/2018 [Accessed: 15/02/2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT01632345.

Merck Sharp & Dohme. Multicenter, double-blind, randomized, 2-part, dose ranging study to compare the safety, and antiretroviral activity of MK-1439 Plus TRUVADA versus efavirenz plus TRUVADA in antiretroviral treatment-naïve, HIV-1 infected patients [online]. In: EU Clincal Trials Register. [Accessed: 15/02/2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-001573-93.

Merck Sharp & Dohme. Multicenter, double-blind, randomized, 2-part, dose ranging study to compare the safety, and antiretroviral activity of MK-1439 plus TRUVADA versus efavirenz plus TRUVADA in antiretroviral treatment-naïve, HIV-1 infected patients: clinical trial results [online]. In: EU Clincal Trials Register. 01/04/2017 [Accessed: 15/02/2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2012-001573-93/results.

018

Merck Sharp & Dohme. A phase 3 multicenter, double-blind, randomized, active comparator-controlled clinical trial to evaluate the safety and efficacy of doravirine (MK-1439) 100 mg once daily versus darunavir 800 mg once daily plus ritonavir 100 mg once daily, each in combination with TRUVADA or EPZICOM/KIVEXA, in treatment-naïve HIV-1 infected subjects: study MK-1439-018; study protocol amendment 01 [unpublished]. 2015.

Merck Sharp & Dohme. A phase 3 multicenter, double-blind, randomized, active comparator-controlled clinical trial to evaluate the safety and efficacy of doravirine (MK-1439) 100 mg once daily versus darunavir 800 mg once daily plus ritonavir 100 mg once daily, each in combination with TRUVADA or EPZICOM/ KIVEXA, in treatment-naïve HIV-1 infected subjects: study MK-1439-018; clinical study report [unpublished]. 2018.

Merck Sharp & Dohme. Safety and efficacy of doravirine (MK-1439) in participants with human immunodeficiency virus 1 (HIV-1) (MK-1439-018): study details [online]. In: ClinicalTrials.gov. 23/10/2018 [Accessed: 15/02/2019]. URL: https://clinicaltrials.gov/ct2/show/NCT02275780.

Merck Sharp & Dohme. Safety and efficacy of doravirine (MK-1439) in participants with human immunodeficiency virus 1 (HIV-1) (MK-1439-018): study results [online]. In: ClinicalTrials.gov. 23/10/2018 [Accessed: 15/02/2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT02275780.

Merck Sharp & Dohme. A phase 3 multicenter, double-blind, randomized, active comparator-controlled clinical trial to evaluate the safety and efficacy of doravirine (MK-1439) 100 mg once daily versus darunavir 800 mg once daily plus ritonavir 100 mg once daily, each in combination with TRUVADA or EPZICOM/KIVEXA, in treatment-naïve HIV-1 infected subjects [online]. In: EU Clinical Trials Register. [Accessed: 15/02/2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-001127-69.

Molina JM, Squires K, Sax PE, Cahn P, Lombaard J, DeJesus E et al. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 48-week results of a randomised, double-blind, phase 3, non-inferiority trial. Lancet HIV 2018; 5(5): e211-e220.

021

Merck Sharp & Dohme. A phase III multicenter, double-blind, randomized, 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; study protocol amendment 04 [unpublished]. 2016.

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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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 (status: 17 October 2018)
- bibliographical literature search on DOR (last search on 17 October 2018)
- search in trial registries for studies on DOR (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 in combination with other antiretroviral drugs in comparison with the ACT in pretreated HIV-1 infected adults. Hence, there was no hint of an added benefit of DOR in combination with other antiretroviral drugs 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 in combination with other antiretroviral drugs in comparison with the ACT in treatment-naive HIV-1 infected adults, an added benefit of DOR in combination with other antiretroviral drugs 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 for the benefit assessment.

2.5 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of DOR in combination with other antiretroviral drugs in comparison with the ACT is summarized in Table 17.

Table 17: Doravirine – 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. DOR: doravirine; HIV-1: human immunodeficiency virus type 1; G-BA: Federal Joint Committee; NNRTI: non-nucleoside reverse transcriptase inhibitor		

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

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Please see full dossier assessment for full reference list.

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